Optimizing Outcomes in Advanced Prostate Cancer

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Conflict of Interest Disclosures

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Prostate Cancer: HSPC
Which of the following non-CRPC prostate cancer patients are candidates for docetaxel therapy?

a) 68 year old man with localized, Gleason 9 prostate cancer and PSA of 34 being treated with IMRT and ADT

b) 71 year old man with newly diagnosed metastatic prostate cancer with 2 bone metastases on bone scan

c) 63 year old man with newly diagnosed metastatic prostate cancer with liver metastases

d) All of the above

e) 2 and 3

f) 3 only
ECOG 3805 (CHAARTED): Chemo-Hormonal vs Androgen Ablation Randomized Trial in Extensive Disease

3-year OS: 69.0% vs. 52.5%

3-year OS in pts with a high extent of metastatic disease: 63.4% vs. 43.9%

“Patients with a high extent of metastatic disease accounted for most of the benefit in the OS from Docetaxel plus ADT”
Primary Endpoint: Overall Survival

- 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)

<table>
<thead>
<tr>
<th>Months</th>
<th>ADT+docetaxel</th>
<th>ADT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>397</td>
<td>393</td>
</tr>
<tr>
<td>12</td>
<td>333</td>
<td>318</td>
</tr>
<tr>
<td>24</td>
<td>189</td>
<td>168</td>
</tr>
<tr>
<td>36</td>
<td>89</td>
<td>71</td>
</tr>
<tr>
<td>48</td>
<td>46</td>
<td>27</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>72</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>84</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
In patients with high volume metastatic disease, there is a 17 month improvement in median overall survival from 32.2 months to 49.2 months. We projected 33 months alone in the ADT alone arm with collaborations of SWOG9346 team.
High Volume Disease

• ≥4 bone lesions and
• ≥1 lesion in any bony structure beyond the spine/pelvis
OR
• Visceral disease
GETUG-AFU 15 TRIAL DESIGN

Stratification:
- Prior systemic TT
- Glass risk group

Arm A:
ADT + Docetaxel
D: 75 mg/m² q3 up to 9 cycles

Arm B:
ADT alone
ADT:
- LHRH agonist
- or maximum androgen blockade
- or orchiectomy
OVERALL SURVIVAL

- Median follow-up 81.3 months [69.2-83.7]

Low Volume

High Volume

Median OS
ADT alone: NR [61.8- NR]
ADT + D: 83.1 [ 69.5- NR]
HR: 1.0 [0.6-1.5]
p=0.87

Median OS
ADT alone: 35.1 [29.9- 44.2]
ADT + D: 39 [ 28- 52.6]
HR: 0.8 [0.6-1.2]
p=0.35
Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First survival results from STAMPEDE

Nicholas James
University of Warwick and Queen Elizabeth Hospital Birmingham

on behalf of

Matthew Sydes, Malcolm Mason, Noel Clarke, David Dearnaley, Melissa Spears, Robin Millman, Chris Parker, Alastair Ritchie, J. Martin Russell, John Staffurth, Robert Jones, Shaun Tolan, John Wagstaff, Andrew Protheroe, Rajaguru Srinivasan, Alison Birtle, Joe O’Sullivan, Richard Cathomas, Mahesh Parmar and the STAMPEDE Investigators
### Inclusion Criteria

**Newly Diagnosed:**
- Any of:
  - Metastatic
  - Node-positive
  - ≥2 of:
    - Stage T3/4
    - PSA ≥ 40 ng/ml
    - Gleason 8-10

**All Patients:**
- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

**Relapsing after previous RP or RT with ≥1 of:**
- PSA ≥4 ng/ml & rising with doubling time <6 m
- PSA ≥20 ng/ml
- Node positive
- Metastatic

**Full Criteria:**
- www.stampedetrial.org

Presented By Nicholas James at 2015 ASCO Annual Meeting
STAMPEDE: All Docetaxel & Zoldronic Acid Comparisons

A = ~1200 pts --> ~404 primary outcome measure events
B = ~600 pts, C = ~600 pts, D = ~600 pts

SOC = ADT (+/- RT)
SOC + zoledronic acid
SOC + celecoxib
SOC + zoledronic acid + docetaxel
SOC + zoledronic acid + celecoxib
SOC + (enzo + abi)^^
SOC + (abi)^
SOC + M1 | RT {M1}

^ Abiraterone
^^ Enzalutamide + abiraterone
### Patient Characteristics

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Description</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1%</td>
<td>WHO PS 2</td>
<td>[s]</td>
</tr>
<tr>
<td>21%</td>
<td>WHO PS 1</td>
<td>[s]</td>
</tr>
<tr>
<td>65 yr</td>
<td>Median Age</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(min 40, max 84)</td>
<td>[s]</td>
</tr>
<tr>
<td>61%</td>
<td>Metastatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(85% bony mets)</td>
<td>[s]</td>
</tr>
<tr>
<td>15%</td>
<td>N+M0</td>
<td></td>
</tr>
<tr>
<td>24%</td>
<td>N0M0</td>
<td></td>
</tr>
<tr>
<td>98%</td>
<td>LNRH analogues</td>
<td></td>
</tr>
<tr>
<td>29%</td>
<td>Planned for RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(72% of N0M0 pts)</td>
<td>[s]</td>
</tr>
<tr>
<td>6%</td>
<td>Previous local therapy</td>
<td></td>
</tr>
</tbody>
</table>

Balanced by arm

[s] Stratification factors + hospital + NSAID/aspirin
Docetaxel: Failure-Free Survival

SOC: 750 FFS events
SOC+Doc: 371 FFS events

HR (95% CI) 0.62 (0.54, 0.70)
P-value <0.0000000001*

Non-PH p-value 0.0002

Restricted mean FFS time
SOC 35.3m
SOC+Doc 44.4m
Diff (95%CI) 9.1m (6.3, 11.9m)

*exact p-value: 0.00000000000002014
Docetaxel: Survival

- SOC: 405 deaths
- SOC+Doc: 165 deaths
- HR (95% CI): 0.76 (0.63, 0.91)
- P-value: 0.003

Median OS (95% CI):
- SOC: 67m (60, 91m)
- SOC+Doc: 77m (70, NR)

Restricted mean OS time:
- SOC: 58.8m
- SOC+Doc: 63.4m
- Diff (95% CI): 4.6m (1.8, 7.3m)

Presented By Nicholas James at 2015 ASCO Annual Meeting
Docetaxel: Survival – M1 Patients

- SOC: 343 deaths
- SOC+Doc: 134 deaths
- 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]

- Restricted mean OS time:
  - SOC: 49.3m
  - SOC+Doc: 56.1m
  - Diff (95% CI): 6.8m (2.8, 11.0m)
## Grade 3+ Adverse Events Ever Reported

<table>
<thead>
<tr>
<th>Category</th>
<th>A (SOC)</th>
<th>B (SOC+ZA)</th>
<th>C (SOC+Doc)</th>
<th>E (SOC+ZA+Doc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomised</td>
<td>1184</td>
<td>593</td>
<td>592</td>
<td>593</td>
</tr>
<tr>
<td>Patients with adverse event data</td>
<td>1174</td>
<td>587</td>
<td>579</td>
<td>564</td>
</tr>
<tr>
<td>Grade 3-5 AE (G5)</td>
<td>N</td>
<td>363 (3)</td>
<td>185 (1)</td>
<td>291 (3)</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>31%</td>
<td>31%</td>
<td>51%</td>
</tr>
<tr>
<td>Endocrine disorder</td>
<td>12%</td>
<td>12%</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td>Blood and lymphatic (<em>febrile neutropenia</em>)</td>
<td>1%</td>
<td>2%</td>
<td>12%</td>
<td>12%</td>
</tr>
<tr>
<td>Blood/bone marrow (<em>neutrophils</em>)</td>
<td>1%</td>
<td>1%</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>General disorder</td>
<td>4%</td>
<td>5%</td>
<td>8%</td>
<td>11%</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>5%</td>
<td>5%</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>3%</td>
<td>3%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Renal</td>
<td>5%</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>
Recommendation

Men with high-risk metastatic prostate cancer, especially those presenting with metastases at or soon after diagnosis, who are judged fit to receive chemotherapy, should be offered 6 cycles of docetaxel in addition to ADT.
Role of Chemotherapy for Localized High-Risk PC (M0) After Radiation Therapy
A phase III protocol of androgen suppression and radiotherapy vs AS and RT followed by chemotherapy with docetaxel and prednisone for localized, high-risk prostate cancer (NRG Oncology/RTOG 0521)


2015 ASCO Annual Meeting May 31, 2015
<table>
<thead>
<tr>
<th>Stage</th>
<th>Gleason Score</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any T Stage</td>
<td>≥9</td>
<td>&lt;150</td>
</tr>
<tr>
<td></td>
<td>7-8</td>
<td>≥20-150</td>
</tr>
<tr>
<td>≥T2</td>
<td>8</td>
<td>&lt;20</td>
</tr>
</tbody>
</table>

**ARM 1**
Androgen Suppression (24 months) +
External RT (8 weeks)

**ARM 2**
Androgen Suppression (24 months) +
External RT (8 weeks) +
Docetaxel beginning 4 weeks after RT (6 cycles)
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Arm 1 and Arm 2 (N = 563)</th>
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</thead>
<tbody>
<tr>
<td>Risk Category (stratification) (%)</td>
<td></td>
</tr>
<tr>
<td>Gleason ≥9, PSA ≤150, Any T-stage</td>
<td>53</td>
</tr>
<tr>
<td>Gleason 8, PSA &lt;20, ≥T2</td>
<td>21</td>
</tr>
<tr>
<td>Gleason 8, PSA ≥20-150, Any T-stage</td>
<td>10</td>
</tr>
<tr>
<td>Gleason 7, PSA ≥20-150, Any T-stage</td>
<td>16</td>
</tr>
<tr>
<td>Gleason Score, no. (%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
</tr>
<tr>
<td>9-10</td>
<td>53</td>
</tr>
<tr>
<td>Serum PSA, ng/ml, Median (Q1-Q3)</td>
<td>15 (7-34)</td>
</tr>
<tr>
<td>Age, Median</td>
<td>66</td>
</tr>
<tr>
<td>cT3-T4</td>
<td>27%</td>
</tr>
<tr>
<td>pN0</td>
<td>33%</td>
</tr>
</tbody>
</table>
Conclusions

• For the first time, improvement in overall survival observed with (tolerable) adjuvant chemotherapy for localized, high-risk, hormone-sensitive prostate cancer
  • Cumulative incidence of DM reduced

• The potential role of docetaxel in hormone-sensitive prostate cancer is consistent with and supported by our data and other studies, such as STAMPEDED and CHAARTED.

• This analysis is relatively early and additional follow-up will likely be enlightening.
Role of chemotherapy for localized high-risk PC (M0) after radiation therapy

• GETUG-12 (Fizazi et al; Lancet Oncol, 2015)
  • ADT +/- 4 cycles Docetaxel/Estramustine (N=413)
  • RFS: 199 events: HR=0.71 (0.54-0.94)
  • OS: 91 deaths: too early

• STAMPEDE (Not all M0 men had RT)
  • ADT +/- 6 cycles Docetaxel/Prednisone (N=689)
  • RFS: 229 events; HR=0.57 (0.42-0.76)
  • OS: 93 deaths; HR=1.01 but too early

• RTOG 0521
  • ADT +/- 6 cycles Docetaxel/Prednisone (N=563)
  • RFS: 221 events: HR=0.76 (0.58-0.99)
  • OS: 102 deaths: HR=0.70 (0.51-0.98)
Recommendation 2

Men with localized M0 prostate cancer who are able to receive local treatment with radiotherapy should not be offered docetaxel in addition to ADT.

This opinion might change with longer follow-up of the GETUG-12, STAMPEDE, and RTOG 0521 trials.
The following non-CRPC prostate cancer patients are candidates for Docetaxel therapy:

- 68 year old man with localized, Gl 9 prostate cancer and PSA of 34 being treated with IMRT and ADT
  - RTOG 0521: not yet but depends on how early an adopter you are, or the patient in front of you.
- 71 year old man with newly diagnosed metastatic prostate cancer with 2 bone mets on BS
  - CHAARTED/GETUG suggests YES. STAMPEDE strengthens that.
- 63 year old man with newly diagnosed metastatic prostate cancer with liver mets
  - CHAARTED and STAMPEDE say YES.
- All of the above
  - MAYBE – see above.
- 2 and 3
  - YES as of this ASCO.
- 3 only
  - DEFINITELY, but from STAMPEDE, can be less advanced than this and still benefit.
Prostate Cancer: CRPC
Recent CRPC Guidelines
Systemic Therapy in Men With Metastatic Castration-Resistant Prostate Cancer: American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline

Ethan Basch, D. Andrew Loblaw, Thomas K. Oliver, Michael Carducci, Ronald C. Chen, James N. Frame, Kristina Garrels, Sebastien Hotte, Michael W. Kattan, Derek Raghavan, Fred Saad, Mary-Ellen Taplin, Cindy Walker-Dilks, James Williams, Eric Winquist, Charles L. Bennett, Ted Wootton, R. Bryan Rumble, Stacie B. Dusetzina, and Katherine S. Virgo
Androgen-Deprivation Therapy:

• Continuous androgen deprivation (pharmaceutical or surgical) should be continued indefinitely regardless of additional therapies

  • Benefit: Moderate
  • Harm: Moderate
  • Evidence strength: Weak
  • Recommendation strength: Moderate
ASCOC-CO Guideline Update: Systemic Therapies Improving Survival and QoL mCRPC

<table>
<thead>
<tr>
<th>Therapies*</th>
<th>Benefit</th>
<th>Harm</th>
<th>Evidence Strength</th>
<th>Recommendation Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate + Prednisone</td>
<td>Moderate</td>
<td>Low</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Moderate</td>
<td>Low</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Radium-223 (in men with bone mets)</td>
<td>Moderate</td>
<td>Low</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Docetaxel + Pred</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cabazitaxel + Pred (after progression with docetaxel)</td>
<td>Moderate</td>
<td>Moderate to high</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

* In addition to ADT

Basch et al. JCO 2014
Therapies with biologic activity and unknown survival or quality-of-life benefit:

- **Antiandrogens (eg, bicalutamide, flutamide, nilutamide) may be offered.** (Benefit: low; harm: low; evidence strength: weak; recommendation strength: weak)

- **Ketoconazole may be offered.** (Benefit: low; harm: moderate; evidence strength: weak; recommendation strength: weak)

- **Low-dose corticosteroid monotherapy may be offered.** (Benefit: low; harm: low; evidence strength: weak; recommendation strength: weak)

- **Mitoxantrone chemotherapy may be offered.** (Benefit: low; harm: moderate to high; evidence strength: weak; recommendation strength: weak)
Palliative Care Services

• Palliative care should be offered to all patients, particularly to those exhibiting symptoms or quality-of-life (QOL) decrements, regardless of treatment type

  • Benefit: Moderate
  • Harm: None
  • Evidence strength: Moderate
  • Recommendation strength: Strong
The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC)

Fred Saad, MD, FRCSC; Kim N. Chi, MD, FRCPC; Antonio Finelli, MD, FRCSC; Sebastien J. Hotte, MD, FRCPC; Jonathan Izawa, MD, FRCSC; Anil Kapoor, MD, FRCSC; Wassim Kassouf, MD, FRCSC; Andrew Loblaw, MD, MSc, FRCPC; Scott North, MD, FRCPC; Ricardo Rendon, MD, FRCSC; Alan So, MD, FRCSC; Nawaid Usmani, MD, FRCPC; Eric Vigneault, MD, FRCPC; Neil E. Fleshner, MD, FRCSC

*Centre Hospitalier de l’Université de Montréal, Montréal, QC; †BC Cancer Agency, Vancouver, BC; ‡University of Toronto, Princess Margaret Cancer Centre, Toronto, ON; ††Sunnybrook Health Sciences Centre, Toronto, ON; †‖Sunnybrook Health Sciences Centre, Toronto, University of Toronto, ON; †‖‖Cross Cancer Institute, University of Alberta, Edmonton, AB; †‡Hotel-Dieu de Québec, Université de Laval, Québec City, QC
• What is Castration-Resistant Prostate Cancer?
  • “disease progression despite castrate levels of testosterone and may present as either a continuous rise in serum PSA levels, progression of pre-existing disease, and/or the appearance of new metastases

• What does it encompass?
  • “from pts without metastases or symptoms with rising PSA despite ADT to pts with metastases and significant debilitation due to cancer symptoms”
2015 CUA-CUOG Guideline

**NON-MET CRPC**
- There is no standard of care and no approved regimen in M0 CRPC

- Detection of mets
  - Pts with PSADT < 8 mos: image every 3-6 mos
  - Pts with PSADT > 12 mos: image every 6-12 mos

- Imaging
  - Commonly with bone scans, abdominal/pelvic CT and chest X-ray
  - MRI and PET still unclear
Asymptomatic or minimally symptomatic:
“pain that is relieved by acetaminophen or a non-steroidal anti-inflammatory”

Symptomatic:
“require regular pain medication opioid/narcotics)* treatment”
2015 CUA-CUOG Guideline

MET CRPC (symptomatic or minimally symptomatic)

- Anti-androgen (AA) should be discontinued
- Introduction of, or changes to, 1st generation AA or use of corticosteroids with or without ketoconazole may be considered

- Abiraterone acetate 1000 mg/day plus prednisone 5 mg/twice daily is recommended as first-line therapy (Level 1, Grade A).
- Enzalutamide 160 mg/day is recommended as first-line therapy (Level 1, Grade A).
- Treatment with docetaxel 75 mg/m² every 3 weeks plus 5 mg oral Prednisone twice daily can be offered (Level 1, Grade A).
Should mCRPC pts be treated when they are asymptomatic?

Despite limitation exists in subgroup analysis, pts with baseline BPI 0-1 had better outcome than those with baseline BPI 2-3.

Another retrospective analysis found that mCRPC “pts who have worse performance status (PS) derive less benefit (specifically OS) from abiraterone, indicating that earlier treatment before PS declines could improve outcomes.”
Met CRPC (who progress after docetaxel-based chemo)

• Options with survival benefit
  • Cabazitaxel (25 mg/m2) plus prednisone (5 mg/day) (Level 1, Grade A)
  • Abiraterone acetate (1000 mg per day) plus prednisone (5 mg twice daily) (Level 1, Grade A)
  • Enzalutamide (160 mg/day) (Level 1, Grade A)
  • Radium-223 q 4 weeks for 6 cycles (Level 1 Grade A)

• Options with unknown survival benefit
  • Docetaxel plus Prednisone re-exposure in patients who have had a previous favorable response to docetaxel may be reasonable
    • (Expert Opinion). Mitoxantrone plus prednisone may be offered for palliative pain relief (Grade C).
CRPC with Bone mets (includes pre/post chemo settings)

• Denosumab (120 mg subcutaneous) or zoledronic acid (4 mg intravenous) every 4 weeks, along with daily calcium and vitamin D supplementation, is recommended to prevent disease-related skeletal complications (Level 1, Grade A).

• Treatment with zoledronic acid should not be used in men with baseline creatinine clearance <30 mL/min.

• Optimal duration of zoledronic acid and denosumab in men with CRPC and bone metastases is undefined. The risk of ONJ appears to be related to time on bone-targeted therapy; therefore caution should be taken in using these agents more than 2 years.
• Radium-223: Funded if symptomatic bone mets with no visceral disease, either pre or post docetaxel (one series of 6 injections per lifetime) but…

• Cabazitaxel:
  • Cabazitaxel will be used in combination with prednisone for the treatment of metastatic castrate-resistant prostate cancer (mCRPC) who have progressed on or within 12 months of completing docetaxel-containing therapy
  • Cabazitaxel is not funded if used:
    • in combination with abiraterone (Zytiga) or enzalutamide (Xtandi) for metastatic castrate-resistant prostate cancer; or
    • in patients who have failed (i.e., disease progression) abiraterone or enzalutamide for metastatic castrate-resistant prostate cancer in the post-docetaxel setting; or
    • as the first line treatment of metastatic castrate-resistant prostate cancer
  • For patients currently on abiraterone or enzalutamide in the post-docetaxel setting, requests to switch over to cabazitaxel may be considered provided
    • the above criteria are met,
    • disease progression on abiraterone or enzalutamide has not yet occurred,
    • the patient initiated treatment with either abiraterone or enzalutamide within the past 3 months of making the request for cabazitaxel
Reimbursement - Ontario

Abiraterone

- **For the treatment of metastatic castrate-resistant prostate cancer (mCRPC)** in patients who meet the following criteria:
  - Zytiga is being used in combination with prednisone; AND
  - The patient’s cancer has progressed after having received prior docetaxel containing therapy; AND
  - The patient has ECOG* ≤ 2.
  - Patients must not meet ANY of the exclusion criteria for funding stated below.

- Requests for patients who initiated Jevtana (cabazitaxel) or Xtandi (enzalutamide) therapy within the three (3) months preceding the EAP request for Zytiga and who have not had disease progression, will be considered on a case-by-case basis.

- **Exclusion Criteria**: Funding for Zytiga will NOT be approved in patients who meet any ONE (or more) of the following exclusion criteria:
  - the Patient has viral hepatitis or chronic liver disease; OR
  - the Patient has clinically significant heart disease; OR
  - Zytiga is being prescribed for combination use with Jevtana or Xtandi for mCRPC; OR
  - the Patient has already used Zytiga in the pre-docetaxel setting.
Reimbursement - Ontario

Enzalutamide

• **For the treatment of metastatic castration resistant prostate cancer** in patients who meet the following criteria;
  • Xtandi is being used in patients who have progressed on docetaxel-based chemotherapy.
  • Patient has an ECOG* ≤ 2 (prior to the start of Xtandi therapy).
  • Requests for Xtandi for patients who meet the above criteria and who have initiated therapy with Jevtana or Zytiga (abiraterone) during the three months prior to the request for reimbursement of Xtandi and who have not had disease progression will be considered.

• **Note:** Xtandi is now also funded in the docetaxel-naïve patients using criteria similar to abiraterone and to post-docetaxel Xtandi conditions.

• **Exclusion criteria:**
  • Xtandi will not be funded in patients who have the following exclusion criteria;
  • Patient has risk factors for seizures;
  • Patient is using Xtandi in combination with Jevtana (cabazitaxel) or Zytiga for metastatic castration-resistant prostate cancer;
  • Patient is using Xtandi for 1st line metastatic castration-resistant prostate cancer.
In theory…

- LHRH alone
- TAB
- Abiraterone
- Enzalutamide
- Docetaxel
- ?
- Enzalutamide
- Abiraterone
- Cabazitaxel
- Radium-223
People whose hindsight is less than 20/20
Case 1: Asymptomatic Metastatic Castrate Resistant Prostate Cancer
Case 1: Presentation

76-year-old male

• 2004
  • Radical prostatectomy for Gleason 4.3, T2cN0M0 disease

• 2010
  • Rising PSA – no metastases
  • LHRH agonist started

• 2015
  • PSA rising over 2 years
  • $2.7 \rightarrow 6.0 \rightarrow 13 \rightarrow 26 \rightarrow 62 \text{ ug/L} \rightarrow q6 \text{ months}$
  • Bone scan: New metastases – vertebrae, ribs, femur – compared to 1 year ago
  • Asymptomatic
  • Has HTN, Type 2 DM on one oral agent
Case 1: Question

What treatment would you recommend?

A. Observation
B. Abiraterone
C. Enzalutamide
D. Docetaxel
E. Bicalutamide
Case 1: Variations on the theme

• Does the PSA doubling time influence your treatment decision?
  • ~ 6 months in this case

• What if the PSA doubling time was
  ➢ 2-3 months?
  ➢ 12 months?
Case 1: More variations

• Does the length of time the patient was hormone sensitive influence your treatment decision?
  • ~ 3 years in this case

• What if he had hormone sensitive disease for
  ➢ < 1 year?
  ➢ 10 years?
Case 1: Million Dollar Question

If drug access is not an issue, what factors influence your decision to choose either Abiraterone or Enzalutamide?
Case 1: Question

In asymptomatic men, what is your follow-up schedule on Enzalutamide?

A. Every 4 weeks
B. Every 8 weeks
C. Every 12 weeks
D. Other
Case 1: Question

In asymptomatic men, what is your follow-up schedule on Abiraterone?

A. Every 4 weeks
B. Every 8 weeks
C. Every 12 weeks
D. Other
Oral Agents: Abiraterone

• The most common side effects of abiraterone include ↑ cholesterol and lipids, myopathy, arthralgia, ↑ LFTs, edema, hot flashes, diarrhea, ↓ K, urinary tract infection and cough.

• Severe hepatotoxicity has been reported in ± 7% of patients and is more common in patients with abnormal LFTs at baseline. Most cases of hepatotoxicity appear to be reversible after discontinuation of abiraterone. Clinical trials excluded patients with active hepatitis, significantly abnormal LFTs and in some trials, patients with liver metastases.

• Mineralocorticoid effects, which include hypertension, fluid retention and hypokalemia, are commonly reported. Patients on prednisone may require an increased dose of a corticosteroid before, during and after stressful conditions, such as surgery, trauma or severe infections.

• There were slightly more cardiac events (mainly grades 1 or 2) reported in the abiraterone group (11-16%) than in the placebo group (7-14%).
For AST and ALT

- If >5x ULN, interrupt treatment and monitor liver function closely until normalized
- When patient returns to baseline, restart at reduced dose (500 mg OD)
  - If hepatotoxicity recurs at the reduced dose of 500 mg daily, discontinue treatment with ZYTIGA
- If >20 ULN, discontinue treatment and do not restart

For bilirubin, if >3x ULM, interrupt treatment and monitor liver function closely until normalized
## Potential DDI: Abiraterone

<table>
<thead>
<tr>
<th>Substrates</th>
<th>IA2</th>
<th>2B6</th>
<th>2C8</th>
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</table>
Oral Agent: Enzalutamide

• The most common side effects for enzalutamide include fatigue, ↑ LFTs, androgen deprivation symptoms, headache and hypertension.

• Enzalutamide is associated with an increased risk of seizure, especially at doses above 160mg. The lowering of the seizure threshold may be due to enzalutamide and its active metabolite crossing the blood brain barrier and inhibiting GABAgated chloride channel activity.

• Treatment-emergent hypertension should be managed appropriately. Seventy-five percent of patients with hypertension required new or changes in antihypertensives.

• Increases in non-pathological fractures and falls were observed as compared to placebo. No concomitant neurological symptoms or presyncope were reported concurrently with the falls.
Oral Agent: Enzalutamide

**Serious Warnings and Precautions**

Xtandi (enzalutamide capsules) should only be prescribed by a qualified healthcare professional who is experienced with the treatment of prostate cancer and the use of antineoplastic endocrine therapies.

The following are clinically significant adverse events:
- Seizures (see Neurologic section, below),
- Posterior Reversible Encephalopathy Syndrome (see Neurologic section, below).

**Recommended Clinical Monitoring**

- Blood pressure; baseline and regular
- Close INR monitoring for patients on warfarin
- ECG; baseline and regular, in patients at risk of QT prolongation (risk factors for torsades de pointes or on medications known for QT prolongation
- Clinical toxicity assessment for androgen withdrawal effects, fatigue, seizures and other neuropsychiatric effects (cognitive or memory impairment, hallucinations etc), falls, musculoskeletal and fractures, edema, diarrhea; regular

CCO Formulary November 2013; Enzalutamide Product Monograph 2015
**Potential DDI: Enzalutamide**

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<tr>
<th>SUBSTRATES</th>
<th>1A2</th>
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<th>2C9</th>
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## Potential DDI with Other Commonly Used Drugs

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<th>Rank 2010</th>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Abiraterone Interactions</th>
<th>Abiraterone Comments</th>
<th>Enzalutamide Interactions</th>
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<td>Atorvastatin</td>
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Case 1

- Abiraterone plus prednisone is chosen
- Initial PSA response 62 → 3 ug/L over 8 months
- Then PSA slowly increasing over 6 months and now back to 62 ug/L
- Still asymptomatic and bone scan shows 2 new lesions
Case 1: Question

What would you do now?

A. Stay on Enzalutamide
B. Switch to Abiraterone
C. Switch to Docetaxel
D. Switch to Cabazitaxel
E. Switch to Radium 223
Case 1: Question

What factors influence you when you change therapies in this clinical context?
What happens if PSA does not decline?

COU-AA-302 Protocol: Treatment was continued on patients who have increasing PSA values in the absence of radiographic or unequivocal clinical progression. Although serial PSA’s were measured on this study, progression or change in PSA values was not considered a reliable measure of disease progression, and should not be used as an indication to discontinue study therapy.

Tumour responses following a steroid switch from prednisone to dexamethasone in castration-resistant prostate cancer patients progressing on abiraterone

D Lorente¹, A Omlin¹,², R Ferraldeschi¹, C Pezaro¹, R Perez¹, J Mateo¹, A Altavilla¹, Z Zafeirou¹, N Tunariu¹, C Parker³, D Dearnaley³, S Gillessen², J de Bono*¹ and G Attard¹

Figure 1. Waterfall graph representing PSA declines on steroid switch (A) PSA declines at 12 weeks. (B) Maximum PSA declines. Striped bars represent patients with prior single agent dexamethasone; nonstriped bars represent patients with no prior single agent dexamethasone. PSA increases have been capped at +50%.
What is progression?

Three criteria determine progression:
   1. PSA increase
   2. Radiographic progression
   3. Clinical progression

_If you think patient has progressed ..._

- DO NOT stop (oral) therapy immediately
- CONTINUE patient on drug while seeking medical oncology opinion or referring them back to medical oncology
Case 2:
Metastatic Castrate Resistant Prostate Cancer Post-Docetaxel
Case 2: Presentation

72-year-old male

• 2007
  • T3aNxMo Gleason 4, 3 prostate cancer
  • Treated with 3 years of ADT and radiation

• 2010
  • Rising PSA – ADT reinitiated when PSA was 22 ug/L
    • No metastases

• 2013
  • PSA rising again – 129 ug/L; testosterone low
  • Bone scan – 9 lesions
  • ↑ fatigue and aches in pelvis
Case 2: Presentation

• Treatment
  • Docetaxel x 10 cycles
    • Improvement in PSA (2.7 ug/L), bone scan, and pain
    • Remained on Prednisone 5 mg b.i.d.
  • 12 months after stopping Docetaxel
    • ↑ bony pelvic discomfort
    • Bone scan – 5 new lesions
    • PSA – 97 ug/L
Case 2: Question

What second-line therapy would you recommend at this time?

A. Docetaxel Retreatment
B. Abiraterone
C. Enzalutamide
D. Cabazitaxel
E. Radium 223
Case 2: Question

What do you base your treatment decision on at this point?

Are there any patients who you are more likely to recommend

  • Chemotherapy $\rightarrow$ chemotherapy?
  versus
  • Chemotherapy $\rightarrow$ oral hormonal agent?
Monitoring:
Progression in mCRPC is inevitable

• Monitor patients frequently for signs of progression
  • A program of frequent radiologic imaging, PSA tests and clinical exams is recommended by the Prostate Cancer Clinical Trials Working Group 2
    • CT/MRI scans for visceral metastases every 12 weeks
    • PSA tests every 3 or 4 weeks
    • Alkaline phosphatases, lactate dehydrogenase every 3 or 4 weeks
    • Bone scans every 12 weeks
    • Symptoms by cycle (every 3 or 4 weeks)
  
• The National Comprehensive Cancer Network also recommends monitoring patients with bone scans, abdominal or pelvic CT/MRI scans, and PSA tests

• Vigilant monitoring may help to ensure patients receive the appropriate therapy at the appropriate time

Primary resistance to AR-targeted agents

Radiological progression-free survival

Abiraterone\(^1\) (COU-AA-301)

- Primary resistance 1 out of 3 patients

Enzalutamide\(^2\) (AFFIRM)

- Primary resistance 1 out of 4 patients

Duration of Response to ADT and Efficacy of Secondary Hormone Therapy, Docetaxel, and Cabazitaxel in mCRPC

- Retrospective analysis of 132 patients. All received first HT, D and C, and 94 of them received second HT.
- Rapid progression to CRPC (<12 m) is associated with a low response to second-HT.
- PSA response to taxanes does not seem to be affected by time to CRPC.

<table>
<thead>
<tr>
<th>PSA response ≥ 30%</th>
<th>Time to CRPC &lt;12 m (34 pts)</th>
<th>Time to CRPC ≥ 12 m (98 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First HT*</td>
<td>90.1%</td>
<td>91.3%</td>
</tr>
<tr>
<td>Second HT**</td>
<td>25.0%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>59.4%</td>
<td>77.4%</td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>51.6%</td>
<td>55.7%</td>
</tr>
</tbody>
</table>

* Includes orchiectomy, LHRH agonist, LHRH agonist + anti-androgen. ** Before (46.8%) or after (53.2%) docetaxel: includes antiandrogen, diethystilboestrone, estramustine, ketoconazole, abiraterone (after D), enzalutamide (after D).
Cross-resistance between these new therapies?
**Poor response to abiraterone in patients progressing on enzalutamide?**

<table>
<thead>
<tr>
<th></th>
<th>Loriot&lt;sup&gt;1&lt;/sup&gt; (n=38)</th>
<th>Noonan&lt;sup&gt;2&lt;/sup&gt; (n=30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Enzalutamide</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Median PFS (mo)</td>
<td>2.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>7.2</td>
<td>11.8</td>
</tr>
<tr>
<td>↓PSA ≥50%&lt;sup&gt;*&lt;/sup&gt;</td>
<td>8%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Confirmed by a second value

Loriot<sup>1</sup> and Noonan<sup>2</sup> trials are retrospective studies conducted in 38 and 30 patients, respectively

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<sup>1</sup>Loriot Y et al. Ann Oncol 2013; 24: 1907-12
<sup>2</sup>Noonan KI et al. Ann Oncol 2013; 24: 1802-04
Poor response to enzalutamide in patients progressing on abiraterone?

<table>
<thead>
<tr>
<th></th>
<th>Schrader¹ (n=35)</th>
<th>Bianchini² (n=39)</th>
<th>Thomsen³ (n=24)</th>
<th>Badrising⁴ (n=61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior ABI</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Partial response</td>
<td>2.9%</td>
<td>4.3%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Median PFS°</td>
<td>-</td>
<td>2.8</td>
<td>-</td>
<td>3.0</td>
</tr>
<tr>
<td>Median OS°</td>
<td>7.1**</td>
<td>-</td>
<td>4.8</td>
<td>7.9</td>
</tr>
<tr>
<td>↓PSA ≥50%</td>
<td>28.6%</td>
<td>12.8%*</td>
<td>16.7%</td>
<td>21%</td>
</tr>
</tbody>
</table>

° in months; *PSA response confirmed by a second value;

[1-4] trials are retrospective studies

Does abiraterone prior to docetaxel decrease efficacy of taxanes in mCRPC pts?

<table>
<thead>
<tr>
<th></th>
<th>VENICE(^1) DOC/Pbo n=612</th>
<th>De Bono(^2) ABI→DOC n=35</th>
<th>Schweizer(^3)</th>
<th>Azad(^4) ABI→DOC n=40</th>
<th>De Bono(^5) ABI→DOC n=261</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOC therapy line</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PSA decrease ≥50%</td>
<td>63.5%</td>
<td>25.7%</td>
<td>63.0%</td>
<td>38.0%</td>
<td>30.0%*</td>
</tr>
<tr>
<td>Median time to PSA progression</td>
<td>8.1 mths</td>
<td>4.6 mths</td>
<td>6.7 mths</td>
<td>4.1 mths</td>
<td>3.25 mths*</td>
</tr>
<tr>
<td>OS, median</td>
<td>21.2 mths</td>
<td>12.5 mths</td>
<td>-</td>
<td>-</td>
<td>≈12.5 mths*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

[2-4] trials are retrospective studies


ABI: Abiraterone; DOC: Docetaxel; OS: Overall survival ; Pbo: Placebo
Cabazitaxel: PSA response based on prior AA treatment

Best PSA Response (%)

-50% threshold

Prior AA

No prior AA

35.3% 42.9%

Saad et al. ASCO 2014
Second-Line Agents: Cabazitaxel

- The most common side effects for cabazitaxel include myelosuppression, diarrhea, fatigue, nausea, vomiting, constipation, hematuria, musculoskeletal pain, anorexia, peripheral neuropathy and dysgeusia.
- The major dose-limiting adverse effect of cabazitaxel is myelosuppression which may be severe. Febrile neutropenia occurs in up to 8% of patients and may be fatal.
- Severe hypersensitivity reactions characterized by hypotension, bronchospasm or generalized rash/erythema may occur within a few minutes of cabazitaxel infusions. Patients should be observed closely for these reactions, especially during the 1st and 2nd infusions. Because of the significant risk of hypersensitivity reactions, premedications are recommended prior to each treatment; emergency medications and resuscitation equipment must be readily available. Patients who experience severe hypersensitivity reactions should not be rechallenged.
- Common gastrointestinal symptoms associated with cabazitaxel include diarrhea, nausea and/or vomiting. These symptoms may be treated with commonly used antidiarrheal or antiemetic medications and hydration as needed. If left untreated, renal failure may ensue.
- Patients should be monitored closely for cardiovascular effects. Preclinical studies suggest a QTc effect; although no formal QT prolongation study has been conducted, cardiac arrhythmias have been reported in patients treated with cabazitaxel.
Second-Line Agents: Cabazitaxel

Contraindications in pts:
- with neutrophil counts of ≤1.5 x 10^9/L
- in hepatic impairment (bilirubin ≥1 x ULN, or AST/SGOT and/or ALT/SGPT ≥1.5 x ULN)
- concomitant use of yellow fever vaccines or other live vaccines

Precautions in pts:
- at risk of developing GI complications
  - patients with neutropenia, with a prior history of pelvic radiotherapy, GI disease (e.g. ulceration, bleeding), the elderly, concomitant use of NSAIDs, antiplatelet therapy or anticoagulants.

Recommended Clinical Monitoring
- CBC; on a weekly basis during cycle 1, before each treatment cycle and as indicated
- Liver function tests; baseline and regular
- Renal function tests; baseline and regular
- Clinical toxicity assessment for infusion reactions, GI effects, infection, hypersensitivity, bleeding, respiratory effects and peripheral neuropathy; at each visit
Radium-223 Targets Bone Metastases

- Radium-223 acts as a calcium mimic
- Alpha emitter with shorter travel distance than previous agents such as strontium, samarium
- Naturally targets new bone growth in and around bone metastases
- Radium-223 is excreted by the small intestine

<table>
<thead>
<tr>
<th>Periodic Table of the Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrogen</td>
</tr>
<tr>
<td>H</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Al</td>
</tr>
<tr>
<td>13</td>
</tr>
<tr>
<td>K</td>
</tr>
<tr>
<td>19</td>
</tr>
<tr>
<td>Rb</td>
</tr>
<tr>
<td>37</td>
</tr>
<tr>
<td>Cs</td>
</tr>
<tr>
<td>55</td>
</tr>
<tr>
<td>Fr</td>
</tr>
<tr>
<td>87</td>
</tr>
</tbody>
</table>
Patients with symptomatic CRPC and ≥ 2 bone metastases with no known visceral metastases, either post-docetaxel or unfit for docetaxel (N = 921)

- Primary endpoint: OS
- Secondary endpoints: time to first SRE, time to total ALP progression, total ALP response, ALP normalization, time to PSA progression, safety, QoL

Radium-223 (50 kBq/kg) + Best standard of care

Placebo (saline) + Best standard of care

Stratified by total ALP, previous docetaxel, and bisphosphonate use

Randomized 2:1

Up to 6 treatments at 4-wk intervals

**ALSYMPCA: Update of Overall Survival (ASCO 2012)**

HR 0.695; 95% CI: 0.552–0.875  
*p = 0.00185*

Radium-223, n = 541  
Median OS: 14.0 months

Placebo, n = 268  
Median OS: 11.2 months

**Graph Notes:**
- **Radium-223** (n = 541) vs. **Placebo** (n = 268)
- Median OS: 14.0 months for Radium-223 vs. 11.2 months for Placebo
- Hazard Ratio (HR): 0.695, 95% Confidence Interval (CI): 0.552–0.875
- *p* value: 0.00185

**Table:**

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>541</td>
<td>268</td>
</tr>
<tr>
<td>3</td>
<td>450</td>
<td>218</td>
</tr>
<tr>
<td>6</td>
<td>330</td>
<td>147</td>
</tr>
<tr>
<td>9</td>
<td>213</td>
<td>89</td>
</tr>
<tr>
<td>12</td>
<td>120</td>
<td>49</td>
</tr>
<tr>
<td>15</td>
<td>72</td>
<td>28</td>
</tr>
<tr>
<td>18</td>
<td>30</td>
<td>15</td>
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<td>21</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Parker C, et al. *J Clin Oncol* 2012;30(suppl 5;abstr 8)
Median time to first SRE significantly prolonged with radium-223
- Radium-223: 13.5 mos
- Placebo: 8.4 mos

Patients, n (%)
<table>
<thead>
<tr>
<th>First SRE Component</th>
<th>Radium-223 (n = 541)</th>
<th>Placebo (n = 268)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>External beam radiotherapy</td>
<td>122 (23)</td>
<td>72 (27)</td>
<td>.0038</td>
</tr>
<tr>
<td>Spinal cord compression</td>
<td>17 (3)</td>
<td>16 (6)</td>
<td>.016</td>
</tr>
<tr>
<td>Pathologic bone fracture</td>
<td>20 (4)</td>
<td>18 (7)</td>
<td>.013</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>9 (2)</td>
<td>5 (2)</td>
<td>.69</td>
</tr>
</tbody>
</table>

HR: 0.610 (95% CI: 0.461-0.807; \( P = .00046 \))
ALSYMPCA - Summary

• Patients in the trial who received radium-223
  • Had a median overall survival of 14 months, versus 11.2 months for those on placebo
  • Had a median time to first SRE of 13.6 months compared to 8.4 months in the placebo group - an improvement of 64%
  • 33% of radium-223 patients had a total ALP (alkaline phosphatase) normalization, compared to just 1% in the placebo group
  • Had an improvement of 49% in time to PSA progression

• Adverse events
  • 15% experienced non-hematologic adverse events, including bone pain, nausea, diarrhea, constipation and vomiting.
  • Anemia was the most common hematologic event, affecting 18% of patients.
  • Bone pain, the most common Grade 3 to 4 adverse event, was experienced by 18% of patients on radium-223
Radium-223 Before or After Chemotherapy? Practical Considerations

• Only HC/FDA approved for patients WITHOUT visceral metastases
• Stringent eligibility criteria for treatment
  • Initial ANC of 1.5 or higher with subsequent 1.0 or higher
  • Hb 100 or higher
  • Platelets 100,000 or higher
• Targets bone micro-environment and not cancer cells directly and significant PSA decreases uncommon
  • May not be agent of choice if high burden of disease and symptoms not directly related to bone involvement (cachexia, anorexia, nausea, etc)
Case 3: Presentation and History

• 56-year old male with known nodal metastatic prostate cancer managed with CAB
• PSA nadirs at 0.8, now 19.2 with a PSA DT of 4 months
• Asymptomatic, bone scan NED, CT progressive nodal disease
• Abiraterone/prednisone started
• 6 months later, patient presents with a PSA of 0.8, with progressive weight loss and anorexia
• Bone scan NED
• What do you do next?
Case 3: Next steps

1. Change to enzalutamide
2. Continue with abiraterone but change prednisone to dexamethasone
3. Change to docetaxel chemotherapy
4. Restage with a CT scan before deciding on which treatment to recommend
5. Change to enzalutamide but also restage with a CT scan in the next weeks
Case 3: Imaging
Thank You.
Questions?

hotte@hhsc.ca