Advanced/Metastatic Prostate Cancer

Effective Date: July, 2020
Background

Prostate cancer is the most common cancer among Canadian men, and is the 3rd leading cause of cancer related death in men in Canada. In 2017, it is estimated that 21,300 (age-standardized incidence rate of prostate cancer is 115 per 100,000) men will be diagnosed with prostate cancer in Canada, representing 21% of all new cancers in men. Approximately 1 in 7 Canadian men is expected to develop prostate cancer during their lifetime, and 1 in 27 will die from prostate cancer. In Alberta, approximately 2600 new prostate cancer diagnoses were made in 2016.1

The majority of advanced prostate cancers are diagnosed after localized treatment, with disseminated disease being identified by rising PSA post-definitive treatment, however, some men present with metastatic disease.

Guideline Questions

1. How should advanced/ metastatic prostate cancer be staged?
2. How should advanced/ metastatic prostate cancer be treated?
3. How should advanced/ metastatic prostate cancer patients be followed after treatment?

Search Strategy

For the 2020 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in Appendix A).

For the 2016 guideline, select literature was reviewed by a working group at the Alberta GU Tumour Team meeting. No formal systematic literature review was performed.

For the 2015 update, no formal literature review was conducted.

For the 2014 update of this guideline, the Pubmed database was searched using the search terms Locally Advanced Prostate Cancer and Metastatic Prostate Cancer from 2010 to 2014. Only phase III trials were evaluated for inclusion.

For the 2012 update of this guideline, Ovid Medline was searched using the term Prostatic neoplasms (MeSH term, subheadings drug therapy, surgery, therapy and radiotherapy), limited to clinical trials involving humans published in English, between August 2011 and August 2012. Articles were excluded if they were not phase II-IV trials, did not include survival or recurrence outcomes, was retrospective. Cochrane Database of Systematic Reviews was searched using the term “prostate cancer”, published 2011-2012.

Medline & Embase were further searched using the term prostate cancer (keyword), limited to clinical trials related to “therapy (best balance of sensitivity and specificity) involving male humans published in English between August 2011-2012.
Ovid MEDLINE and EMBASE (1965 to August 2011) and clinical practice guideline databases, including the Cochrane Library and the National Guidelines Clearinghouse, were searched in order to obtain evidence relevant to this topic.

**Target Population**

Adult patients (18 years of age or older) who have been diagnosed or have suspected advanced/metastatic prostate cancer.

**Recommendations**

**Bone Health**

Please see the bone health guideline (available soon):
(http://www.albertahealthservices.ca/info/cancerguidelines.aspx)

**Locally Advanced Disease (Stage T1-4, N1, M0)**

Patients with nodal involvement (with or without previous local definitive therapy).

**Staging**

At minimum patients should have CT abdomen and pelvis, bone scan, and optional chest imaging (chest CT or CXR).

**Management**

1. These patients are unique and management can vary widely; patients should be discussed at multidisciplinary rounds.

2. Radiotherapy is an option for low-volume pelvic lymph node only disease in addition to ADT. ADT should be administered for 18-36 months.²

**Biochemical Recurrence³**

**Following prostatectomy**

- Any rise in PSA.

**Following radiotherapy with or without hormonal therapy**

- Rise by 2 ng/mL (mcg/L) or more above the nadir PSA (defined as the lowest PSA achieved).
- Date of failure should be determined “at call” and not backdated.
- Patients not meeting these PSA criteria for failure who undergo salvage therapies should also be declared as failures at the time a positive biopsy is obtained or salvage therapy is administered.
Patients with Rising PSA after Curative Intent Treatment without Metastases

It is recommended that patients be referred to a cancer clinic or re-referred to their treating urologist. Please refer to definition of biochemical recurrence above.

Staging

- Bone scan
- CT scan
- MRI
- Consideration for prostate re-biopsy

Post-radical prostatectomy local recurrence

Recommended options include:

- Radiotherapy, with or without ADT
- ADT alone
- Observation, with the option of delayed ADT

Post-radiotherapy local recurrence

Recommended options include:

- Cryosurgery, with or without ADT
- Brachytherapy, with or without ADT
- ADT alone
- Observation, with the option of delayed ADT

Castrate Sensitive Metastatic Disease (Stage T1-4, N0-1, M+)

Indications include symptomatic disease or asymptomatic disease.

Staging

- Physical Exam.
- PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN) within the last 1 month.
- Bone scan (within the last 3 months).
- CT scan, (abdomen and pelvis, +/- chest) (within the last 3 months).
Management

1. Androgen Deprivation Therapy is the backbone of therapy. Medical and surgical castration are equivalent in terms of efficacy and both are viable options. Lower rates of fracture, peripheral arterial disease, and cardiac-related complications have been reported in surgical castration patients when compared to medical castration patients in a large retrospective cohort study.4

A. Castrate level serum testosterone can cause a number of undesirable side effects. For this reason intermittent ADT has theoretical advantages, however, in patients with metastatic prostate cancer continuous ADT is recommended unless survival is considered secondary to quality of life. The phase III intergroup trial reported that intermittent ADT cannot be considered non-inferior compared to continuous ADT in terms of overall survival.5,6

B. Medical castration

   i. Treatment with an LHRH analogue (agonist ex: Leuprolide or antagonist ex: Degarelix)

   a. When first introduced, a non-steroidal antiandrogen (e.g. bicalutamide 50 mg daily, flutamide 250 mg three times a day or nilutamide 300mg daily) should be given concurrently with the first administration of LHRH for 2 weeks to 1 month in order to block the potential initial testosterone flare.

   b. The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward.

   c. Medical and surgical castration is equally effective and the risks, benefits, and economic implications should be discussed with the patient.

   ii. Treatment with gonadotropin-releasing hormone (GnRH)

   a. The GnRH antagonist Degarelix is as effective at suppressing testosterone and may achieve testosterone suppression faster7 than GnRH Agonists. Treatment with a GnRH antagonist (Degarelix) avoids the risk of testosterone ‘flare” that occurs with GnRH agonists.7,8 Treatment with a GnRH antagonist eliminates the need for concomitant administration of a non-steroidal anti androgen.

   b. PSA reduction occurred significantly faster with Degarelix when compared to GnRH agonists without increases in treatment related side effects.7

   c. No survival benefit has been demonstrated with Degarelix compared to raditional LHRH agonists and injections are administered monthly.

   d. Degarelix is not presently funded in Alberta.

C. Single agent antiandrogens

   i. Monotherapy with non-steroidal AA is inferior to medical castration with LHRH or GnRH
agents. However, it may be considered for rare circumstances. To date there is insufficient data to recommend bicalutamide at 150 mg/day (not Health Canada approved). Options include:

ii. Biclutamide 50 mg orally once a day.

iii. Flutamide 250 mg orally three times daily.

iv. Nilutamide 300 mg orally once a day for one month, then decrease to 150 mg daily.

D. Patients undergoing androgen deprivation therapy for prostate cancer have an improved quality of life if they continue to be physically active. Patients should be counseled on the role of maintaining physical fitness and activity while on hormonal therapy.9

NOTE: Ongoing total androgen blockade (e.g. castration with LHRH agonist/antagonist plus a nonsteroidal antiandrogen) is not recommended.

2. Systemic Therapy

A. All patients presenting with metastatic castrate sensitive prostate cancer who are starting ADT should be considered for intensification of systemic therapy beyond ADT.

B. Chemotherapy (Docetaxel)

i. Data from the CHAARTED trial10 demonstrated significant overall survival benefit of 13 months when docetaxel was administered to patients with castrate sensitive metastatic prostate cancer who are about to start or just have recently (within 4 months) started hormonal therapy. The greatest benefit was seen in patients with high volume disease (defined as the presence of visceral metastases or ≥4 bony lesions with 1 beyond the vertebral bodies and pelvis),

ii. Data from the STAMPEDE trial11 demonstrated a significant overall survival benefit of 14 months in all patients (low and high volume) with metastatic CSPC.

iii. Patients receiving chemotherapy for this indication should be offered 6 cycles of docetaxel chemotherapy at 75 mg/m² every 3 weeks (given with or without prednisone). Androgen deprivation therapy as above is continued throughout and after docetaxel completion.

C. Abiraterone Acetate (Currently not publicly funded in Alberta as of Nov. 2019)

i. The phase 3 LATITUDE trial demonstrated that ADT plus 1000mg abiraterone acetate (plus 5 mg prednisone) daily resulted in superior median overall survival (not reached vs. 34.7m; HR 0.62, 95%CI 0.51-0.76, p<0.001) and improved pain progression, time to subsequent therapy for prostate cancer, time to initiation of chemotherapy, and PSA progression (all p<0.001) versus ADT plus placebo in newly diagnosed, metastatic,
castration-sensitive prostate cancer patients. Rates of grade 3 hypertension and hypokalemia were higher in the abiraterone group compared to placebo.\textsuperscript{12}

ii. The phase 3 STAMPEDE trial randomized patients with metastatic disease (52%), node-positive or node-indeterminate M0 disease (20%) or node-negative M0 disease (28%) of which 95% were newly diagnosed, to received ADT alone or in combination with abiraterone acetate (1000 mg daily with 5mg daily prednisolone). The ADT plus abiraterone group showed superior survival (HR: 0.63, 95\%CI: 0.52-0.76, p<0.001). HR was 0.75 in patients with M0 disease vs 0.61 in patients with M1 disease. Grade 3 to 5 adverse events were higher in the combination group (47\% vs. 33\%).\textsuperscript{13}

D. There is insufficient evidence to recommend one strategy over another (Docetaxel vs Abiraterone). Clinical decision making should be based on patient factors and access.

3. Consideration of clinical trials is recommended

Follow-up

Frequency:
- If on chemotherapy or abiraterone acetate, patients should be evaluated as per standard protocol.
- If on ADT alone: q3–6 months following the initiation of therapy to evaluate and then as clinically indicated
- Duration: age-dependent.

\textbf{Castrate Resistant Metastatic Disease (Stage M0, M+)}

Castrate resistant disease is defined as either clinical, biochemical, or radiographic disease progression in the presence of castrate level (<1.7nmol/L) testosterone levels.

\textbf{Staging}
- Bone scan
- CT scan of chest, abdomen, and pelvis
- Serum PSA, serum testosterone (to ensure that testosterone is in the castrate range)
- Other imaging may be required as clinically indicated

\textbf{Management of M0 Disease}

1. Monitoring
   - \textbf{A.} PSA should be monitored q3-6monthly
   - \textbf{B.} Systemic therapy may be considered in patients with a doubling time \leq 10 months and no measurable disease on conventional imaging (bone scan and CT CAP)
2. Systemic therapy

A. APALUTAMIDE

i. A PSA doubling time calculator should be used (e.g. MSKCC link).

ii. In the SPARTAN phase III clinical trial\textsuperscript{14}, apalutamide compared to placebo, in men with PSA doubling times ≤10 months, demonstrated an improvement in metastasis-free survival from 16.2 m to 40.5 m (p< 0.001). Overall survival data is immature. Apalutamide could be considered in patients meeting the doubling time criteria with no metastases (LN less than 2cm SA were allowed on the trial).

iii. Apalutamide is currently Health Canada approved, but not publicly funded in Alberta.

B. ENZALUTAMIDE

i. In the PROSPER phase III clinical trial\textsuperscript{15}, enzalutamide compared to placebo in men with PSA doubling times ≤10 months, demonstrated an improvement in metastasis-free survival from 14.7 m to 36.6 m (p<0.001). Overall survival data is immature.

ii. Currently Health Canada approved, but not publicly funded in Alberta.

Management of M+ Disease

1. All patients with mCRPC should be considered for novel anti-androgen therapy (abiraterone, enzalutamide) or clinical trial options PRIOR to initiation of previously used agents (such as NSAA's).

2. Systemic Therapy

Clinical trials should be given first consideration where appropriate. Currently, there is no data to support one of these agents/sequences over the other.

A. 1\textsuperscript{st} line options:

i. Abiraterone acetate 1g oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.\textsuperscript{16,17}

ii. Docetaxel 75mg/m\textsuperscript{2} IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.\textsuperscript{54}

iii. Enzalutamide 160mg oral daily can be used prior to docetaxel (PREVAIL).\textsuperscript{18}

B. 2\textsuperscript{nd} line options:

i. Post progression on docetaxel chemotherapy:

a. Abiraterone acetate\textsuperscript{19} or enzalutamide \textsuperscript{20}

b. Cabazitaxel IV every 3 weeks in combination with prednisone 10 mg oral daily.\textsuperscript{56}

• 20 mg or 25 mg can be considered, as the PROSELICA trial\textsuperscript{21} demonstrated that 20 mg dose was non-inferior to the 25 mg dose and was associated with decreased toxicity.
c. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA). Ra 223 is administered upon referral to nuclear medicine and given at a dose of 50 kBq (1.35 microcurie) per kg body weight at 4 week intervals for a total of 6 injections. Radium 223 is not funded or available in Alberta.

ii. Post progression on Abiraterone or Enzalutamide
   a. Docetaxel chemotherapy

C. Subsequent lines:
   i. Sequencing with another agent listed above not previously used.
   ii. Optimal sequencing of these agents is unknown.
      a. If a patient has already received docetaxel and one ARAT, the CARD trial would suggest that cabazitaxel would be the preferred subsequent agent provided the patient is medically fit for therapy.
      iii. Docetaxel re-challenge or Mitoxantrone 12mg/m² every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.

D. Bone targeted therapy: treatment with bisphosphonates bone targeted agents should be considered for some patients with metastatic castrate resistant prostate cancer. See the bone health guideline (available: https://www.albertahealthservices.ca/info/cancerguidelines.aspx).

3. Palliative Radiotherapy

For a complete list of recommendations, see the Alberta Palliative Radiotherapy guidelines located (http://www.albertahealthservices.ca/info/cancerguidelines.aspx in the Radiotherapy Special Topics section).

Management of Oligometastatic Disease

1. Radiotherapy to the prostate
   A. The STAMPEDE trial failed to demonstrate improvement in overall survival after radiotherapy in newly diagnosed metastatic prostate cancer.
      i. However, pre-specified subgroup analysis of patients with low metastatic burden (by CHAARTED clinical trial criteria) demonstrated an improvement in overall survival with radiotherapy to the prostate compared to standard of care (81% vs. 73% OS at 3 years; HR:0.68, 95%CI: 0.52-0.90).
      ii. Discussion in multidisciplinary tumour group meetings is advised if radiotherapy is being considered.

Follow-up

- Patients on docetaxel, abiraterone, enzalutamide, or cabazitaxel should be monitored as per standard protocols. At a minimum, PSA response should be evaluated 12 weeks after starting treatment.
• Once therapy with one of these agents has been discontinued, patients should be assessed for further therapy.
• Repeat staging investigations are recommended at the time of progression.
• Duration: as clinically indicated
References


### Table 1. Systemic Therapy Trials for the Treatment of Metastatic Castration Sensitive Prostate Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name</th>
<th>Indication</th>
<th>Arms of Study</th>
<th>PFS</th>
<th>p-value</th>
<th>Median OS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADT (Intermittent versus continuous)⁵</td>
<td>INT 0162 (NCT00002651)</td>
<td>Newly diagnosed mCSPC</td>
<td>(n=765) continuous ADT Vs. (n=770) intermittent ADT</td>
<td>N/A</td>
<td>N/A</td>
<td>5.8 years (Continuous) vs. 5.1 years (intermittent)</td>
<td>HR for intermittent 1.10 (90%CI 0.99-1.20)</td>
</tr>
<tr>
<td>Abiraterone¹²</td>
<td>LATITUDE (NCT01715285)</td>
<td>Newly diagnosed mCSPC</td>
<td>ADT + placebo Vs. ADT + Abiraterone</td>
<td>ADT+ placebo: 14.8m ADT+ Abiraterone: 33.0 months</td>
<td>ADT+ placebo: 34.7 months ADT+ Abiraterone: not reached</td>
<td>HR: 0.47, 95%CI: 0.39-0.55, p&lt;0.001</td>
<td>HR:0.62, 95%CI: 0.51-0.76, P&lt;0.001</td>
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<tr>
<td>Abiraterone¹³</td>
<td>STAMPEDE (NCT00268476)</td>
<td>mCSPC (52%), N1/Nx M0 (20%), N0M0 (28%)</td>
<td>ADT + placebo Vs. ADT + Abiraterone</td>
<td>(3-year) ADT+ placebo: 45% ADT+Abiraterone: 75%</td>
<td>(3-year) ADT+ placebo: 76% ADT+ Abiraterone: 83%</td>
<td>HR: 0.29, 95%CI: 0.25-0.34, p=0.001</td>
<td>HR: 0.63, 95%CI: 0.52-0.76, p&lt;0.001, HR for M0: 0.75 HR for M1: 0.81</td>
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<tr>
<td>Docetaxel/ Zoledronic acid¹¹</td>
<td>STAMPEDE (NCT00268476)</td>
<td>high-risk, locally advanced, metastatic or recurrent PC, starting long-term hormone therapy</td>
<td>(2:1:1:1 randomization, N=2962) Standard of care (SOC) Vs. (1)SOC + zoledronic acid (ZA) Vs. (1)SOC + docetaxel (Doc) Vs. (1)SOC+ ZA + Doc</td>
<td>SOC: 20m SOC+ZA: 22m SOC+Doc: 37m SOC+ZA+Doc: 36m</td>
<td>SOC+ZA: HR: 0.92, p=0.198 SOC+Doc: HR: 0.61, p&lt;0.001 SOC+ZA+Doc: HR: 0.62, p&lt;0.001</td>
<td>SOC: 71m (5y: 55%) SOC+ZA: not reached (5y:57%) SOC+Doc: 81m (5y: 63%) SOC+ZA+Doc: 76m (5y: 60%)</td>
<td>SOC+ZA: HR: 0.94, p=0.450 SOC+Doc: HR:0.78, p=0.006 SOC+ZA+Doc: HR:0.82, p=0.022</td>
</tr>
<tr>
<td>Docetaxel¹⁰</td>
<td>CHAARTED (NCT00309985)</td>
<td>mCSPC with bone metastases</td>
<td>ADT + placebo Vs. ADT + Docetaxel (Doc)</td>
<td>(Median time to CRPC) ADT+ Placebo: 11.7m ADT+ Doc: 20.2m</td>
<td>ADT+ Placebo: 44.0m ADT+ Doc: 57.6m</td>
<td>HR: 0.61, 95%CI: 0.51-0.72, P&lt;0.001</td>
<td>HR: 0.61, 95%CI: 0.47-0.80, P&lt;0.001</td>
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<tr>
<td>Docetaxel²⁶</td>
<td>GETUG-AFU 15 (NCT00104715)</td>
<td>mCSPC</td>
<td>ADT + placebo Vs. ADT + Docetaxel (Doc)</td>
<td>(bRFS) ADT+ Placebo: 12.9m ADT+ Doc: 22.9m</td>
<td>ADT+ Placebo: 54.2m ADT+ Doc: 58.9m</td>
<td>HR: 0.72m, 95%CI: 0.57-0.91, p=0.005</td>
<td>HR: 1.01, 95%CI: 0.75-1.36, p=0.955</td>
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</table>
## Table 2. Systemic Therapy Trials for the Treatment of Metastatic Castration Resistant Prostate Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial Name</th>
<th>Indication</th>
<th>Arms of Study</th>
<th>PFS</th>
<th>p-value</th>
<th>Median OS</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Abiraterone&lt;sup&gt;19,27&lt;/sup&gt;</td>
<td>COU-AA-301 (NCT00638690)</td>
<td>Post Docetaxel</td>
<td>5 mg of prednisone twice daily with 1000mg (4x 250mg) of abiraterone acetate (797 patients) or placebo (4x 250mg) daily</td>
<td>Abiraterone group: 5.6mo Placebo: 3.6mo</td>
<td>p &lt; 0.001</td>
<td>Abiraterone group: 14.8mo Placebo: 10.9mo</td>
<td>p &lt; 0.001</td>
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<td>p&lt;0.0001, HR: 0.52, 95%CI: 0.45-0.61</td>
<td></td>
<td>Abiraterone group: 36.3mo Placebo: 30.1mo</td>
<td>p &lt; 0.0037</td>
</tr>
<tr>
<td>Abiraterone&lt;sup&gt;16,17&lt;/sup&gt;</td>
<td>COU-AA-302 (NCT00887198)</td>
<td>Pre Docetaxel</td>
<td>Abiraterone acetate 1000mg (4 x 250mg) plus prednisone (5mg twice daily) (544 patients) vs placebo plus prednisone (544 patients)</td>
<td>Radiographic PFS Abiraterone group: 16.5mo vs placebo: 8.2mo median follow-up 22.2mo</td>
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<td></td>
<td>p&lt;0.001, HR: 0.19, 95%CI: 0.15-0.23</td>
<td></td>
<td>OS was 72% in the enzalutamide group vs 63% (532 patients) in the placebo group</td>
<td>p &lt; 0.001</td>
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<tr>
<td>Enzalutamide&lt;sup&gt;18&lt;/sup&gt;</td>
<td>PREVAIL (NCT01212991)</td>
<td>Pre Docetaxel</td>
<td>872 in the enzalutamide group, 845 in the placebo group</td>
<td>Radiographic PFS Enzalutamide group: 8.3mo Placebo: 2.9mo</td>
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<td>p&lt;0.001, HR: 0.40</td>
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<td>Enzalutamide group: 18.4mo Placebo: 13.6mo</td>
<td>p = 0.0151</td>
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<tr>
<td>Enzalutamide&lt;sup&gt;20,28&lt;/sup&gt;</td>
<td>AFFIRM (NCT00974311)</td>
<td>Post Docetaxel</td>
<td>Enzalutamide 160mg once daily (four capsules) (800 patients) vs placebo (399 patients).</td>
<td>Radiographic PFS Enzalutamide group: 8.3mo Placebo: 2.9mo</td>
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<td>p&lt;0.001, HR: 0.79, 95%CI: 0.60-0.84</td>
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<tr>
<td>Docetaxel&lt;sup&gt;29-32&lt;/sup&gt;</td>
<td>TAX 327</td>
<td>Metastatic CRPC</td>
<td>Docetaxel 75 mg/m&lt;sup&gt;2&lt;/sup&gt; q3 weekly + prednisone 5 mg bid vs Mitoxantrone 12 mg/m&lt;sup&gt;2&lt;/sup&gt; + prednisone 5 mg bid (3rd arm of weekly docetaxel demonstrated no benefit)</td>
<td>N/A</td>
<td>N/A</td>
<td>Docetaxel 18.9 vs Mitoxantrone 16.5 months</td>
<td>p &lt; 0.009</td>
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<td>p&lt;0.0001, HR: 0.76, 95%CI: 0.62-0.94</td>
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<tr>
<td>Cabazitaxel&lt;sup&gt;33,34&lt;/sup&gt;</td>
<td>TROPIC (NCT00417079)</td>
<td>Post Docetaxel</td>
<td>10mg oral prednisone daily and 12mg/m&lt;sup&gt;2&lt;/sup&gt; mitoxantrone intravenously over 15-30min (377 patients) or 25 mg/m&lt;sup&gt;2&lt;/sup&gt; cabazitaxel intravenously over 1h (379 patients) every 3 weeks</td>
<td>cabazitaxel group:2.8mo mitoxantrone group:1.4mo</td>
<td></td>
<td>Cabazitaxel group: 15.1mo Mitoxantrone 12.7mo</td>
<td>p &lt; 0.001</td>
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<td></td>
<td>p&lt;0.001, HR: 0.63, 95%CI: 0.53-0.75</td>
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<tr>
<td>Sipuleucel-T (Not Health Canada Approved)&lt;sup&gt;16&lt;/sup&gt;</td>
<td>IMPACT (NCT000065442)</td>
<td>Asymptomatic or minimally symptomatic CRPC</td>
<td>Sipuleucel-T (341 patients) vs placebo (171 patients).</td>
<td>Similar</td>
<td>p&lt;0.40, HR: 0.92, 95%CI: 0.75-1.12</td>
<td>Sipuleucel-T group: 25.8mo Placebo: 21.7mo</td>
<td>p &lt; 0.03</td>
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<td>Radium-233 (Xofigo)&lt;sup&gt;22,23&lt;/sup&gt;</td>
<td>ALSYMPCA (NCT00699751)</td>
<td>Post docetaxel or non-docetaxel candidates</td>
<td>Radium-233- six injections (1 every 4 weeks), 50kBq/kg of body weight, intravenously vs matching placebo</td>
<td>Time to First Symptomatic Skeletal Event (median): Radium-233: 15.6mo Placebo: 9.8mo</td>
<td>p&lt;0.001, HR: 0.66, 95%CI: 0.52-0.83</td>
<td>Radium-233: 14.9mo Placebo: 11.3mo</td>
<td>p &lt; 0.03</td>
</tr>
</tbody>
</table>

Last revision: June 2018
Development and Revision History
This guideline was reviewed and endorsed by the Alberta GU Tumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2019.

Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity</td>
</tr>
<tr>
<td>II</td>
<td>Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
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<tr>
<td>III</td>
<td>Prospective cohort studies</td>
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<tr>
<td>IV</td>
<td>Retrospective cohort studies or case-control studies</td>
</tr>
<tr>
<td>V</td>
<td>Studies without control group, case reports, expert opinion</td>
</tr>
</tbody>
</table>

Strength of Recommendations

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit; strongly recommended</td>
</tr>
<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended</td>
</tr>
<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome; generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome; never recommended</td>
</tr>
</tbody>
</table>

Maintenance
A formal review of the guideline will be conducted in 2021. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations
ADT Androgen deprivation therapy, ALT Alanine transamine, AST Aspartate transaminase, BUN Blood urea nitrogen, EBRT External beam radiotherapy, GnRH Gonadotropin-releasing hormone agonist, LHRH Luteinizing hormone-releasing hormone, PSA Prostate-specific antigen

Disclaimer
The recommendations contained in this guideline are a consensus of the Alberta Provincial GU Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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