

Advanced/Metastatic Prostate Cancer

Effective Date: November, 2021



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 2020, it is estimated that 23,300 men will be diagnosed with prostate cancer in Canada and 4200 men will die from their disease.¹

Many patients with advanced prostate cancers are diagnosed after localized treatment, with disseminated disease being identified by rising PSA post-definitive treatment. However, some men present with de novo 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 2021 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).

1. Staging

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

2. Management

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

3. Biochemical Recurrence³

See the Local Prostate guideline [[link](#)].

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

Indications include symptomatic disease or asymptomatic disease.

1. Staging

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

2. Management

Androgen Deprivation Therapy to achieve a castrate level serum testosterone (<1.7 nmol/L) 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 (<1.7 nmol/L) 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 agonist/GnRH antagonist.

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 leuprolide, goserelin, or buserelin 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.

d. Patients who are intolerant to Leuprolide or unable to achieve castrate testosterone should have a trial of Buserelin.

e. 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} A non steroidal antiandrogen is not required to be given concurrently with the first dose of GnRH antagonist.

f. Patients who meet the following criteria are eligible for Degarelix upfront: previous stroke, myocardial infarction, angina, TIA, abdominal aortic disease, previous coronary revascularization, or peripheral arterial disease.

g. if a patient is intolerant to Leuprolide and Buserelin then Degarelix can be tried.

h. Local Drug Access Coordinators or Nurse Navigators can assist with obtaining access to injection clinics for Degarelix.

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. Bicalutamide 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

F. Ongoing total androgen blockade (e.g. castration with LHRH agonist/antagonist plus a nonsteroidal antiandrogen) is not recommended for patients in this setting.

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. An androgen receptor axis targeted therapy (ie: ARAT - e.g. apalutamide, enzalutamide, abiraterone acetate) is typically used in this setting, with consideration of docetaxel in certain circumstances (see below).

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 a starting dose of 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. Patients must meet LATITUDE trial criteria to qualify for this treatment. Currently, this is not available through Cancer Care Alberta or a special access program. Criteria are as listed here.

i. The LATITUDE Inclusion criteria¹²:

a. Adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology.

b. Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI.

c. At least 2 of the following high-risk prognostic factors: Gleason score ≥ 8 ; presence of 3 or more lesions on bone scan; presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI.

D. Docetaxel plus abiraterone acetate with prednisone 5 mg twice a day may be considered for patients with de novo high volume metastatic disease (defined as the presence of visceral

metastases or ≥ 4 bony lesions with 1 beyond the vertebral bodies and pelvis), as per the PEACE-1 trial.¹³

E. Enzalutamide (Not publicly funded, special access program required).^{14, 15}

F. Apalutamide (All risks/volumes. Not publicly funded, special access program required).¹⁶

G. There is insufficient evidence to recommend one single agent ARAT strategy over another. Clinical decision making should be based on patient factors and access.

H. For selected men, chemotherapy plus ARAT (either concurrent if Abiraterone or sequential if Enzalutamide/Apalutamide) can be considered. It is highly advised to discuss these cases at tumour board. This strategy is not publicly funded at the time of guideline publication.

3. Radiation Therapy

Referral to RO for consideration of radiation therapy to the prostate for patients with de novo low volume metastatic disease (see Management of Oligometastatic Disease below), as per STAMPEDE.¹⁷

4. Follow-up

Frequency:

A. If on either docetaxel chemotherapy or ARAT (eg: abiraterone acetate, enzalutamide, apalutamide), patients should be evaluated as per standard protocol.

B. If on ADT alone: q3–6 months following the initiation of therapy to evaluate and then as clinically indicated.

C. Patients should be treated until development of castrate resistant disease

i. Castrate resistance defined as either clinical, biochemical, or radiographic disease progression in the presence of castrate level ($<1.7\text{nmol/L}$) testosterone levels.

Non-Metastatic Castration Resistant Disease (Stage M0, M+)

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

1. Staging

A. Bone scan.

B. CT scan of chest, abdomen, and pelvis.

C. Serum PSA, serum testosterone (to ensure that testosterone is in the castrate range).

D. Other imaging may be required as clinically indicated.

Management of M0 CRPC Disease

2. Monitoring

A. Baseline ECG recommended. PSA, testosterone, and TSH should be monitored q3-

6monthly.

B. Systemic therapy may be considered in patients with high-risk disease, where a PSA doubling time is ≤ 10 months and no measurable disease on conventional imaging (bone scan and CT chest, abdomen, and pelvis). A PSA doubling time calculator is recommended in calculation (e.g. MSKCC [link](#)).

3. Systemic therapy

A. APALUTAMIDE

i. In the SPARTAN phase III clinical trial¹⁸, 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 ($p < 0.001$). After a median 52 m follow-up, median OS was 73.9 m in the apalutamide group versus 59.9 m in the placebo group (HR: 0.78; 95%CI: 0.64-0.96; $p=0.016$).¹⁹

ii. Apalutamide can be considered in patients meeting the doubling time criteria with no bone metastases but with lymph node less than 2 cm in the short axis.

B. ENZALUTAMIDE

i. In the PROSPER phase III clinical trial²⁰, 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 ($p < 0.001$). After a median 48 m follow-up, median OS was 67.0 m in the enzalutamide group vs 56.3 m in the placebo group (HR: 0.73; 95%CI: 0.61-0.89; $p=0.001$).²¹

C. DAROLUTAMIDE.¹⁶

i. ARAMIS criteria: ≥ 18 years of age, baseline PSA ≥ 2 ng/mL, nonmetastatic, castration-resistant prostate cancer and a PSA doubling time of 10 months or less. After a median 29.0 m follow-up, OS at 3 years was 83% in the darolutamide group versus 77% in the placebo group (HR: 0.69; 95%CI: 0.53-0.88; $p=0.003$).²²

Management of M+ Castrate Resistant Prostate Cancer (mCRPC)

1. All patients with mCRPC should be considered for novel anti-androgen therapy (abiraterone/prednisone or 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. Following an ARAT (eg: , ARAT in the mCSPC setting) subsequent ARAT is discouraged, and taxane based chemotherapy should be strongly considered. Genetic testing for BRCA1/2 or ATM alterations following AR targeted therapy may also be considered, although testing is not yet standard of care and only available via patient pay programs. Genetic testing may have prognostic, therapeutic and familial screening implications, and special access to Poly ADP ribose Polymerase (PARP) inhibitor after treatment with an ARAT at any

point of advanced prostate cancer management may be obtained if BRCA1/2 or ATM gene alteration is identified. Discussion at multi-disciplinary rounds is encouraged.

A. 1st line options:

- i. Abiraterone acetate 1000 mg oral daily in combination with prednisone 5 mg oral twice daily (COUGAR 302) can be used prior to docetaxel.^{23, 24}
- ii. Docetaxel 75mg/m² IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.
- iii. Enzalutamide 160mg oral daily can be used prior to docetaxel (PREVAIL).²⁵

B. 2nd line options:

- i. Post progression on docetaxel chemotherapy:
 - a. Abiraterone acetate²⁶ or enzalutamide.²⁷
 - b. Cabazitaxel IV every 3 weeks in combination with prednisone 10 mg oral daily.
 - 20 mg or 25 mg can be considered, as the PROSELICA trial.²⁸ demonstrated that 20 mg dose was non-inferior to the 25 mg dose and was associated with decreased toxicity.
 - c. Radium 223 is not funded or available in Alberta. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).^{29, 30} 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.
- ii. Post progression on Abiraterone, apalutamide, darolutamide or Enzalutamide.
 - a. Docetaxel chemotherapy.
 - b. Olaparib - for patients with BRCA1/2 or ATM alterations. (Not publicly funded, special access program required).³¹

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.³²
- iii. Docetaxel re-challenge 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 trial¹⁷ 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.
- B. SBRT is an investigational option and may be considered for some patients.
- C. PSMA PET/CT is an investigational option and is not currently standard of care.

2. Follow-up

- A. Patients on docetaxel, abiraterone, enzalutamide, apalutamide, darolutamide, or cabazitaxel should be monitored as per standard protocols. At a minimum, PSA response should be evaluated 12 weeks after starting treatment.
- B. Once therapy with one of these agents has been discontinued, patients should be assessed for further therapy.
- C. Repeat staging investigations are recommended at the time of progression on any therapy. During the course of chemotherapy, restaging should be considered approximately every 3 months, or as clinically indicated.

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Appendix A: Clinical Trial Summaries

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

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
ADT (Intermittent versus continuous) ⁵	INT 0162 (NCT00002651)	Newly diagnosed mCSPC	(n=765) continuous ADT Vs. (n=770) intermittent ADT	N/A	N/A	5.8 years (Continuous) vs. 5.1 years (intermittent)	HR for intermittent 1.10 (90%CI 0.99-1.20)
Abiraterone ¹²	LATITUDE (NCT01715285)	Newly diagnosed mCSPC	(N=1199) ADT + placebo Vs. ADT + Abiraterone	ADT+ placebo: 14.8m ADT+ Abiraterone: 33.0 months	HR: 0.47, 95%CI: 0.39-0.55, p<0.001	ADT+ placebo: 34.7 months ADT+ Abiraterone: not reached	HR:0.62, 95%CI 0.51-0.76, P<0.001
Abiraterone ³³	STAMPEDE (NCT00268476)	mCSPC (52%), N1/Nx M0 (20%), N0M0 (28%)	(N=1917) ADT + placebo Vs. ADT + Abiraterone	(3-year) ADT+placebo: 45% ADT+Abiraterone: 75%	HR: 0.29, 95%CI: 0.25-0.34, p<0.001	(3-year) ADT+ placebo: 76% ADT+ Abiraterone: 83%	HR: 0.63, 95%CI: 0.52-0.76, p<0.001, HR for M0: 0.75 HR for M1: 0.61
Docetaxel/ Zoledronic acid ¹¹	STAMPEDE (NCT00268476)	high-risk, locally advanced, metastatic or recurrent PC, starting long-term hormone therapy	(2:1:1:1 randomization, N=2962) (2)Standard of care (SOC) Vs. (1)SOC + zoledronic acid (ZA) Vs. (1)SOC + docetaxel (Doc) Vs. (1)SOC+ ZA + Doc	SOC: 20m SOC+ZA: 22m SOC+Doc: 37m SOC+ZA+Doc: 36m	SOC+ZA: HR: 0.92, p=0.198 SOC+Doc: HR: 0.61, p<0.001 SOC+ZA+ Doc: HR:0.62, p<0.001	SOC: 71m (5y: 55%) SOC+ZA: not reached (5y:57%) SOC+Doc: 81m (5y: 63%) SOC+ZA+Doc: 76m (5y: 60%)	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
Docetaxel ¹⁰	CHAARTED (NCT00309985)	mCSPC with bone metastases	(N=790) ADT + placebo Vs. ADT + Docetaxel (Doc)	(Median time to CRPC) ADT+ Placebo: 11.7m ADT+ Doc: 20.2m	HR: 0.61, 95%CI: 0.51-0.72, P<0.001	ADT+ Placebo: 44.0m ADT+ Doc: 57.6m	HR: 0.61, 95%CI: 0.47-0.80, P<0.001
Docetaxel ³⁴	GETUG-AFU 15 (NCT00104715)	mCSPC	(N=385) ADT + placebo Vs. ADT + Docetaxel (Doc)	(bRFS) ADT+ Placebo: 12.9m ADT+ Doc: 22.9m	HR: 0.72, 95%CI: 0.57-0.91, p=0.005	ADT+ Placebo: 54.2m ADT+ Doc: 58.9m	HR: 1.01, 95%CI: 0.75-1.36, p=0.955
Enzalutamide ¹⁴	ARCHES (NCT02677896)	mCSPC	(N=1150) Enzalutamide + ADT vs. Placebo + ADT	(radiographic) rPFS (events) Enzalutamide+ ADT =15.9% Placebo+ ADT =34.9%	HR: 0.39, 95%CI: 0.30-0.50, p>0.001	Deaths Enzalutamide+ ADT (n=39) Placebo+ ADT (n=45)	HR:0.81, 94%CI: 0.53-1.25, p=0.3361
Enzalutamide ¹⁵	ENZAMET (NCT02446405)	mCSPC	(N=1125) Testosterone suppression plus either Enzalutamide vs. nonsteroidal antiandrogen therapy (Standard care)	PSA Events: Enzalutamide: 174 SOC: 333	HR: 0.39 p<0.001	Deaths: Enzalutamide: 102 SOC: 143	HR: 0.67, 95%CI: 0.52-086, p=0.0002
Apalutamide ³⁵	TITAN (NCT02489318)	mCSPC	(N=525) Apalutamide+ ADT vs Placebo+ ADT	rPFS at 24 mo Apalutamide: 68.2% Placebo: 47.5%	HR: 0.48, 95%CI: 0.39-0.60, p<0.001	OS at 24 mo Apalutamide: 82.4% Placebo: 73.5%	HR: 0.67, 95%CI: 0.51-0.89, p=0.005

Table 2. Systemic Therapy Trials for the Treatment of Metastatic Castration Resistant Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Abiraterone ^{26, 36}	COU-AA-301 (NCT00638690)	Post Docetaxel	5 mg of prednisone twice daily with 1000mg (4x 250mg) of abiraterone acetate (797 patients) or placebo (4x 250mg) daily	Abiraterone group: 5.6mo Placebo: 3.6 mo	p <0.001	Abiraterone group: 14.8mo Placebo: 10.9mo Median follow-up: 12.8mo	p<0.001, HR: 0.65, 95%CI: 0.54-0.77
Abiraterone ^{23, 24}	COU-AA-302 (NCT00887198)	Pre Docetaxel	Abiraterone acetate 1000mg (4 x 250mg) plus prednisone (5mg twice daily) (544 patients) vs placebo plus prednisone (544 patients)	Radiographic PFS Abiraterone group: 16.5mo vs placebo: 8.2mo median follow-up 22.2mo	p<0.0001, HR: 0.52, 95%CI: 0.45-0.61	Abiraterone: 35.3mo Placebo: 30.1 mo	p=0.0037 HR: 0.80; 95%CI: 0.69-0.93
Enzalutamide ²⁵	PREVAIL (NCT01212991)	Pre Docetaxel	872 in the enzalutamide group, 845 in the placebo group	Radiographic PFS at 12 months was 65% in the enzalutamide group compared to 14% in the placebo group	p<0.001, HR: 0.19, 95%CI: 0.15-0.23	OS was 72% (626 patients) in the enzalutamide group vs 63% (532 patients) in the placebo group	p<0.001, HR: 0.71, 95%CI: 0.60-0.84
Enzalutamide ^{27, 37}	AFFIRM (NCT00974311)	Post Docetaxel	Enzalutamide 160mg once daily (four capsules) (800 patients) vs placebo (399 patients).	Radiographic PFS Enzalutamide group: 8.3mo Placebo: 2.9mo	p<0.001, HR: 0.40	Enzalutamide group: 18.4mo Placebo: 13.6mo	p=0.0151, HR: 0.79, 95%CI: 0.66-0.95
Docetaxel ³⁸⁻⁴⁰	TAX 327	Metastatic CRPC	Docetaxel 75 mg/m ² q3 weekly + prednisone 5 mg bid vs. Mitoxantrone 12 mg/m ² + prednisone 5 mg bid (3rd arm of weekly docetaxel demonstrated no benefit)	N/A	N/A	Docetaxel 18.9 vs Mitoxantrone 16.5 months	p=0.009, HR: 0.76, 95%CI: 0.62-0.94)
Cabazitaxel ^{41, 42}	TROPIC (NCT00417079)	Post Docetaxel	10mg oral prednisone daily and 12mg/m ² mitoxantrone intravenously over 15-30min (377 patients) or 25 mg/m ² cabazitaxel intravenously over 1h (378 patients) every 3 weeks	cabazitaxel group:2.8mo mitoxantrone group:1.4mo	p<0.0001, HR:0.74 95%CI: 0.64-0.86	Cabazitaxel group: 15.1mo Mitoxantrone group: 12.7mo	p<0.001, HR: 0.63, 95%CI: 0.53-0.75
Sipuleucel-T (Not Health Canada Approved) ⁴³	IMPACT (NCT000065442)	Asymptomatic or minimally symptomatic CRPC	Sipuleucel-T (341 patients) vs placebo (171 patients).	Similar	p=0.40, HR: 0.92, 95%CI: 0.75-1.12	Sipuleucel-T group: 25.8mo Placebo: 21.7mo	p=0.03, HR 0.78, 95%CI: 0.61-0.98
Radium-233 (Xofigo) ^{29, 30}	ALSYMPCA (NCT00699751)	Post docetaxel or non-docetaxel candidates	Radium-233- six injections (1 every 4 weeks), 50kBq/kg of body weight, intravenously vs matching placebo	Time to First Symptomatic Skeletal Event (median): Radium-223: 15.6mo Placebo: 9.8mo	p<0.001, HR: 0.66, 95%CI: 0.52-0.83	Radium-233: 14.9mo Placebo: 11.3mo	p=0.03, HR: 0.78, 95%CI: 0.61-0.98
Cabazitaxel vs. Abiraterone or Enzalutamide ³²	CARD (NCT02485691)	mCRPC, previously treated with docetaxel, with progression within 12 mo while on abiraterone or enzalutamide	(N=255) Cabazitaxel vs. Abiraterone or Enzalutamide (whichever wasn't used initially)	median PFS: Cabazitaxel: 4.4 mo Abi/Enz: 2.7 mo	HR: 0.52, 95%CI: 0.40-0.68, p<0.001	median OS Cabazitaxel: 13.6 mo Abi/Enz: 11.0 mo	HR: 0.64, 95%CI: 0.46-0.89, p=0.008

Table 3. Systemic Therapy Trials for the Treatment of Nonmetastatic Castration Resistant Prostate Cancer

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
Darolutamide ¹⁶	ARAMIS (NCT02200614)	M0 CRPC with a PSA doubling time of 10 months or less	(N=1509) (2:1) Darolutamide+ ADT vs. Placebo+ ADT	Metastasis-free survival Darolutamide: 40.4 mo Placebo: 18.4 mo	HR: 0.41, 95%CI: 0.34- 0.50, p<0.001	Deaths: Darolutamide: n=78 Placebo: n=58	HR: 0.71, 95%CI: 0.5-0.99, p=0.045

Development and Revision History

This guideline was reviewed and endorsed by the Alberta GU Tumour Team. Members include urologists, 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.

Maintenance

A formal review of the guideline will be conducted in 2022. 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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Conflict of Interest Statements

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