Advanced/ Metastatic Prostate Cancer

Effective Date: June, 2018
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.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the Outpatient Cancer Drug Benefit Program Master List.

Participation of members of the Alberta Provincial GU Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial GU Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.
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

- How should advanced/ metastatic prostate cancer be staged?
- How should advanced/ metastatic prostate cancer be treated?
- How should advanced/ metastatic prostate cancer patients be followed after treatment?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial GU Tumour Team. Members of the Alberta Provincial GU Tumour Team include medical oncologists, radiation oncologists, urologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial GU Tumour Team and a Knowledge Management Specialist 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 to include early stage prostate cancer in 2005 (updated in January 2009, January 2011, September 2013, October 2014, March 2015) and subsequently split into an advanced/ metastatic only guideline in June 2018.

TARGET POPULATION

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

RECOMMENDATIONS

Bone Health

Bone health should be assessed in patients being treated for advanced prostate cancer, as they are at an increased risk for osteoporosis.
**Advanced Disease (Stage T1-4, N1, M0)**

Advanced prostate cancer is defined as rising PSA after definitive treatment.

**Staging**
- Radiologically node positive: obviously enlarged lymph nodes on CT scanning

**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.\(^2\)

**Follow-up**
- Age dependent.
- Investigation at the discretion of the physician.

**Biochemical Recurrence**\(^3\)

**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 recurrence**
- Radiotherapy with or without concurrent or adjuvant ADT is recommended
- Observation is also an option, depending on the findings during staging

**Post-radiotherapy recurrence**
Recommended options include:
- Active surveillance within a cancer clinic
- Cryosurgery
- Brachytherapy
- 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 traditional 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. Chemotherapy
i. All patients presenting with metastatic castrate sensitive prostate cancer who are starting ADT should be considered for docetaxel chemotherapy
ii. 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),
iii. Data from the STAMPEDE trial11 demonstrated a significant overall survival benefit of 14 months in all patients with metastatic CSPC.
iv. Patients with high volume disease castrate sensitive metastatic prostate cancer who are about to or just recently started hormonal therapy should be offered 6 cycles of docetaxel chemotherapy at 75 mg/m² every 3 weeks (given with or without prednisone). Hormone therapy as above is carried through and after docetaxel completion.

B. Abiraterone Acetate (Currently not publicly funded in Alberta as of June 2018)
i. The phase 3 LATUTUDE trial (N=1199) 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.12
ii. The phase 3 STAMPEDE trial (N=1917) 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%).13

C. – 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.

Biochemical Recurrence

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- Any rise in PSA.

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- Rise by 2 ng/mL (mcg/L) or more above the nadir PSA (defined as the lowest PSA achieved).
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- Bone scan
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Post-radical prostatectomy recurrence
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Post- radiotherapy recurrence
Recommended options include:
- Active surveillance within a cancer clinic
- Cryosurgery
- Brachytherapy
- ADT
Castrate Resistant Metastatic Disease (Stage M0, M+)

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

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

Management

The benefits of treatment are primarily palliative and related to quality of life, although some systemic therapies confer a small survival advantage.

Management of M0 Disease

1. The standard of care is monitoring PSA. In patients with a rapid doubling time (<6 months), more frequent imaging and closer clinical follow-up should be undertaken.
2. Clinical trial options should be considered.

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. 1st 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.14,15
      ii. Docetaxel 75mg/m² IV every 3 weeks in combination with prednisone at a dose of 5 mg twice daily.54
      iii. Enzalutimide 160mg oral daily can be used prior to docetaxel (PREVAIL).16 Funding is currently being sought.

   B. 2nd line options:
      i. Post progression on docetaxel chemotherapy:
         a. Abiraterone acetate17 or enzalutamide (AFFIRM)17
         b. Cabazitaxel 25mg/m² IV every 3 weeks in combination with prednisone 10 mg oral daily.56
         c. Radium 223 can be given to patients with symptomatic bony metastatic CRPC without visceral metastases (ALSYMPCA).18,19 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 in Alberta.
            - Patient selection is important. These patients should be discussed in
multidisciplinary tumor board rounds.

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

C. Subsequent lines:
   i. Sequencing with another agent listed above not previously used. For example, abiraterone → docetaxel → enzalutamide → cabazitaxel is a reasonable sequence. There are many others. There is no data to suggest the preferred sequence.
   ii. Docetaxel rechallenge or Mitoxantrone 12mg/m² every 3 weeks in combination with prednisone 5 mg oral twice a day may provide palliation.
   iii. Sipuleucel-T is not Health Canada approved.

D. Mitoxantrone 12mg/m² every 3 weeks in combination with prednisone 5 mg oral twice a day can provide adequate palliation in 2nd or subsequent line.

E. 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).

F. It is important to note that chemotherapy is NOT indicated in patients without evidence of metastatic disease on imaging whose only have manifestation of hormone insensitive disease is a rising PSA.

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). In brief:

   A. EBRT to symptomatic sites
   B. Strontium 89 (Metastron®) can be considered for appropriate indications, including:
      i. Multiple painful sites of bone metastases on both sides of diaphragm
      ii. Patient and/or tumor factors contraindicating the use of multiple fields of EBRT for palliation
      iii. Adequate bone marrow reserve (NB: Platelet count > 100)
      iv. No evidence of impending spinal cord compression
      v. No plans for systemic chemotherapy

Management of Oligometastatic Disease

1. The role of local therapy to the prostate (i.e. RT or prostatectomy) and the role of SBRT to sites of metastatic disease remains investigational and should be considered in the context of a clinical trial or based on review in multidisciplinary rounds.

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.
- Patients who have responded well to docetaxel chemotherapy can be re-challenged in the case of subsequent progressive disease.
- Duration: as clinically indicated
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADT</td>
<td>Androgen deprivation therapy</td>
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<tr>
<td>ALT</td>
<td>Alanine transamine</td>
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<tr>
<td>AST</td>
<td>Aspartate transaminase</td>
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<td>BUN</td>
<td>Blood urea nitrogen</td>
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<td>EBRT</td>
<td>External beam radiotherapy</td>
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<td>GnRH</td>
<td>Gonadotropin-releasing hormone agonist</td>
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<td>LHRH</td>
<td>Luteinizing hormone-releasing hormone</td>
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<td>PSA</td>
<td>Prostate-specific antigen</td>
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DISSEMINATION

- Present the guideline at the local and provincial Tumour Team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2019. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

REFERENCES


APPENDIX A

Literature Search Strategy:

For the 2018 guideline updates, PubMed was searched using the following terms:

- "prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "prostate cancer"[All Fields]
- "secondary"[Subheading] OR "secondary"[All Fields] OR "metastatic"[All Fields]
- "castration-resistant"[All Fields] OR "castration-sensitive"[All Fields]

Inclusion criteria: phase III clinical trials, published between January 1, 2010 and June 1, 2018, English language. A total of 6 studies were included in Table 1 and 8 studies in Table 2.

For the 2015 and 2016 guideline updates, select literature was reviewed for inclusion in the guideline by a working group at the annual provincial Alberta GU Tumour Team meeting. No formal systematic literature review was performed.

For the 2014 guideline updates, the Pubmed database was searched using the 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, and was limited to publications in the years 2011 and 2012. Medline and Embase were 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. Clinical practice guideline databases (Cochrane Library and the National Guidelines Clearinghouse) and websites were searched in order to obtain evidence relevant to this topic.
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>
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<tbody>
<tr>
<td>ADT</td>
<td>INT 0162 (NCT00002651)</td>
<td>Newly</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>
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<td>mCSPC</td>
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<tr>
<td>Abiraterone12</td>
<td>LATITUDE (NCT01715285)</td>
<td>Newly</td>
<td>ADT + placebo Vs. ADT + Abiraterone</td>
<td>ADT+ placebo: 14.8m ADT+ Abiraterone: 33.0 months</td>
<td>HR: 0.47, 95%CI: 0.39-0.55, p&lt;0.001</td>
<td>ADT+ placebo: 34.7 months ADT+ Abiraterone: not reached</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>HR: 0.29, 95%CI: 0.25-0.34, p&lt;0.001</td>
<td>(3-year) ADT+ placebo: 76% ADT+ Abiraterone: 83%</td>
<td>HR: 0.63, 95%CI: 0.52-0.76, p&lt;0.001, HR for M0: 0.75, HR for M1: 0.61</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) (2)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=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>
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<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>HR: 0.61, 95%CI: 0.51-0.72, P&lt;0.001</td>
<td>ADT+ Placebo: 54.2m ADT+ Doc: 58.9m</td>
<td>HR: 0.61, 95%CI: 0.47-0.80, p&lt;0.001</td>
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<td>Docetaxel20</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>HR: 0.72m, 95%CI: 0.57-0.91, p=0.005</td>
<td>ADT+ Placebo: 54.2m ADT+ Doc: 58.9m</td>
<td>HR: 1.01, 95%CI: 0.75-1.36, p=0.955</td>
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<tr>
<td>Drug</td>
<td>Trial Name</td>
<td>Indication</td>
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<td>Abiraterone</td>
<td>COU-AA-301 (NCT00638690)</td>
<td>Post Docetaxel</td>
<td>5 mg of prednisone twice daily with 1000mg (4x250mg) of abiraterone acetate (797 patients) or placebo (4x250mg daily)</td>
<td>Abiraterone group: 5.6mo Placebo: 3.6mo</td>
<td>&lt;0.001</td>
<td>Abiraterone group: 14.8mo Placebo: 10.9mo</td>
<td>0.54-0.77</td>
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<td>Abiraterone</td>
<td>COU-AA-302 (NCT00887198)</td>
<td>Pre Docetaxel</td>
<td>Abiraterone acetate 1000mg (4x250mg) 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>
<td>&lt;0.0001</td>
<td>Abiraterone: 35.3mo Placebo: 30.1mo</td>
<td>0.69-0.93</td>
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<td>Enzalutamide</td>
<td>PREVAIL (NCT01212991)</td>
<td>Pre 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>
<td>&lt;0.001</td>
<td>Enzalutamide group: 18.4mo Placebo: 13.6mo</td>
<td>0.60-0.84</td>
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<td>Enzalutamide</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>
<td>&lt;0.001</td>
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<td>0.60-0.84</td>
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<td>Docetaxel</td>
<td>TAX 327</td>
<td>Metastatic CRPC</td>
<td>Docetaxel 75 mg/m² q3 weekly + prednisone 5 mg bid vs Mitoxantrone 12 mg/m² + 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>0.62-0.94</td>
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<td>Cabazitaxel</td>
<td>TROPIC (NCT00417079)</td>
<td>Post Docetaxel</td>
<td>10mg oral prednisone daily and 12mg/m² mitoxantrone intravenously over 15-30min (377 patients) or 25 mg/m² cabazitaxel intravenously over 1h (378 patients) every 3 weeks</td>
<td>cabazitaxel group:2.8mo mitoxantrone group:1.4mo</td>
<td>&lt;0.0001</td>
<td>Cabazitaxel group: 15.1mo Mitoxantrone group: 12.7mo</td>
<td>0.53-0.75</td>
</tr>
<tr>
<td>Sipuleucel-T</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=0.40, HR: 0.92, 95%CI: 0.75-1.12</td>
<td>Sipuleucel-T group: 25.8mo Placebo: 21.7mo</td>
<td>0.61-0.98</td>
</tr>
<tr>
<td>Radium-233</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>&lt;0.001</td>
<td>Radium-233: 14.9mo Placebo: 11.3mo</td>
<td>0.61-0.98</td>
</tr>
</tbody>
</table>