CUA Guideline on the Management of Castration-Resistant Prostate Cancer (CRPC)


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Disclosures

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Every author reported conflicts of interest
Conflicts of interest were reported with over 25 different companies
CRPC is defined by disease progression despite castrate levels of testosterone and may present either as:
- A continuous rise in serum PSA levels
- The progression of pre-existing disease
  and/or
- The appearance of new metastases

The continuum of CRPC includes patients without metastases or symptoms with rising PSA despite ADT to patients with metastases and significant debilitation due to cancer symptoms.

ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; PSA: prostate-specific antigen
Methods

- MEDLINE search in English for literature and conference proceedings
- Levels of evidence and grades of recommendation employ the ICUD/WHO modified Oxford Center for Evidence-Based Medicine grading system (Based on a modified GRADE methodology)
  - Wherever Level 1 evidence is lacking, the guideline provides expert opinion
- The strength of each recommendation is represented by the words STRONG or WEAK

ICUD: International Consultation on Urologic Diseases; WHO: World Health Organization
ADT

• It is recommended that ADT be continued for the remainder of a patient’s life (*Level 3, Weak recommendation*)

• In patients who develop CRPC, the addition or change of first-generation androgen receptor antagonists may be considered (*Level 3, Weak recommendation*)

ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer
Non-metastatic CRPC

- Patients with a rapid PSADT (<10 months) or elevated PSA levels (>20) are at high risk for developing metastases earlier. Imaging in these patients should be performed every 3–6 months. Patients with a slower PSADT (>10 months) should be screened every 6–12 months (Expert opinion)

nmCRPC: non-metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time
Non-metastatic CRPC

- ADT should be maintained in nmCRPC. First-generation androgen receptor antagonists (i.e., bicalutamide, flutamide, etc.) should be discontinued if patients are receiving these agents (*Level 3, Weak recommendation*).

- Men with high-risk nmCRPC with an estimated life expectancy of >5 years should be offered apalutamide, enzalutamide, or darolutamide (*Level 1, Strong recommendation*).

nmCRPC: non-metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time
Non-metastatic CRPC

• In men with high-risk nmCRPC who are felt to be unsuitable or refuse approved therapies, observation or use of first-generation androgen receptor antagonists may be attempted (Level 3, Weak recommendation).

• For men with nmCRPC who are not considered high-risk, observation or secondary hormonal treatments may be attempted (Level 3, Weak recommendation).

• Patients who are untreated for nmCRPC should be followed with regular imaging every 6–12 months depending on PSADT (Level 3, Weak recommendation).

nmCRPC: non-metastatic castration-resistant prostate cancer; PSA: prostate-specific antigen; PSADT: prostate-specific antigen doubling time
Bone health in the non-metastatic patient

- Increased rates of fractures have been observed with all ARATs.
- It is unlikely that these agents are themselves responsible.
- Patients treated with ARATs will remain on ADT and non-metastatic for much longer than in the past.
- Consider bone-supportive agents to prevent the risk of fractures.

ADT: androgen deprivation therapy; ARAT: androgen receptor-axis-targeted therapy
mCRPC – First-line therapy

- In the chemo-naive setting for asymptomatic or minimally symptomatic mCRPC:
  - Abiraterone acetate 1000 mg/day plus prednisone 5 mg twice daily is recommended for first-line therapy for asymptomatic or minimally symptomatic mCRPC (*Level 1, Strong recommendation*)
  - Enzalutamide 160 mg per day (*Level 1, Strong recommendation*)
  - Docetaxel 75 mg/m^2^ IV every three weeks with 5 mg oral prednisone twice daily can be used in select cases (*Level 1, Strong recommendation*)
  - Consider a clinical trial

IV: intravenous; mCRPC: metastatic castration-resistant prostate cancer
mCRPC – Second-line therapy

- In the post-docetaxel setting (if neither received previously):
  - Abiraterone acetate 1000 mg per day plus prednisone 5 mg twice daily (*Level 1, Strong recommendation*)
  - Enzalutamide 160 mg per day (*Level 1, Strong recommendation*)
- Docetaxel 75 mg/m² IV every three weeks with 5 mg oral prednisone twice daily (*Level 1, Strong recommendation*)
  - For patients who have had a good response to first-line docetaxel, re-treatment with docetaxel can be considered (*Expert opinion, Weak recommendation*)

IV: intravenous; mCRPC: metastatic castration-resistant prostate cancer
Second-line therapy cont’d

- Cabazitaxel 25 mg/m$^2$ vs. 20 mg/m$^2$ every three weeks plus 5 mg oral prednisone twice daily for patients progressing on or following docetaxel (*Level 1, Strong recommendation*)

- Radium-223 every four weeks for six cycles is recommended in patients with pain due to bone metastases and who do not have visceral metastases (*Level 1, Strong recommendation*)
  - Radium 223 should not be combined with abiraterone, and not be combined with any other life-prolonging agent used for mCRPC
  - A bone-supportive agent (denosumab or zoledronic acid) should always be used with radium-223

mCRPC: metastatic castration-resistant prostate cancer
Second-line therapy cont’d

• Olaparib 300 mg twice daily is recommended for patients with mCPRC and homologous recombination repair (HRR) mutation who have progressed on a previous ARAT (Level 1, Strong recommendation).

• For patients who have had a good response to first-line docetaxel, re-treatment with docetaxel can be considered (Expert opinion, Weak recommendation).

• Mitoxantrone has not shown any survival advantage but may provide symptomatic relief. Mitoxantrone may be considered a therapeutic option in symptomatic patients with mCRPC in the first- or second-line setting (Expert opinion, Weak recommendation).

• Consider a clinical trial

ARAT: androgen receptor-axis-targeted therapy; mCRPC: metastatic castration-resistant prostate cancer
mCRPC – Third-line therapy

If not received in the past:

• Cabazitaxel
• Radium-223
• Olaparib*
• Consider clinical trial

*For patients with HRR mutation and having progressed on an NHT

HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer
mCRPC – Considerations

• Alternative therapies that have not demonstrated improvement in OS but can provide disease control, palliation, and improve quality of life include weekly docetaxel plus prednisone, and mitoxantrone plus prednisone (Level 2, Weak recommendation).

• The timing of docetaxel therapy in men with evidence of metastases but without symptoms should be discussed with patients, and therapy should be individualized based on patients’ clinical status and preferences (Level 3, Weak recommendation).

mCRPC: metastatic castration-resistant prostate cancer; OS: overall survival
## Treatment options for mCRPC

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| Abiraterone        | Abiraterone acetate 1000 mg/day plus prednisone 5 mg BID | **First line:** Improved PFS (16.5 vs. 8.3 months) HR 0.53; 95% CI (0.45–0.62; p<0.001)  
Statistically significant 4.4-month improvement in OS (HR 0.81; p=0.0033)  
**Second line:** Significantly prolonged median OS by 4.6 months; HR 0.74; p=0.0001 | Level 1, Strong recommendation |
| Enzalutamide       | 160 mg per day                            | **First line:** Decreased the risk of progression or death by 81% (HR 0.19; 95% CI 0.15–0.23; p<0.001) and the risk of death by 29% (HR 0.71; 95% CI 0.60–0.84; p<0.001)  
**Second line:** Significant advantage in OS of 4.8 months (18.4 vs. 13.6 months; HR 0.62; p<0.0001) | Level 1, Strong recommendation |
| Docetaxel          | 75 mg/m² intravenous (IV) every 3 weeks with 5 mg oral prednisone BID | **First line:** Median survival 18.9 vs. 16.5 months compared with mitoxantrone-prednisone (HR 0.76; 95% CI 0.62–0.94; p=0.009)  
No OS benefit was observed with docetaxel given on a weekly schedule (HR 0.91; 95% CI 0.75–1.11; p=0.36) | Level 1, Strong recommendation |
| Olaparib           | 300 mg BID                                | Recommended for patients with HRR mutation.  
PFS 7.39 vs. 3.44 months [HR 0.34, 95% CI (0.25, 0.47 p<0.001)] compared with enzalutamide/abiraterone  
Median OS of 19.1 vs. 14.7 months (HR 0.69, 95% CI 0.50, 0.97, p=0.02).  
Significant improvements in overall measurable RR of 33.3% vs. 2.3% (odds ratio [OR] 20.86, 95% CI 4.18, 379.18, p<0.001) | Level 1, Strong recommendation |
| Radium-223         | 55 kB/kg Every 4 weeks for 6 cycles      | OS improved by 3.6 months (HR 0.7; p<0.0001) and symptomatic SREs were delayed by 5.8 months (p<0.0001) | Level 1, Strong recommendation |
| Cabazitaxel        | 25 mg/m² or 20 mg/m² plus prednisone 5 mg BID | Median survival of 15.1 vs. 12.7 months compared with mitoxantrone (HR 0.70; 95% CI 0.59, 0.83; p<0.0001) | Level 1, Strong recommendation |
Supportive agents

- In men with CRPC and bone metastases, denosumab (120 mg SC) or zoledronic acid (4 mg IV) every four weeks are recommended to prevent disease-related SREs (*Level 1, Strong recommendation*)
- Treatment with zoledronic acid should not be used in men with baseline creatinine clearance <30 mL/min

CRPC: metastatic castration-resistant prostate cancer; IV: intravenous; SC: subcutaneous; SRE: skeletal-related events
Supportive agents

• The 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 beyond two years (*Level 3, Weak recommendation*).

• Denosumab and zoledronic acid are not approved and not indicated for SRE prevention in the treatment of metastatic castration-sensitive prostate cancer or for bone metastases prevention.

CRPC: metastatic castration-resistant prostate cancer; IV: intravenous; SC: subcutaneous; SRE: skeletal-related events
Considerations

• Patients who do not respond to first-line ADT or who progress clinically or radiologically without significant PSA elevations may have neuroendocrine differentiation.
• Biopsy of accessible lesions should be considered to identify these patients; these patients should then be treated with combination chemotherapy, such as cisplatin/etoposide or carboplatin/etoposide (Level 3, Weak recommendation).

ADT: androgen deprivation therapy; PSA: prostate-specific antigen
Considerations for sequencing in CRPC

• There is little data to support the re-use of an ARAT once patients have progressed.

• A median time to progression of less than four months was observed when patients were re-treated with an ARAT.

• In the CARD study, cabazitaxel was shown to be superior in the third-line setting following ARAT and docetaxel, rather than returning to an ARAT.

• Several sequencing trials are underway.

ARAT: androgen receptor-axis-targeted therapy; CRPC: castration-resistant prostate cancer
Other considerations

- Systemic corticosteroid therapy may offer improvements in PSA values and/or palliative outcomes in up to 30% of patients.
- Palliative radiation
  - Most men will experience partial or complete pain relief from external beam radiation to a specific lesion.
- Malignant spinal cord compression is an oncological emergency that requires immediate diagnosis with an MRI if suspected.
- Good oral hygiene, baseline dental evaluation for high-risk individuals, and avoidance of invasive dental surgery during therapy are recommended to reduce risk of ONJ for patients treated with bone-targeted therapies (Expert opinion).

MRI: magnetic resonance imaging; ONJ: osteonecrosis of the jaw; PSA: prostate-specific antigen
Recommendation summary

**CRPC without metastases**
- **High-risk (PSADT <10 m)**
  - Apalutamide
  - Enzalutamide
  - Darolutamide
- **Not high-risk (PSADT >10 m)**
  - Observation

**mCRPC first-line (if not received in the past)**
- Abiraterone
- Enzalutamide
- Docetaxel (select cases)
- Clinical trial
- Olaparib*

**mCRPC second-line (if not received in the past)**
- Docetaxel
- Radium-223 (symptomatic and no visceral metastases)
- Abiraterone or Enzalutamide (if neither received previously)
- Cabazitaxel (only post-docetaxel)
- Clinical trial
- Olaparib*

**mCRPC third-line (if not received in the past)**
- Cabazitaxel
- Radium-223
- Clinical trial
- Olaparib*

*For patients with HRR mutation and having progressed on an NHT

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In the presence of bone metastases:

Denosumab or zoledronic acid are recommended to reduce the risk of skeletal complications

Palliative radiation therapy should be considered in patients with pain
Recommendations cont’d

1. The optimal sequence of available options remains unknown. In general, it is felt that changing therapeutic mechanism of action with each line of therapy is likely to lead to better and longer-lasting response (*Expert opinion*).

2. Patients who have had little or no response to hormonal agents OR who progress with minimal change in PSA OR with significant visceral metastases should be considered for early chemotherapeutic options.

3. Radium-223 is not approved for patients with visceral metastases.

4. Whenever possible, clinical trials should remain the first choice in patients with CRPC.