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

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Disclosures

Dr. Saad has been an advisory board member for and has received payment/ honoraria from Amgen, Astellas, AstraZeneca, Bayer, Janssen, Knight, Myovant, Novartis, Pfizer, Sanofi, and Tolmar; and has participated in clinical trials supported by Amgen, Astellas, AstraZeneca, Bayer, Janssen, Novartis, Pfizer, and Sanofi.

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Dr. Gleave has been a consultant for and has received honoraria/grants from Abbvie, Amgen, Astellas, Bayer, GDx, Janssen, MDX, Pfizer, and Sanofi; and is founder/holds a patent with OncoGenex.

Dr. Kapoor has been an advisory board member for Astellas, AstraZeneca, Bayer, Janssen, Merck, Novartis, TerSera, Tolmar, and Sanofi; has received grants/honoraria from Amgen, Novartis, and Pfizer; and has participated in clinical trials supported by Amgen, BMS, CCTG, Merck, Novartis, and Pfizer.

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Background

- 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, Strong 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, Strong 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.
- Depending on evaluation risk, 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
  - Olaparib*

*For patients with HRR mutation and having progressed on an NHT. IV: intravenous; mCRPC: metastatic castration-resistant prostate cancer; NHT: novel hormonal therapy; HRR: homologous recombination repair

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/m^2 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 or are unfit for chemotherapy 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).*
- ^{177}Lu-PSMA-617 (^{177}Lu vipivotide tetraxetan) for up to six cycles is recommended in patients with mCRPC and PSMA-expressing metastatic lesions who have progressed on at least one previous taxane chemotherapy and an androgen receptor-axis-targeted therapy (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)*.

ARAT: androgen receptor-axis-targeted therapy; mCRPC: metastatic castration-resistant prostate cancer; PSMA: Prostate-specific membrane antigen

Second-line therapy cont'd

- 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

mCRPC: metastatic castration-resistant prostate cancer

mCRPC – Third-line therapy

If not received in the past:

- Cabazitaxel
- Radium-223
- Olaparib*
- Consider clinical trial
- ^{177}Lu-PSMA-617**

*For patients with HRR mutation and having progressed on an NHT; **In patients having progressed on at least one line of taxane chemotherapy and an ARAT.
HRR: homologous recombination repair; mCRPC: metastatic castration-resistant prostate cancer; NHT: novel hormonal therapy; PSMA: Prostate-specific membrane antigen

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).*
- 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).*

mCRPC: metastatic castration-resistant prostate cancer; OS: overall survival; ADT: androgen deprivation therapy

Treatment options for mCRPC

Drug	Dose	Evidence	Level of Evidence
Abiraterone **First-line or second line**	Abiraterone acetate 1000 mg/day plus prednisone 5 mg BID	**First line:** Improved FPS (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 **First-line or second line**	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 bs 13.6 months; HR 0.62; p<0.0001)	Level 1, Strong recommendation
Docetaxel **First-line or second line**	75 mg/m^2 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 **First-line, second line or third line**	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 **Second-line or third-line**	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 **Second-line or third line**	25 mg/m^2 or 20 mg/m^2 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
^{177}Lu-PSMA-617 **Second-line or third line**	7.4 GBq intravenously every 6 weeks for up to six cycles	Recommended for up to 6 cycles in patients having progressed on at least one line of taxane chemotherapy and an ARAT Median OS was prolonged by 4 months (15.3 vs. 11.3 months with SoC alone) and the risk of death was decreased by 38% (HR 0.62, 95% CI 0.52–0.74; p<0.001). Radiographic PFS was prolonged by 5.3 months (8.7 vs. 3.4 months) and the risk of disease progression was decreased by 60% (HR 0.40, 99.2% CI 0.29–0.57; p<0.001)	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 cont'd

- 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.

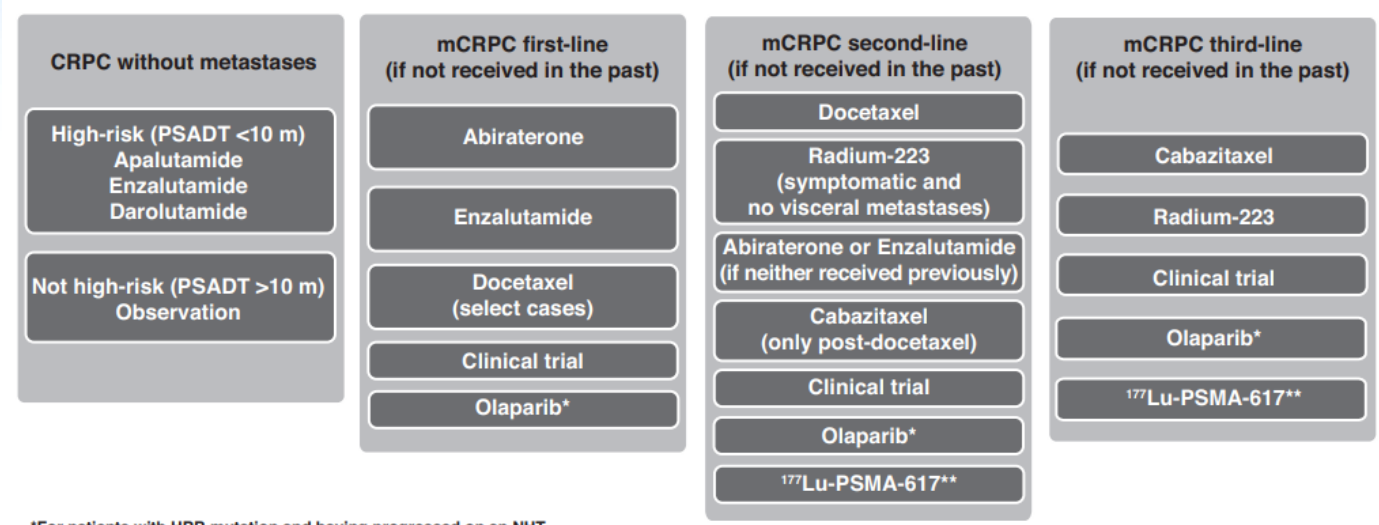
CRPC: metastatic castration-resistant prostate cancer; IV: intravenous; SC: subcutaneous; SRE: skeletal-related events

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. Options for treatment are debulking surgery + RT, vertebrectomy with stabilization and RT, or RT + steroids *(Level 1, Strong recommendation).*
- 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; RT: radiotherapy

Recommendation summary



*For patients with HRR mutation and having progressed on an NHT
**In patients having progressed on at least one line of taxane chemotherapy and an ARAT

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.

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