

Singapore Cancer Network (SCAN) Guidelines for the Management of Advanced Castrate-Resistant Prostate Cancer

The Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup

Abstract

Introduction: The SCAN genitourinary cancer workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the management of advanced castrate-resistant prostate cancer. **Materials and Methods:** The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. **Results:** Five international guidelines were evaluated—those developed by the National Comprehensive Cancer Network (2014), the European Society of Medical Oncology (2013), the American Urological Association (2013), the National Institute of Health and Clinical Excellence (2014) and the American Society of Clinical Oncology and Cancer Care Ontario (2014). Recommendations on the management of advanced castrate-resistant prostate cancer were developed. **Conclusion:** These adapted guidelines form the SCAN Guidelines 2015 for the management of advanced castrate-resistant prostate cancer.

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Key words: Abiraterone, Cabazitaxel, Docetaxel, Ketoconazole, Enzalutamide, Radium-223

Introduction

Prostate cancer is the third most common cancer among the male population in Singapore, and the sixth most frequent cause of cancer death.¹ The age-standardised incidence rate for prostate cancer has increased significantly over the last 40 years from 5.2 per 100,000 in 1973 to 1977 to 28.3 per 100,000 in 2008 to 2012. This may be a result of the increase in use of prostate specific antigen (PSA) testing. Overall, there was also an increase in the age-standardised mortality rate for prostate cancer. Most prostate cancers are diagnosed in the early stages, and about 21% of prostate cancer patients will have stage IV disease at diagnosis. Despite high response rates to initial androgen deprivation therapy, nearly all men with metastatic prostate cancer become castrate-resistant. Metastatic castrate-resistant prostate cancer (mCRPC) is a form of prostate cancer that has spread beyond the prostate and is resistant to medical or surgical treatments that lower testosterone level. In recent years, a number of novel agents that have improved survival in men with this disease have entered the clinic. There is therefore a need to review the available data, especially in the Singapore setting.

The SCAN Guidelines for the Management of Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

The SCAN Guidelines are clinical practice guidelines for the management of mCRPC.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group reflecting their views on current existing international guidelines for the management of mCRPC. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, urologists, allied health workers and general practitioners involved in the management of patients with mCRPC.

Guideline Recommendations/Development

The SCAN genitourinary cancer workgroup comprises a panel of 7 medical oncologists from Singapore with

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special interests in the management of genitourinary cancers. Membership of the workgroup was by invitation. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by the section lead with input from the workgroup members. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework² was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

These guidelines set out to address the 4 main management issues which were selected for this topic:

1. Androgen deprivation therapy
2. Hormone therapy
3. Chemotherapy
4. Radium-223

Five international guidelines were selected for review (Supplementary Table 1):

- “NCCN Clinical Practice Guidelines in Oncology Prostate Cancer” (version 1.2014) by the National Cancer Comprehensive Network (NCCN, USA)³
- “Prostate cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up” by the European Society for Medical Oncology (ESMO), 2013⁴
- “Castrate-Resistant Prostate Cancer: AUA Guideline”

by the American Urological Association (AUA), 2013⁵

- “Prostate Cancer: Diagnosis and Treatment (CG175)” by the National Institute of Health and Clinical Excellence (NICE), 2014⁶
- “Systemic Therapy in Men With Metastatic Castration-Resistant Prostate Cancer: American Society of Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline” by the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO), 2014⁷

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of mCRPC, it will be reviewed earlier.

1. Androgen Deprivation Therapy

Androgen suppression should be continued with luteinizing hormone-releasing hormone (LHRH) agonist or antagonist unless previous bilateral orchidectomy had been performed. Patients who progress on LHRH treatment or orchidectomy, should be started on an anti-androgen such as bicalutamide. Following further disease progression, the anti-androgen should be withdrawn.⁸ As per the Prostate Cancer Working Group 2⁹ consensus, there is no need to wait for a withdrawal response before initiating further therapy if there has been no response to adding anti-androgen to LHRH treatment or orchidectomy. Retrospective studies have also demonstrated limited PSA response when alternative anti-androgens, e.g. bicalutamide, flutamide, nilutamide, are used following progressive disease.¹⁰

2. Hormone Therapy

Abiraterone

Recent research has shown that drugs that target the hormone synthesis pathway can be clinically active in patients with castrate-resistant prostate cancer. Abiraterone is a potent and irreversible inhibitor of CYP17 that has shown clinical activity in patients. In patients who had disease progression after docetaxel chemotherapy, overall survival was significantly longer in patients who received abiraterone-prednisone compared to the placebo-prednisone group (14.8 months vs 10.9 months; hazard ratio (HR) = 0.65; 95% confidence interval (CI), 0.54 to 0.77; $P < 0.001$).¹¹ All secondary endpoints, including time to PSA progression (10.2 vs 6.6 months; $P < 0.001$), progression-free survival (PFS) (5.6 months vs 3.6 months; $P < 0.001$), and PSA response rate (29% vs 6%, $P < 0.001$), favoured the treatment group. In addition, there were significant benefits compared with prednisone alone in terms of pain relief, delayed pain progression, prevention of skeletal-related events, and patient reported health-related quality of

life.^{12,13} In chemotherapy-naïve patients, radiographic PFS was significantly increased with abiraterone-prednisone compared with placebo-prednisone (median 16.5 vs 8.2 months, HR = 0.52; 95% CI, 0.45 to 0.61).¹⁴ At a median follow-up of 49.2 months (IQR 47.0 to 51.8), overall survival was increased with abiraterone-prednisone compared to the placebo-prednisone group (median 34.7 vs 30.3 months, HR = 0.81; 95% CI, 0.70 to 0.93; $P = 0.0033$).¹⁵

There have been no cost-effectiveness analyses on abiraterone performed using local cost data and Singaporean societal norms. Based on NICE appraisal,¹⁶ the manufacturer's base-case incremental cost-effectiveness ratio (ICER) for abiraterone plus prednisolone compared with prednisolone alone is USD \$71,756 per quality-adjusted life-year (QALY) gained for the one prior chemotherapy subgroup. The NICE committee determined that the most plausible ICER was likely to be higher than the manufacturer's base-case estimate for the one prior chemotherapy subgroup, but would be less than USD \$76,645 per QALY gained.

Enzalutamide

Enzalutamide is a novel anti-androgen agent that has significant antitumour activity in patients with castrate-resistant prostate cancer who have progressed after previous chemotherapy. In the AFFIRM study, patients who had previously received docetaxel chemotherapy were randomised to enzalutamide or placebo.¹⁷ The median overall survival was 18.4 months (95% CI, 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (HR for death in the enzalutamide group = 0.63; 95% CI, 0.53 to 0.75; $P < 0.001$). Treatment was well tolerated. However, seizures were reported in 0.6% of patients who received enzalutamide and none with placebo. In addition, there was improvement in time to first skeletal-related event, time to pain progression, and quality of life in patients who received enzalutamide.^{18,19} The role of enzalutamide in chemotherapy-naïve patients was evaluated in the PREVAIL study.²⁰ Eligible patients had not received cytotoxic chemotherapy, ketoconazole or abiraterone. At the planned interim analysis, there was a median duration of follow-up of 22 months. At that point, overall survival was significantly increased with enzalutamide compared with placebo (estimated median 32.4 vs 30.2 months, HR = 0.71; 95% CI, 0.60 to 0.84). An updated analysis of overall survival with 116 additional deaths showed that 82% of patients in the enzalutamide group and 73% of those in the placebo group were alive at 18 months. There was a significant decrease in the risk of radiographic progression with enzalutamide compared with placebo (12 month PFS 65 vs 14%, HR = 0.19; 95% CI, 0.15 to 0.23). One patient in each study group experienced

a seizure. Patients who received enzalutamide also reported significantly improved patient-related outcomes, with delays in the occurrence of first skeletal-related event.²¹

There have been no cost-effectiveness analyses on enzalutamide performed using local cost data and Singaporean societal norms. On 23 July 2014, NICE recommended enzalutamide for the treatment of metastatic hormone-relapsed prostate cancer that has progressed during or after docetaxel-containing chemotherapy.²² The NICE Committee determined a probable pairwise ICER of USD \$22,213 per QALY for enzalutamide versus abiraterone and USD \$78,391 per QALY for enzalutamide versus best supportive care. For patients who had received 2 or more previous courses of cytotoxic chemotherapy, the NICE Committee's estimated ICER for enzalutamide compared with best supportive care was USD \$73,600 per QALY gained.

Ketoconazole

Ketoconazole is an imidazole antifungal agent that inhibits adrenal androgen synthesis, although it does have a direct cytotoxic effect on prostatic cancer cells in vitro. Ketoconazole is less specific than abiraterone. In a phase III trial conducted by the Cancer and Leukemia Group B (CALGB 9583), a subgroup of patients who had progressed on androgen deprivation therapy were assigned to anti-androgen withdrawal alone.⁸ Upon PSA progression, patients were treated with ketoconazole plus hydrocortisone. Thirty-two percent had a PSA response, and 7% with measurable disease had an objective response.

A retrospective study of 32 patients given ketoconazole at 200 mg thrice daily at 2 tertiary cancer centres in Singapore demonstrated a PSA response rate (defined as at least 50% decrease in PSA level from baseline) of 38% and a median duration of response of 6.75 months.²³ The median time to reach PSA nadir was 3.5 months (range, 1.5 to 11 months).

3. Chemotherapy

Docetaxel

Docetaxel was the first chemotherapy to demonstrate improvement in survival in patients with mCRPC. In the TAX 327 study, patients received 5 mg of prednisone twice daily and were randomly assigned to receive 12 mg of mitoxantrone per square metre of body-surface area every 3 weeks, 75 mg of docetaxel per square metre every 3 weeks, or 30 mg of docetaxel per square metre weekly for 5 of every 6 weeks.²⁴ The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the group given docetaxel every 3 weeks, and 17.4 months in the group given weekly docetaxel. As compared with the survival rate in the mitoxantrone group, the survival rate was significantly

higher ($P = 0.009$) in the group given docetaxel every 3 weeks but not in the group given weekly docetaxel ($P = 0.36$). With an extended follow-up that included death of 86% of the patients, the 3-year survival rates were higher in those treated with the 2 docetaxel schedules (18.6 and 16.6 vs 13.5% with mitoxantrone, respectively).²⁵ Apart from cardiac events, which were more frequent in the mitoxantrone group, other adverse events were more frequent among patients receiving docetaxel, and there was no trend toward a lower frequency with weekly docetaxel than with docetaxel given every 3 weeks. The addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficacy.²⁶

A retrospective study of 89 patients with castrate-resistant prostate cancer treated at the National Cancer Centre Singapore evaluated the efficacy and tolerability of 2 attenuated regimens—60 mg of docetaxel per square metre every 3 weeks, and weekly docetaxel (20 to 35 mg per square metre) (unpublished data). The use of 60 mg of docetaxel per square metre every 3 weeks had similar efficacy and an acceptable toxicity profile compared to the standard 75 mg of docetaxel per square metre every 3 weeks. Weekly docetaxel had significant palliative benefits among symptomatic patients despite lower overall survival.

Cabazitaxel

Cabazitaxel is a semi-synthetic novel tubulin-binding taxane drug with antitumour activity in docetaxel-resistant cancers. In the phase III open label randomised TROPIC trial, men with mCRPC who had received previous hormone therapy, but whose disease had progressed during or after treatment with a docetaxel-containing regimen were enrolled.²⁷ Patients were treated with 10 mg of oral prednisone daily, and were randomly assigned to receive either 12 mg of mitoxantrone per square metre of body-surface area intravenously over 15 to 30 min or 25 mg per square metre of cabazitaxel intravenously over 1 h every 3 weeks. Men treated with cabazitaxel plus prednisone had a better overall survival compared with those treated with mitoxantrone plus prednisone (HR = 0.70; 95% CI, 0.59 to 0.83; median survival 15.1 vs 12.7 months). PFS was also significantly prolonged (2.8 vs 1.4 months, HR = 0.74; 95% CI, 0.64 to 0.86). With additional follow-up, the 2-year estimated survival was greater than 2 years in 27% of patients treated with cabazitaxel versus 16% in those treated with mitoxantrone.²⁸ The most common clinically significant grade III or higher adverse events were neutropenia (cabazitaxel, 303 [82%] patients vs mitoxantrone, 215 [58%]) and diarrhoea (23 [6%] vs 1 [$<1\%$]). Twenty-eight (8%) patients in the cabazitaxel group and 5 (1%) in the mitoxantrone group had febrile neutropenia. About 5% of patients treated with cabazitaxel

died within 30 days of the last infusion and the most frequent cause of death in the cabazitaxel group was neutropenia and its clinical consequences. In this heavily pretreated, high risk population, current guidelines for prophylactic white blood cell growth factor use should be adhered to.

There have been no cost-effectiveness analyses on cabazitaxel performed using local cost data and Singaporean societal norms. The NICE Committee considered that the most plausible ICER would be above USD \$134,183 per QALY gained.²⁹ The Committee further noted that there remains considerable uncertainty in the robustness of this ICER because the utility values that were used in the model were based on unpublished data from an interim analysis of a small number of patients from the TROPIC study, and the costs associated with managing febrile neutropenia were underestimated.

4. Radium-223

Radium-223 dichloride is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range ($<100\ \mu\text{m}$). As a bone-seeking calcium mimetic, radium-223 is bound into newly formed bone stroma, especially within the microenvironment of osteoblastic or sclerotic metastases. In the phase III ALSYMPCA trial, all patients had castrate-resistant prostate cancer with multiple bone metastases and had either progressed on docetaxel chemotherapy or were not candidates for docetaxel chemotherapy.³⁰ Patients were required to have 2 or more bone metastases and no known visceral metastases. Overall survival, the primary endpoint, was significantly improved compared with placebo (median 14.9 vs 11.3 months, HR = 0.70; 95% CI, 0.58 to 0.83). The 18-month survival was estimated to be 39% for the radium-223 group versus 29% for placebo. The time to first symptomatic skeletal event (which included the first use of external beam radiation therapy (RT) for symptom relief, new pathologic fracture, spinal cord compression, or tumour-related orthopaedic surgery intervention) was also significantly increased (median 15.6 vs 9.8 months, HR = 0.66; 95% CI, 0.52 to 0.83).

There have been no cost-effectiveness analyses on radium-223 performed using local cost data and Singaporean societal norms. The NICE Committee noted that the manufacturer's base case ICER for radium-223 compared with best supportive care was USD \$85,118 per QALY gained and that the Committee's adjustments to the model increased the base-case ICER to USD \$88,008 per QALY gained (National Institute for Health and Care Excellence, Appraisal consultation document—Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases; issue date: December 2014). However, it concluded that it was not possible to determine whether

radium-223 could be considered a cost-effective use of National Health Service (NHS) resources, because the appropriate comparison with docetaxel and abiraterone had not been presented. At the time of publication of these guidelines, NICE has yet to publish their final recommendation on the use of radium-223 in patients with castrate-resistant prostate cancer.

Recommendations for Metastatic Castrate-Resistant Prostate Cancer (mCRPC)

The workgroup voted unanimously to adopt the AUA guidelines (Supplementary Table 1) and made the following adaptations (Table 1):

1. The workgroup recommends that participation in clinical trials should be strongly encouraged.
2. Best supportive care and referral to palliative medicine should be recommended when appropriate.
3. There was consensus that Sipuleucel-T should not be recommended as part of local treatment practice. Sipuleucel-T is currently not licensed for use in Singapore. The Immunotherapy Prostate

Adenocarcinoma Treatment (IMPACT) phase III trial reported a statistically significant 4.1-month median overall survival advantage with sipuleucel-T versus placebo (HR = 0.78; 95% CI, 0.61 to 0.98).³¹ However, the workgroup has considered several issues that have been raised about the registration trial.³² In particular, there was concern that the overall survival benefit may be a result of the detrimental effect of repeated depletion of circulating mononuclear cells in the placebo group.

4. There is lack of evidence demonstrating superiority between abiraterone and enzalutamide. In addition, the workgroup acknowledged that there are several retrospective studies indicating that either using abiraterone after enzalutamide or enzalutamide after abiraterone in castrate-resistant disease has limited activity. The workgroup accepts that there is insufficient data for specific recommendations on the sequencing of hormonal therapy.
5. The workgroup acknowledges that there is lack of definitive phase III trial data showing benefit of ketoconazole, although PSA responses have been observed. Clinicians may continue to recommend the

Table 1. Singapore Cancer Network (SCAN) for the Management of Metastatic Castrate-Resistant Prostate Cancer

Guideline Recommendations (Adapted from AUA Guidelines)	
Androgen Deprivation Therapy	<ol style="list-style-type: none"> a. Androgen suppression should be continued with LHRH agonist or antagonist unless previous bilateral orchidectomy had been performed b. Patients who progress on LHRH treatment or orchidectomy, should be started on an anti-androgen such as bicalutamide. Following further disease progression, the anti-androgen should be withdrawn c. Alternative anti-androgen may be considered
Chemo-naïve, Asymptomatic or Minimally Symptomatic	<ol style="list-style-type: none"> a. Clinical trial participation b. Abiraterone + prednisolone c. Ketoconazole + hydrocortisone d. Enzalutamide e. Observation f. Androgen withdrawal and alternative anti-androgen therapy
Chemo-naïve, Symptomatic, Good Performance Status	<ol style="list-style-type: none"> a. Clinical trial participation b. Docetaxel (chemotherapy may be preferred if the patient failed to achieve a good response to initial hormonal therapy) c. Abiraterone + prednisolone d. Ketoconazole + hydrocortisone (clinicians may continue to recommend the use of ketoconazole on the basis of lower cost) e. Enzalutamide f. Radium-223 (in patients who decline chemotherapy and do not have visceral metastases)
Postchemo, Symptomatic, Good Performance Status	<ol style="list-style-type: none"> a. Clinical trial participation b. Abiraterone + prednisolone c. Ketoconazole + hydrocortisone (clinicians may continue to recommend the use of ketoconazole on the basis of lower cost) d. Enzalutamide e. Cabazitaxel f. Re-challenge docetaxel g. Radium-223 (in patients without visceral metastases)

AUA: American Urological Association; LHRH: Luteinising hormone-releasing hormone

- use of ketoconazole on the basis of lower cost.
6. Docetaxel chemotherapy is the first-line chemotherapy of choice. The workgroup acknowledged that a lower dose (less than 75 mg/m² every 3 weeks) may have a better toxicity profile with comparable efficacy based on the Singapore study. When starting at a lower dose of docetaxel, clinicians should consider dose escalation up to 75 mg/m² in the absence of significant toxicity with the lower dose.
 7. Based on the results of the ALSYMPCA study, the workgroup agreed that radium-223 may be used for the treatment of castrate-resistant prostate cancer patients with symptomatic bone metastases and no known visceral metastatic disease. However, the agent is not recommended if the patient is concurrently receiving chemotherapy. Clinicians should follow instructions in the Food and Drug Administration (FDA) label on haematologic evaluation before each injection.
 8. The workgroup agreed that specific recommendations for castrate-sensitive prostate cancer, and bone metastases and bone health be deferred to subsequent editions of the guidelines.

Conflicts of Interest

Dr Kanesvaran reports receiving advisory board fees from Pfizer, GSK and Bayer and speaker bureau fees from Pfizer and GSK; Dr Ng, receiving advisory board fees from Bayer and Astra Zeneca; Dr Tan, receiving grant support from Pfizer and holding the following pending patents: "A Multigene Assay for Prognosis and Drug Response Prediction in Clear-Cell Renal Cell Carcinoma Patients That Identifies Distinct Biological Subtypes", "Method for Predicting Clinical Toxicities and Outcomes in Patients Receiving Sunitinib Using Gene Polymorphisms", "Self-Assembled Micellar Nanocomplexes Comprising Polyethylene Glycol-Epigallocatechin-3-Gallate Conjugates and Anticancer Drugs", "Antibody specific for Parafibromin, a New Marker of Parathyroid Carcinoma", licensed to Santa Cruz Biotechnology, and "Method for Determining Mutation Status in Colorectal Cancer Patients Using Allele-Specific PCR", licensed to AIT Biotech; Miss Cheng, Dr Tan, Dr Tay, Dr Toh and Dr Wong have nothing to disclose.

Workgroup Members

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Haematology-Oncology, National University Health System, Singapore; Workgroup Members (Non-Voting): Ruijun Cheng, BSc (Hons), Clinical Trials and Epidemiological Sciences Department, National Cancer Centre Singapore, Singapore.

Reviewers

Invited reviewers were Ian F Tannock, MD, PhD, DSc, Princess Margaret Cancer Centre, University of Toronto, Canada; Brian Rini, MD, Taussig Cancer Institute, USA; Daniel Heng, MD, MPH, FRCP, Department of Oncology, University of Calgary and Tom Baker Cancer Center, Canada. An additional invited reviewer chose to be anonymous.

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Supplementary Table 1. International Guidelines Reviewed

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Prostate Cancer Version 1.2014	Prostate Cancer: Diagnosis and Treatment (CG175)	Prostate Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Castration-Resistant Prostate Cancer: AUA Guideline	Systemic Therapy in Men with Metastatic Castrate-Resistant Prostate Cancer: American Society Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline
Date Released	27 November 2013	8 January 2014	27 June 2013	April 2013	8 September 2014
Guideline Developer	National Cancer Comprehensive Network (NCCN), United States	National Institute of Health and Clinical Excellence (NICE), United Kingdom	European Society for Medical Oncology (ESMO)	American Urological Association (AUA)	American Society of Clinical Oncology (ASCO) and Cancer Care Ontario (CCO)
Description of Method of Guideline Validation	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.	Guideline development group made up of health professionals, representatives of patient and carer groups and technical experts assesses the available evidence and makes recommendations. After the guideline development, group finalises the recommendations, the collaborating centre produces the final guideline. NICE formally approves the final guideline and issues its guidance to the NHS.	Recommendations developed from discussion at consensus conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfillment of objectives. Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO).	This document was written by the Castration-Resistant Prostate Cancer Guidelines Panel of the American Urological Association Education and Research, Inc. Members of the Practice Guidelines Committee (PGC) included urologists, oncologists and other clinicians with specific expertise on this disorder. Guideline was approved by AUA Board of Directors in April 2013.	The ASCO Clinical Practice Guidelines Committee and CCO Program in Evidence-Based Care convened an expert panel with multidisciplinary representation in medical oncology, urologic oncology, radiation oncology, community oncology, patient advocacy, health services, implementation research, and guideline methodology. All ASCO guidelines are reviewed and approved by the ASCO Clinical Practice Guidelines Committee on behalf of the ASCO Board before publication. All CCO guidelines are reviewed and approved by the CCO Report Approval Panel and a topic specific disease site group.
Target Population	Metastatic prostate cancer	Metastatic prostate cancer	Metastatic prostate cancer	Castrate-resistant prostate cancer	Metastatic castrate-resistant prostate cancer
mCRPC Recommendations	<p>mCRPC:</p> <ul style="list-style-type: none"> - maintain serum levels of testosterone <p>1. Asymptomatic:</p> <ul style="list-style-type: none"> - sipuleucel-T - secondary hormone therapy: <ul style="list-style-type: none"> - anti-androgen - anti-androgen withdrawal - abiraterone acetate - enzalutamide - ketoconazole - corticosteroids 	<p>mCRPC:</p> <ul style="list-style-type: none"> - anti-androgen - androgen deprivation - dexamethasone (0.5 mg daily) as third-line - abiraterone (post-docetaxel) - DES - corticosteroids 	<p>mCRPC:</p> <ul style="list-style-type: none"> - continue androgen suppression - secondary hormonal therapy: <ul style="list-style-type: none"> - antiandrogen - ketoconazole - corticosteroids - abiraterone (post-docetaxel) - docetaxel - enzalutamide (post-docetaxel) - DES or other estrogen - CYP17 inhibitors 	<p>mCRPC:</p> <ul style="list-style-type: none"> - continue androgen deprivation indefinitely <p>1. Survival and quality of life benefit:</p> <ul style="list-style-type: none"> - abiraterone + prednisolone - enzalutamide - radium-223 for those with bone metastases - docetaxel chemotherapy 	<p>mCRPC:</p> <ul style="list-style-type: none"> - continue androgen deprivation indefinitely <p>1. Survival and quality of life benefit:</p> <ul style="list-style-type: none"> - abiraterone + prednisolone - enzalutamide - radium-223 for those with bone metastases - docetaxel chemotherapy

mCRPC: Metastatic castration-resistant prostate cancer; PS: Performance status

Supplementary Table 1. International Guidelines Reviewed (Cont)

Guideline Title	NCCN Clinical Practice Guidelines in Oncology Prostate Cancer Version 1.2014	Prostate Cancer: Diagnosis and Treatment (CG175)	Prostate Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	Castration-Resistant Prostate Cancer: AUA Guideline	Systemic Therapy in Men with Metastatic Castrate-Resistant Prostate Cancer: American Society Clinical Oncology and Cancer Care Ontario Clinical Practice Guideline
	<ul style="list-style-type: none"> - diethylstilboestrol or other estrogen - clinical trials <p>2. Symptomatic:</p> <ul style="list-style-type: none"> - chemotherapy - abiraterone acetate - enzalutamide - clinical trial - best supportive care 	<ul style="list-style-type: none"> - those with poor initial hormone response or severe symptoms, chemotherapy preferable 	<ul style="list-style-type: none"> - ketoconazole/mitoxantrone/ radiotherapy (for those unwilling to above 2) <p>Chemo-naive, symptomatic, poor PS:</p> <ul style="list-style-type: none"> - abiraterone + prednisolone - ketoconazole/radiotherapy (for those unwilling to above two) - chemo in selected cases 	<p>2. Survival benefit but unclear quality of life benefit:</p> <ul style="list-style-type: none"> - sipuleucel-T (asymptomatic or minimally symptomatic) - cabazitaxel chemotherapy (post-docetaxel) <p>3. No survival benefit and quality of life benefit:</p> <ul style="list-style-type: none"> - mitoxantrone 	<p>4. Biological activity, unknown survival, unknown quality of life:</p> <ul style="list-style-type: none"> - anti-androgens - ketoconazole - low-dose corticosteroid - palliative care should be offered to all patients.
Member Votes	-	-	7 of 7 votes	-	-

mCRPC: Metastatic castration-resistant prostate cancer; PS: Performance status