Current approaches to treating metastatic castration-resistant prostate cancer (mCRPC)

The last decade has witnessed a remarkable increase in the number of agents that have become available for the treatment of mCRPC. A symposium co-organized by Janssen, the Hong Kong Urological Association and the Hong Kong Society of Clinical Oncology, which was held recently in Hong Kong, enabled urologists and oncologists to participate in a case-centred event that brought together the most recent evidence and best practice in mCRPC management. Professor Declan Murphy (Melbourne, Australia) presented an overview of how mCRPC treatment has evolved over the past decade. Thereafter, case studies of mCRPC patients were presented by Hong Kong specialists Professor Anthony CF Ng, Dr Po Chor Tam, Dr Peggy Chu, Dr Angus Leung, and Dr Darren Poon, who debated the relative advantages and disadvantages of treatment options recommended for patients with different clinical characteristics based on American Urological Association (AUA) indices. The meeting concluded with a presentation illustrating that a multi-disciplinary approach to prostate cancer management is best.

The changing landscape of mCRPC treatment

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In addition to standard-of-care androgen deprivation therapy (ADT; comprising a luteinizing hormone-releasing hormone [LHRH] analogue or orchiectomy, with or without an anti-androgen), treatments for advanced prostate cancer now include chemotherapeutic agents (docetaxel and the newer cabazitaxel), novel hormone therapies (abiraterone acetate and enzalutamide), immunologics (sipuleucel-T) and bone-targeting therapies (radium-223, denosumab, zoledronic acid).[1] The emergence of several new agents over the past 4 years has complicated treatment decision-making and planning for patients with mCRPC.[2] Prostate cancer is best treated by a multidisciplinary team that includes surgeons, clinical oncologists, radiation oncologists, nurses, endocrine specialists and psychologists who, collectively, can manage the patient's cancer, side effects of treatments, and quality of life.[3]

During the various clinical states of advancing prostate cancer, serum prostate-specific antigen (PSA) levels are a biomarker for tumour volume and activity, and treatment responses (Figure 1). The patient on which this article is focused is castrate-resistant and asymptomatic (or mildly symptomatic), with the beginnings of radiographically progressive metastatic disease.

Evolution of best practice in mCRPC

Before 2004, treatment of metastatic prostate cancer was palliative. It usually included mitoxantrone plus a corticosteroid, and bisphosphonates or radiotherapy to reduce skeletal complications, but no treatment offered a survival advantage. However, docetaxel was then shown in the TAX 327 and Southwest Oncology Group (SWOG) 99-16 studies to improve survival, time to progression, and rates of response in terms of pain, PSA level and quality of life compared to mitoxantrone/prednisone in patients with mCRPC.[4, 5]

Bone metastases can have serious and debilitating consequences. Skeletal-related events (SRE) are defined in clinical trials as radiation to bone, pathological fracture, spinal cord compression and bone surgery.[6] Compared to the bisphosphonate zoledronic acid, the monoclonal antibody denosumab increased time to SRE by 3.6 months

Figure 1. Clinical states of advancing prostate cancer are reflected in PSA levels

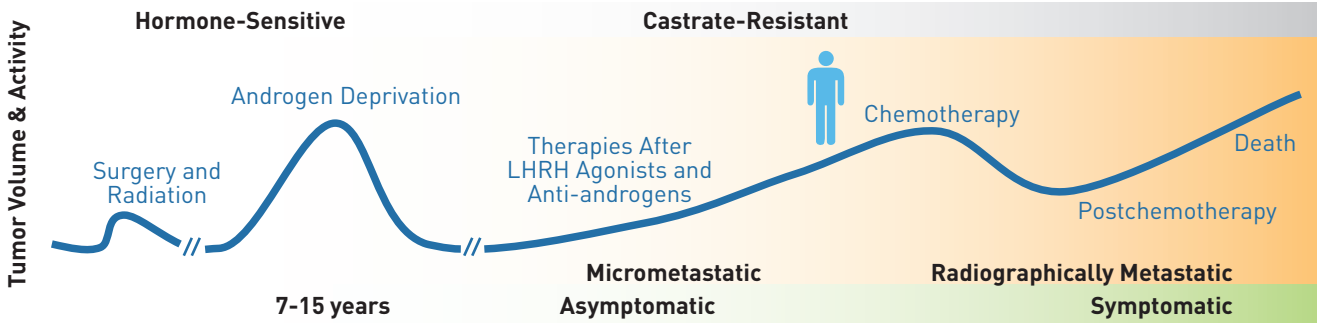


Table. Summary of clinical evidence: Overall survival in Phase III trials of mCRPC treatments

Trial	Design	Patient Population	HR Survival / Months
TAX 327 N=1,006	Docetaxel/prednisone vs mitoxantrone/prednisone	1st line chemo	0.76 18.9 vs 16.5
IMPACT N=512	Sipuleucel-T vs control cells	Pre-chemo asymptomatic	0.78 25.8 vs 21.7
TROPIC N=755	Cabazitaxel/prednisone vs mitoxantrone/prednisone	2nd line chemo	0.70 15.1 vs 12.7
COU-301 N=1,195	Abiraterone/prednisone vs placebo/prednisone	Post-chemo	0.74 15.8 vs 11.2
AFFIRM N=1,199	Enzalutamide vs placebo	Post-chemo	0.63 18.4 vs 13.6
COU-302 N=1,088	Abiraterone/prednisone vs placebo/prednisone	Pre-chemo asymptomatic	0.43 (rPFS) 0.75 (OS) - Not significant
ALSYMPCA N=922	Radium-223/BSC vs placebo/BSC	Bone symptomatic Post-chemo/chemo ineligible	0.70 14.9 vs 11.3
PREVAIL N=1,715	Enzalutamide vs placebo	Pre-chemo asymptomatic	0.70 32.4 vs 30.2 (stopped early)

(hazard ratio [HR], 0.82; p=0.008 for superiority).[6] Zoledronic acid and denosumab are recommended for the prevention of SRE in the European Association for Urology (EAU) guidelines.[7] However, benefits versus toxicities must be balanced when using these agents, and osteonecrosis of the jaw must be avoided.

The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) study on survival outcomes and treatment standards showed that in men with newly diagnosed metastatic disease who were treated only with ADT, median failure-free survival (FFS) was 11.2 months and median overall survival (OS) was 42.1 months.[8] Bone metastases with or without soft tissue metastases were associated with poorer outcomes: men who only had soft-tissue metastases had a 2-year OS rate of 85%, whereas those with soft tissue and bone metastases had a 2-year OS rate of 60%.

Because the median OS in STAMPEDE was more than double the median FFS, the study investigators concluded that the metastatic castrate-resistant phase makes up the majority of the patient's survival time, rather than being a short terminal phase with limited treatment options. Fortunately for mCRPC patients, since 2010, several agents have been shown to provide survival benefits for this group.

New agents and efficacy data change practice

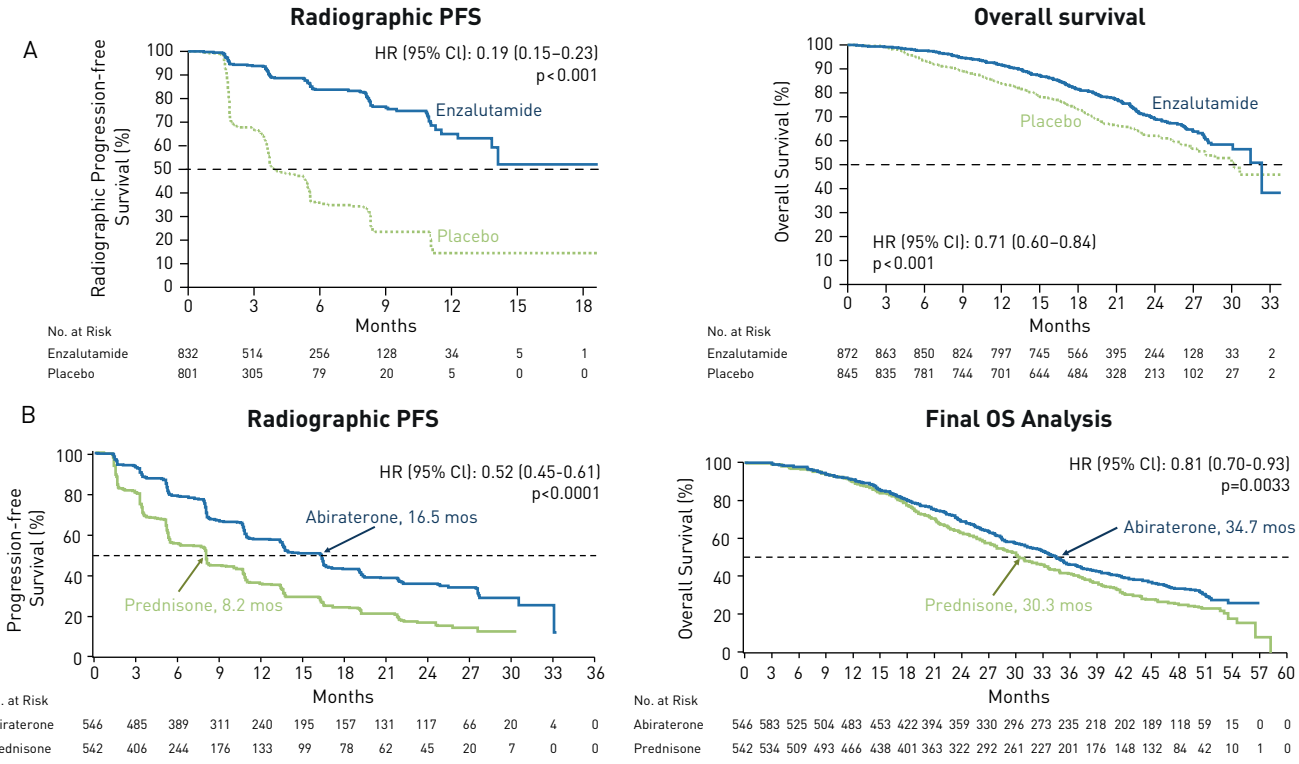
Sipuleucel-T is a cellular immunotherapy that consists of the patient's own peripheral-blood mononuclear cells that have been activated ex vivo with a fusion protein comprising a prostate antigen fused to the immune-cell activator granulocyte-macrophage colony-stimulating factor (GM-CSF).[9] The phase III, Immunotherapy for Prostate Adenocarcinoma Treatment (IMPACT) study showed a 4.1-month improvement in median OS with sipuleucel-T (25.8 months vs 21.7 months with placebo; HR 0.78), although time to progression was not increased (Table).[9] However, Professor Murphy pointed out that this treatment is very expensive, and is unlikely to become available in Hong Kong.

In the phase III XRP6258 Plus Prednisone Compared to Mitoxantrone Plus Prednisone in Hormone Refractory Metastatic Prostate Cancer (TROPIC) study that compared the new taxane cabazitaxel plus prednisone versus mitoxantrone plus prednisone in men with mCRPC who progressed after docetaxel-based treatment, median OS was 15.1 months with cabazitaxel versus 12.7 months with mitoxantrone (HR, 0.70; p<0.0001).[10]

In CRPC, androgen biosynthesis enzymes are upregulated, and androgen receptors become overexpressed or mutated.[11] Abiraterone acetate is a selective inhibitor of androgen biosynthesis that blocks cytochrome P450 c17 (CYP17), an enzyme critical to testosterone synthesis. Hence, androgen synthesis by the adrenal glands and testes and within the prostate tumour is blocked.[11] In the phase III COU-AA-301 study of abiraterone plus prednisone versus placebo in patients with mCRPC who had previously received chemotherapy, a 3.9-month median OS increase was observed with abiraterone after a 12.8-month median follow-up (HR, 0.65; p<0.001). Increased survival was observed in all patient subgroups, and the superiority of abiraterone was shown across all pre-specified secondary endpoints. Abiraterone was well tolerated; adverse events included hypokalemia, hypertension, and fluid retention, which could be largely addressed with the use of low-dose prednisone or prednisolone (5 mg twice daily).[11]

Another recently developed anti-androgen is enzalutamide (MDV3100), which targets androgen

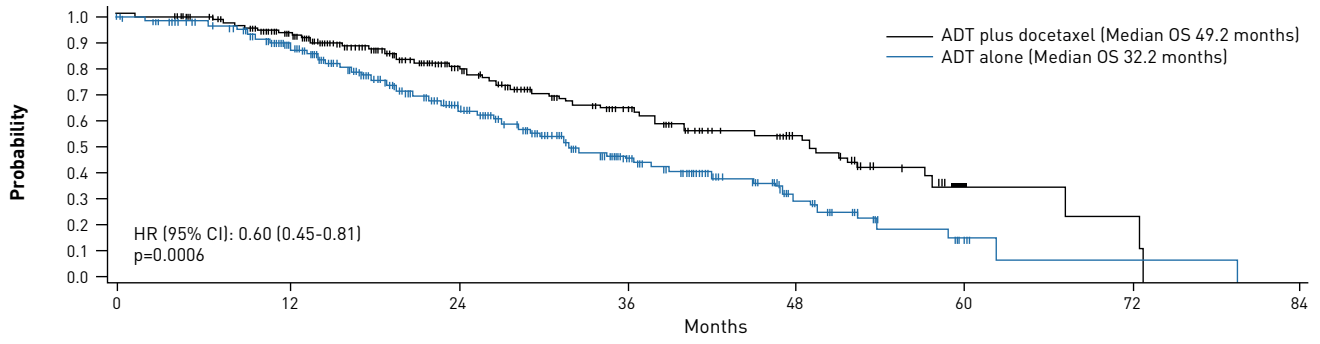
Figure 2. **Survival benefits when AR signal-targeting agents were given before chemotherapy. (A) PFS and OS with enzalutamide in PREVAIL[17] (B) PFS and OS with abiraterone in COU-AA-302[18]**



receptor (AR) signalling and impacts multiple steps in the AR signalling pathway.[12] Binding to AR with greater affinity than bicalutamide, enzalutamide inhibits androgen binding to AR, nuclear translocation of AR, and binding of AR to androgen response elements in DNA. A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100 (AFFIRM) was a phase III study that compared enzalutamide with placebo in men with mCRPC after chemotherapy. The median OS was 18.4 months in the enzalutamide group versus 13.6 months in the placebo group (HR, 0.63; p<0.001), and all secondary endpoints were met.[13] Enzalutamide was well tolerated, although a risk of seizures was detected in less than 1% of patients.

As mentioned previously, bone metastases adversely impact outcomes.[8] More than 90% of mCRPC patients develop bone metastases, which are a major cause of death, disability, decreased quality of life, and increased treatment costs.[14] Although bone-targeted therapies are usually given to improve symptoms and delay SRE, they did not improve survival, until the advent of radium-223. Radium-223 is a targeted alpha-emitter that binds to areas of increased bone turnover in metastases, and induces highly localized tumour killing by introducing double-stranded DNA breaks in dividing cells. Because the alpha particles travel such a short distance, toxic effects on adjacent tissue and bone marrow are minimized. The Alpharadin in Symptomatic Prostate Cancer Patients (ALSYMPCA) study was a phase III, international, randomized, double-blind study that compared the efficacy and safety of radium-223 versus placebo in patients with CRPC and bone metastases who had and had not received docetaxel.[14] Treatment was given

Figure 3. **CHAARTED: OS benefit when docetaxel is combined with ADT in patients with high-volume metastatic CRPC[20]**



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intravenously every 4 weeks for 6 cycles. Radium-223 provided a survival benefit (median OS, 14.9 months vs 11.3 months with placebo; HR, 0.70; p<0.001) that was consistent across all subgroups. Radium-223 also significantly prolonged the time to the first symptomatic SRE (median, 15.6 months vs 9.8 months with placebo; HR, 0.66; p<0.001).

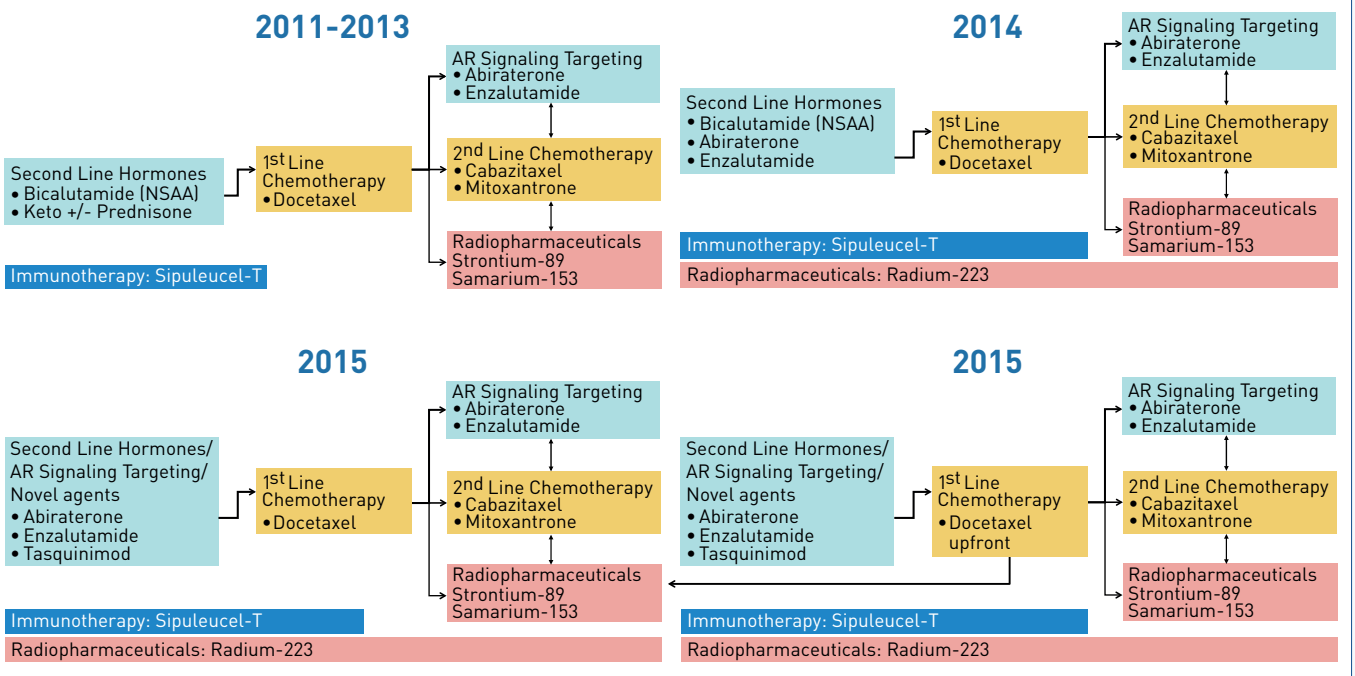
Studies were then conducted to see whether outcomes could be improved by treating CRPC patients earlier in the course of disease, particularly as many patients with mCRPC do not receive docetaxel because they refuse it or may be too frail to withstand its toxic effects.[15, 16] In the phase III PREVAIL study, enzalutamide efficacy was evaluated in patients who would typically have been treated with hormonal agents (ie, those who had asymptomatic or mildly symptomatic metastatic disease that had progressed despite the use of ADT), and who had not received chemotherapy.[15] An 81% reduction in radiographic PFS was observed at 12 months with enzalutamide, compared with 14% in the placebo group (HR, 0.19; p<0.001; Figure 2A). The median OS was estimated at 32.4 months in the enzalutamide group and 30.2 months in the placebo group, and enzalutamide treatment reduced the risk of death by 29% compared with placebo (HR, 0.71; p<0.001).

The efficacy of abiraterone was also evaluated in patients with mCRPC who had not received chemotherapy in the phase III COU-AA-302 study.[16] At the final analysis (median follow-up of 49.4 months), median OS was 34.7 months with abiraterone versus 30.3 months with prednisone (HR, 0.80; p=0.0027), even though a large proportion of patients in the placebo arm had received abiraterone at the regulators' request, based on early efficacy findings (Figure 2B).[18] The time to opiate use was also significantly delayed with abiraterone (33.4 months vs 23.4 months with prednisone alone; HR, 0.72; p<0.0001).[18] The favourable safety profile was consistent with those of previous abiraterone studies[16] and was maintained over the additional 2-year follow-up.[18]

It was suggested that the timing of these treatments, rather than just the treatments themselves, could account for these positive outcomes.[19]

Standard best practice was challenged again by the findings from the Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED), which investigated whether docetaxel given at the same time that ADT is commenced would prolong OS in men with metastatic prostate cancer.[20] Initially, the study design involved enrolment of patients with high-volume metastasis only (ie, visceral metastases and/or ≥4 bone metastases with ≥1 beyond the pelvis or spinal column), but because of slow accrual, the study design was amended to include patients with low-volume disease. In those with high-volume disease, there was a 17-month increase in median OS (from 32.2 months with ADT alone to 49.2 months if docetaxel was added to ADT; HR 0.62; p=0.0012; Figure 3).[20] PSA levels of <0.2 ng/mL after 12 months were seen in 16% of patients who received docetaxel plus ADT, versus 5.2% of patients treated with ADT alone. Median time to progression was 29.5 months with docetaxel plus ADT versus 14.0 months with ADT alone (both p<0.0001).

Figure 4. The changing landscape of treatment sequencing in mCRPC



The clinical interpretation of the CHAARTED study conclusions is that it is appropriate to give six cycles of docetaxel, in addition to ADT, to men with metastatic prostate cancer who can tolerate docetaxel and have high-volume disease. Other implications are that oncologists should become involved in treatment earlier in the course of disease.

Practical use of abiraterone

A consensus-based guide for using abiraterone in patients with mCRPC has been developed.[3] Co-administration with food alters abiraterone absorption, hence abiraterone should be taken at least 2 hours before eating, and nothing should be eaten for at least 1 hour after taking it. Potassium levels, blood pressure and liver function should be tested frequently during the early treatment phase. Levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, and urea should be assessed before starting treatment with abiraterone, then every 2 weeks for the first 3 months of treatment, and monthly thereafter for 6 months. Blood pressure, serum potassium and fluid retention should be tested monthly. Symptoms associated with mineralocorticoid excess can be managed by coadministration of low-dose prednisone or prednisolone.

The decision on whether to stop or continue treatment should not be based on PSA levels alone, but also on imaging to detect radiographic progression; treatment can be stopped at the time of unequivocal clinical progression.

Treatment sequencing in mCRPC

The evolution of mCRPC treatment is shown in Figure 4, with rapid changes occurring after the landmark evidence that emerged during 2011 to 2013.

Before 2011, ADT was given when PSA levels rose initially, followed by chemotherapy upon progression, and finally, palliative treatment. Since then, several agents have shown survival benefits in patients with metastatic disease (Table). Radium-223 can be used across the spectrum of disease,[14] and the new AR signal-targeting agents have also shown efficacy when used before chemotherapy.[15, 16] In the near future, the recent findings from CHAARTED will see docetaxel being given earlier, ie, to patients in the pre-castration-resistant stage.

Abiraterone suppresses external androgen production, while enzalutamide binds intracellular AR to prevent ligand-dependant activation and translocation to the nucleus.[21] Because these agents have different mechanisms, studies have been carried out to determine whether there is any advantage to giving either enzalutamide or abiraterone first, or whether they might have a synergistic effect (or induce cross-resistance). When abiraterone was given after enzalutamide, the median PFS with abiraterone was brief at 15.4 weeks in one study[21] and 12 weeks in another study,[22] leading the investigators to suggest the possibility of cross-resistance. Time to PSA progression was similarly short when enzalutamide was given after abiraterone, ranging from 12 weeks[23] to 16 weeks.[24] PSA response rates (defined as decreases in levels of ⩾50%) were 13%[23] and 46%[24] in the studies in which enzalutamide was given after abiraterone, and 8%[22] and 3%[21] when abiraterone was given after enzalutamide.

Because the cost of treatment with these agents is high, biomarkers that can determine whether patients are likely to respond to treatment would be very useful. Although it remains functional, an AR isoform encoded by a splice variant of the encoding gene lacks the ligand-binding domain that is the target of enzalutamide and abiraterone.[25] When prostate cancer patients who had this genetic variant (termed AR-V7) were treated with enzalutamide or abiraterone, none of them had a PSA response and median PFS was around 2 months. The investigators concluded that AR-V7-positive patients do not respond to these agents and, moreover, that they progress rapidly and die sooner than patients without the variant. AR-V7 could thus become a useful biomarker of response to abiraterone and enzalutamide.

Summary of recent clinical evidence

- Zoledronic acid or denosumab should be considered in patients with bone metastases[1]
- Radium-223 prolongs survival and time to SRE whether given before or after chemotherapy[14]
- Cabazitaxel can be considered after treatment with docetaxel[1]
- Abiraterone and enzalutamide are effective treatments that prolong survival when given either pre- or post-chemotherapy to patients with mCRPC[11, 18]
- To improve survival, docetaxel should be considered in combination with ADT in selected patients who have progressing CRPC[20]
- The optimum sequence of mCRPC treatments is still being defined

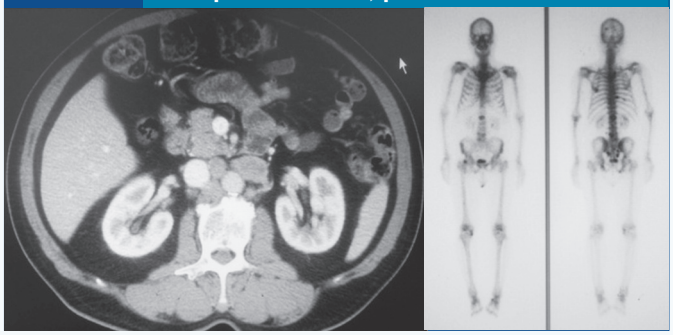
Case studies based on AUA index criteria

Asymptomatic or minimally-symptomatic mCRPC without prior docetaxel chemotherapy (AUA Index Patient 2)

Professor Anthony CF Ng
Department of Surgery
The Chinese University of Hong Kong
Hong Kong

A 76-year-old man presented with right hip pain in January 2008. An X-ray showed sclerotic changes in the right hip and a digital rectal examination (DRE) revealed an irregular, nodular, hard prostate. The serum PSA level was 26.17 ng/mL. A transrectal ultrasound (TRUS)-guided biopsy (8 cores) showed irregular margins and a

Figure 5. **CT scan and bone scan showing kidney lesions and multiple bone metastases in the spinal column, pelvis and ribs**



hypoechoic area in the left anterior part and right base. Pathology showed prostatic adenocarcinoma with a Gleason score of 3+4 in the left middle, apical, lateral, and right apical regions. A magnetic resonance imaging (MRI) scan showed a lesion in the left peripheral zone with periprostatic infiltration to the left seminal vesicle, positive pelvic lymph nodes, and evidence of bony metastasis to the pelvic bone and right hip. A bone scan revealed widespread bony metastases in the pelvis, ribs, skull, spinal column and arms. Stage IIIa disease was diagnosed.

The patient underwent a bilateral orchiectomy in March 2008 and his PSA level decreased from 30 ng/mL to 0.39 ng/mL in July 2009. One year later, his PSA was 0.41 ng/mL; in January 2010 it was 1.05 ng/mL, rising to 4.5 ng/mL in July 2010. He remained clinically well with no symptoms.

Anti-androgen treatment (bicalutamide 50 mg daily) was started and in October 2010, the PSA level had decreased to 0.54 ng/mL. In January 2011 the PSA level was 0.58 ng/mL, rising to 2.3 ng/mL in October 2011 and 9.7 ng/mL in January 2012. The patient was still clinically well and did not complain of any symptoms. Anti-androgen treatment was withdrawn, but the PSA level increased rapidly to 32.0 ng/mL by February 2012. A computed tomography (CT) scan showed metastatic lesions in the kidney and a bone scan showed multiple bone metastases in the spinal column, pelvis and ribs (Figure 5). Although the patient was 79 years old at that point, his performance score was 100, and he continued to work and did not complain of symptoms.

He started abiraterone treatment and in June 2012 his PSA level had decreased to 6.7 ng/mL. However, 3 months later it had risen to 39.9 ng/mL, and it was 119 ng/mL in November 2012. He stopped abiraterone treatment due to the rising PSA levels, and eventually died in July 2013.

Case discussion

Professor Murphy commented that this case was interesting because the patient remained clinically well despite his rising PSA levels and progressing bone metastases, and added that the patient fit the eligibility criteria for the PREVAIL and COU-AA-302 studies. The choice between chemotherapy and abiraterone treatment can be difficult in this type of patient; if his PSA levels had been higher or he had liver metastases, Professor Murphy might have chosen chemotherapy, but he agreed that abiraterone was the correct choice for this patient. Another specialist remarked that it is essential to consider the patient's age and co-morbidities when recommending chemotherapy, and caution should be exercised in the very elderly. If the patient's PSA levels are increasing rapidly, chemotherapy can be considered on a 3-weekly schedule, together with supportive measures such as GCSF. Intermittent ADT therapy has not been shown to improve outcome with any statistical significance; Professor Murphy would use this treatment in patients who had non-metastatic disease and whose PSA levels are rising rapidly following prostatectomy, but he opined that patients who have metastases should be treated with ADT for life.

AUA treatment guidelines for Index 2 patients (asymptomatic or minimally-symptomatic mCRPC without prior docetaxel chemotherapy)[26]

- Abiraterone plus prednisone, docetaxel, or sipuleucel-T should be offered to patients with asymptomatic or minimally symptomatic mCRPC who have good performance status and have not had prior docetaxel chemotherapy. [Standard; Evidence Level Grade A (abiraterone)/ B (docetaxel) / B (sipuleucel-T)]
- First-generation anti-androgen therapy, ketoconazole plus steroids, or observation is recommended for these patients if they have good performance status, have not received prior docetaxel chemotherapy and do not want, or cannot have, one of the standard therapies. (Option; Evidence Level Grade C)

Symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy (AUA Index Patient 3)

Dr Po Chor Tam
Private practice, Hong Kong

A 54-year-old man with a past history of hypertension presented in October 2011 with haematuria, lower back pain and a markedly swollen scrotum and lower abdominal wall. A DRE showed locally advanced prostate cancer. A bone scan revealed numerous foci of increased uptake involving the skull, vertebral column, pelvis, ribs, sternum, scapulae, bilateral femur and fibula (Figure 6). Blood tests showed a haemoglobin level of 10.2 g/dL, creatinine 71 µmol/L, alkaline phosphatase 119 U/L and a PSA level of 2,172 ng/mL. A TRUS guided 12-core biopsy was carried out. The biopsy pathology showed prostatic adenocarcinoma with a Gleason score 5+5; 12/12 cores were involved, with 10–90% core length involvement.

Figure 6. **Diagnostic bone scan of 54-year-old man showing bone metastases in the skull, vertebral column, pelvis, ribs, sternum, scapulae, femur and fibula**

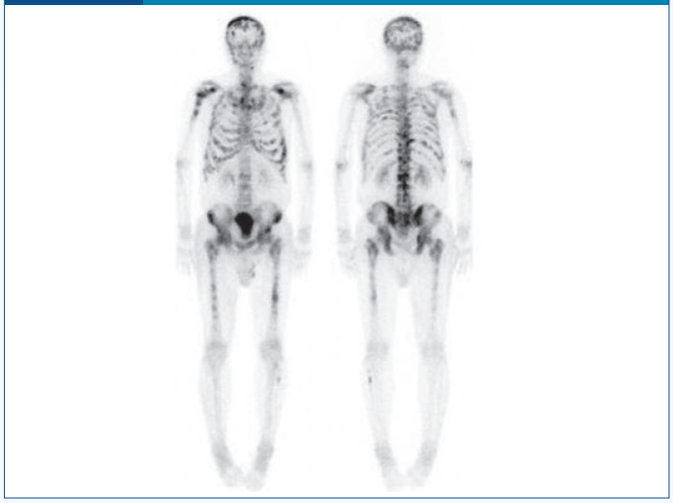
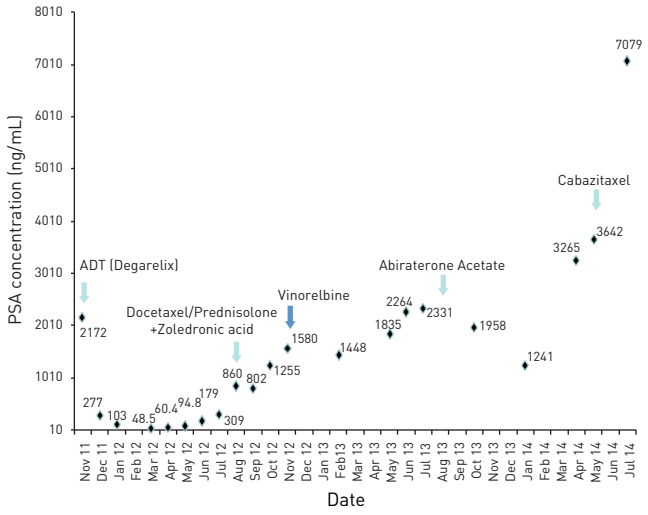


Figure 7. **PSA levels over time in a 54-year-old man being treated for mCRPC**



The patient commenced ADT with degarelix and his PSA level decreased rapidly to 48.5 ng/mL by March 2012, after which it began to increase again (Figure 7).

As well as the AUA recommendations for Index 3 patients that are listed in the text box below, Dr Tam outlined the following considerations that should be taken into account when managing CRPC patients in Hong Kong:

- Is the patient functionally castrated (shown by testosterone levels)?
- Is the disease localized or metastatic?
- Is the patient symptomatic?
- What are the sites of metastasis?
- What is the performance status?
- What is the financial situation of the patient?
- Is the treatment affordable?

Radium-223 was not available in Hong Kong at that time. The patient was offered chemotherapy and abiraterone, but he chose not to accept abiraterone because chemotherapy was available free of charge in hospitals, and he would have had to fund abiraterone himself. With PSA level at 860 ng/mL in August 2012, he commenced treatment with docetaxel/prednisolone and zoledronic acid, and his PSA level decreased briefly to 802 ng/mL, but then increased again to 1,255 ng/mL by October 2012. He received local radiotherapy in January 2013 and vinorelbine in July 2013. In September 2013, he was treated with abiraterone and his PSA level decreased over the next 6 months before rising again. In May 2014, with a PSA level of 3,642 ng/mL, he was given cabazitaxel. After developing complications of treatment, he died in July 2014.

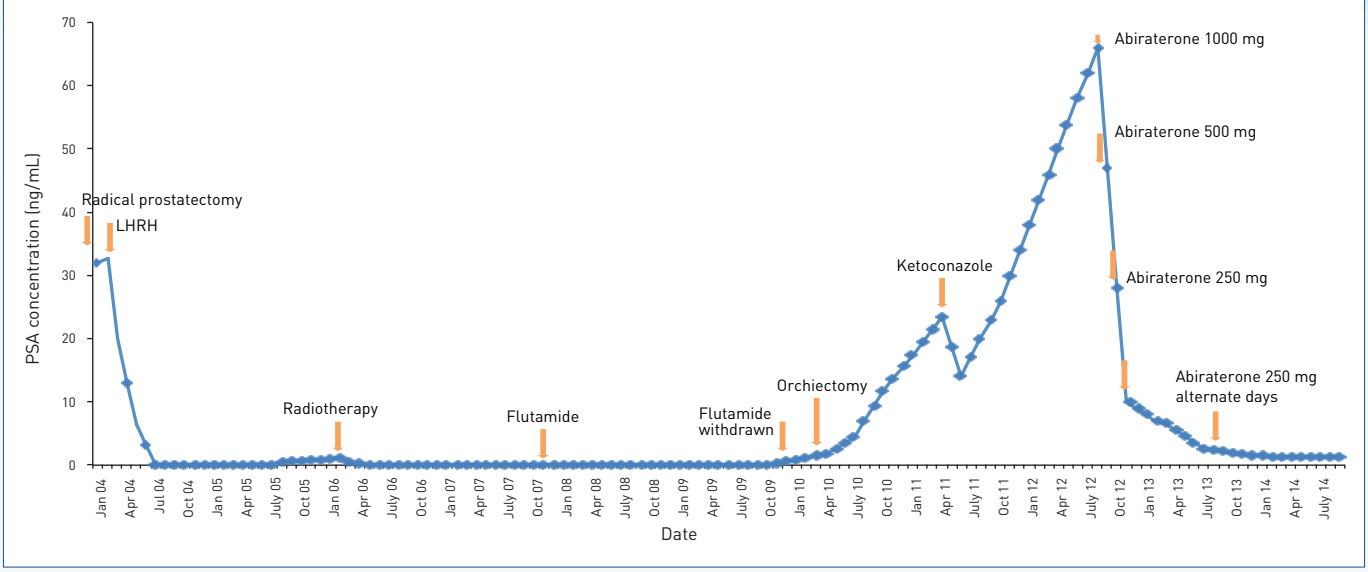
Case discussion

Professor Murphy commented that if this patient had presented in October 2014, chemotherapy could have been given as first-line therapy (ie, together with ADT), based on the data from CHAARTED; the patient's PSA nadir was high, he became castrate-resistant very quickly, he was symptomatic and had a high burden of disease. If he had had lower PSA levels and fewer metastases, he would have been a good candidate to receive abiraterone earlier on, but this was not the case. He nevertheless had a good response to abiraterone when he did receive it. The patient's outcome showed that cabazitaxel can be toxic in cases such as this. Another expert commented that, based on clinical evidence, abiraterone should rather be

AUA treatment guidelines for Index 3 patients (symptomatic mCRPC with good performance status and no prior docetaxel chemotherapy)[26]

- Clinicians should offer docetaxel to these patients. (Standard; Evidence Level Grade B)
- Clinicians may offer abiraterone plus prednisone to these patients. (Recommendation; Evidence Level Grade C)
- Clinicians may offer ketoconazole plus steroid treatment, mitoxantrone, or radionuclide therapy to patients with symptomatic mCRPC who have good performance status, have not been treated with prior docetaxel and who do not want or cannot have one of the standard therapies. [Option; Evidence Level Grade C (ketoconazole) / B (mitoxantrone) / C (radionuclide therapy)]
- Clinicians should offer radium-223 to patients who are complaining of symptoms from bony metastases from mCRPC, but have no known visceral disease, if they have good performance status and have not received prior docetaxel chemotherapy. (Standard; Evidence Level Grade B)
- Clinicians should not offer treatment with either estramustine or sipuleucel-T to these patients. (Recommendation; Evidence Level Grade C)

Figure 8. PSA levels over time in a patient being treated for CRPC



given to asymptomatic or mildly symptomatic patients, so chemotherapy was justified due to this patient's high burden of disease and his symptoms. Professor Murphy added that in younger patients, it is important to obtain and store tissue from biopsies taken at presentation to increase the patient's chances of eligibility for clinical trials.

Symptomatic mCRPC with poor performance status and no prior docetaxel chemotherapy (AUA Index Patient 4)

Dr Peggy Chu
Division of Urology, Department of Surgery
Tuen Mun Hospital
Hong Kong

The patient is a retired general practitioner with a history of ischaemic heart disease who had undergone a radical nephrectomy in 1997. A health check in January 2004 when he was aged in his late 60s revealed a PSA level of 32 ng/mL. Following a TRUS-guided biopsy and MRI, he was diagnosed with T2c prostate cancer with Gleason score 3+4 and apical margin involvement; a bone scan was negative. The patient underwent an open rectal prostatectomy and pelvic lymph node dissection (N0).

In February 2004, with a PSA level of 32.75 ng/mL, he started LHRH treatment. His PSA levels decreased and remained at <0.1 ng/mL between July 2004 and May 2005 (Figure 8).

After the patient's PSA level increased slightly, he consulted with Dr Chu and with a radio-oncologist, and requested local pelvic radiotherapy from February to March 2006, after which PSA level decreased again to <0.1 ng/mL. When his PSA level rose to 0.19 ng/mL in November 2007, he received ADT with flutamide (available free of charge in public hospitals, although patients have to pay for bicalutamide) and the PSA level decreased; flutamide was withdrawn in November 2009 when his PSA level started to increase again. He started treatment with bicalutamide in December 2009, but opted for an orchiectomy in February 2010 for financial reasons. The patient's PSA level continued to increase and an ^{11}C-acetate PET scan in January 2011 showed moderately increased ^{11}C-acetate uptake in the left fifth costal cartilage, which was confirmed in another scan performed 1 month later. The patient started low-dose

AUA treatment guidelines for Index 4 patients (symptomatic mCRPC with poor performance status who have not received prior docetaxel chemotherapy)[26]

- Clinicians may offer treatment with abiraterone plus prednisone. (Option; Evidence Level Grade C)
- Clinicians may offer treatment with ketoconazole plus steroids or radionuclide therapy to patients who are unable or unwilling to take abiraterone plus prednisone. (Option; Evidence Level Grade C)
- Clinicians may offer docetaxel or mitoxantrone chemotherapy to patients in select cases when the performance status is directly related to the cancer. (Expert Opinion)
- Clinicians may offer radium-223 to patients who have symptoms from bony metastases from mCRPC and have no known visceral metastases in selected cases when the performance status is directly related to symptoms related to bone metastases. (Expert Opinion)
- Clinicians should not offer sipuleucel-T to these patients. (Recommendation; Evidence Level Grade C)
- AUA recommendations for enzalutamide have not yet been updated, but enzalutamide was approved in September 2014 by the United States Food and Drug Administration (U.S. FDA) for first-line treatment of CRPC.

ketoconazole treatment (100 mg three times daily) in April 2011, but soon stopped it because of gastric pain, even though his PSA level had decreased.

In November 2011, the patient's PSA level had risen to 30 ng/mL, but he was not a suitable candidate for chemotherapy because he had had to undergo percutaneous coronary intervention (PCI) twice, and was being treated with aspirin and clopidogrel. When his PSA level reached 66 ng/mL in August 2012 and he started complaining of symptoms from his metastases, the patient started treatment with abiraterone (1,000 mg daily) plus prednisolone. When his PSA decreased to 10.1 ng/mL in November 2011, the patient opted to reduce the dosage to 750 mg daily for cost reasons, and again to 500 mg daily in March 2013 (when the PSA was 6.6 mg/mL). As his PSA levels decreased over the next year, he continued to reduce the abiraterone dosage himself, down to 250 mg every other day in March 2014 when his PSA was 1.3 ng/mL. In September 2014, his PSA was 1.4 ng/mL and the patient was still taking this reduced dosage of abiraterone.

Symptomatic mCRPC with good performance status and prior docetaxel chemotherapy (AUA Index Patient 5)

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A 68-year-old man who had complained of lower urinary tract symptoms since January 2007 presented with an enlarged supraclavicular fossa (SCF) lymph node. He had a history of hypertension, which was well controlled with amlodipine besylate. A rectal examination revealed a hard prostate. The patient's PSA level was 354 ng/mL. Fine-needle aspiration cytology of the SCF lymph node confirmed metastatic adenocarcinoma that stained positive for PSA and erythroblast transformation specific-related gene (ERG), which is commonly in found in CRPC and contributes to the development of androgen independence. A bone scan revealed multiple metastases.

The patient refused a bilateral orchiectomy and was treated with an LHRH analogue. His PSA nadir after 12 months was 12 ng/mL (Figure 9). After 4 years, in March 2011, biochemical progression was observed when his PSA was found to be 57 ng/mL. Bicalutamide treatment was given to achieve maximal androgen blockade.

Figure 9. PSA levels over time in a 68-year-old man being treated for mCRPC

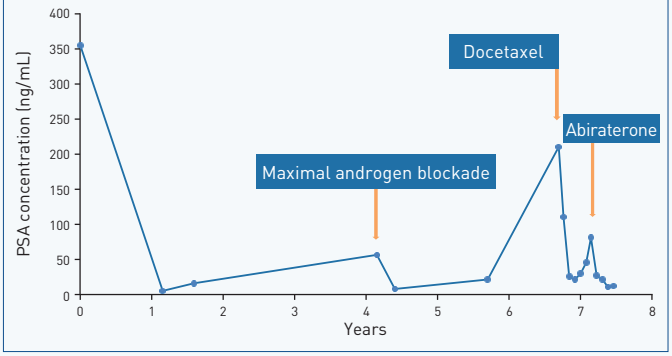
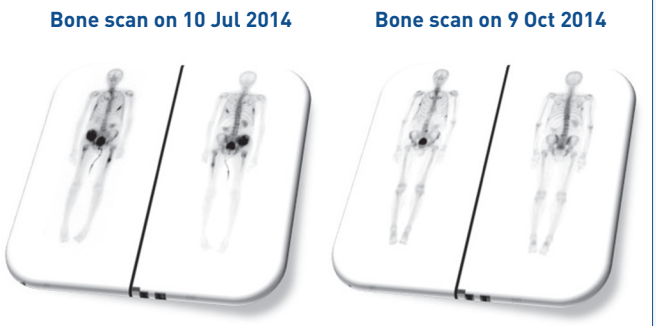


Figure 10. Bone scans showing reduced bone metastases after 3 months' treatment with abiraterone and prednisolone



In September 2013, the patient was admitted to hospital for pelvic pain; his PSA level was 210 ng/mL. Palliative radiotherapy was given to control his pain. LHRH treatment was continued even though he was castrate resistant, on the assumption that some tumour cell clones remained responsive to ADT. Although it was offered, the patient decided not to receive abiraterone, and he started docetaxel treatment with prednisolone. A good biochemical response was achieved, with the PSA level decreasing to 22 ng/mL after 4 cycles; docetaxel treatment was completed after 10 cycles in March 2014. However, the PSA rebounded rapidly and was 80 ng/mL in June 2014.

The patient was admitted for acute retention of urine and was complaining of right pelvic pain, which was treated with oxycodone and etoricoxib. The left SCN lymph node had increased in size to 2 cm in diameter, and his Eastern Cooperative Oncology Group (ECOG) performance status was 1.

Several clinical studies have shown a survival benefit of around 3 months for various agents when they are used to treat AUA Index 5 patients after docetaxel (Table 1). The patient started treatment with abiraterone (1,000 mg daily) combined with prednisolone 5 mg twice daily in June 2014. A good biochemical response was observed over the next 4 months and his PSA level decreased to 12 ng/mL in October; this was reflected by a radiological response in his bone scan that showed reduced uptake throughout, particularly the pelvis (Figure 10).

Dr Leung pointed out that, when deciding on whether to treat these types of patients with cabazitaxel, abiraterone or enzalutamide, it is important to review the patient's characteristics (extent of disease, type of metastases, number of chemotherapy regimens) in light of those observed in the respective drugs' pivotal trials.[27] Around one quarter of patients enrolled in the studies of all

three agents had visceral metastases, 80–90% had bone metastases, and around one third had been treated with two or more chemotherapy regimens. Although the efficacy findings of the various trials cannot be directly compared, enzalutamide appeared to be associated with the best outcomes numerically (OS, PFS, overall response rate and <50% PSA decline). However, these agents have different toxicity profiles.

Dr Leung would consider chemotherapy to be the better choice after relapse under the following circumstances:

- Absence of PSA normalization after initial LHRH analogue
- Early progression while on LHRH analogue
- No response to anti-androgens such as bicalutamide
- High disease load, including the presence of visceral metastases
- Patient requires rapid symptomatic relief

According to Dr Leung, re-challenge with docetaxel is reasonable in patients who have shown a response and relapsed after a long interval, or who have temporarily discontinued treatment due to adverse events, particularly in Hong Kong, where docetaxel is available free of charge. The greater the interval between the last cycle of first-line docetaxel chemotherapy and progression, the greater the PFS efficacy of subsequent docetaxel treatment.[28] A longer interval between initial docetaxel treatment and re-challenge may also improve outcomes: in one study, more partial biochemical responses were observed among the patients who had a 7-month interval (3/4 patients) than among those treated after a shorter interval (8/41 patients).[29] Radium-223 offers another treatment option in patients with bone-only metastases.

Other factors to consider in treating AUA Index 5 patients include PSA doubling time, response to previous endocrine therapy and progression-free interval, the presence or absence of visceral disease, co-morbidities, and the patient's preference.

Dr Leung concluded that clinicians are faced with numerous treatment choices for these patients. Notably, a direct comparison study of docetaxel versus cabazitaxel in chemotherapy-naïve patients (FIRSTANA) is ongoing. Dr Leung expects that enzalutamide should become available in Hong Kong by 2015. New agents such as the microenvironment modulator tasquinimod can be considered when they become available in the future.

AUA treatment guidelines for Index 5 patients (mCRPC with good performance status who have received prior docetaxel chemotherapy)[26]

- Clinicians should offer treatment with abiraterone plus prednisone, cabazitaxel, or enzalutamide to these patients. If the patient has received abiraterone plus prednisone prior to docetaxel chemotherapy, they should be offered cabazitaxel or enzalutamide. [Standard; Evidence Level Grade A (abiraterone) / B (cabazitaxel) / A (enzalutamide)]
- Clinicians may offer ketoconazole plus a steroid to these patients if abiraterone plus prednisone, cabazitaxel or enzalutamide is unavailable. (Option; Evidence Level Grade C)
- Clinicians may offer retreatment with docetaxel to those patients with mCRPC and good performance status who were benefitting at the time of discontinuation (due to reversible side effects) of docetaxel chemotherapy. (Option; Evidence Level Grade C)
- Clinicians should offer radium-223 to these patients if they have symptoms from bony metastases from mCRPC and no known visceral disease. (Standard; Evidence Level Grade B).

Symptomatic mCRPC with poor performance status and prior docetaxel chemotherapy (AUA Index patient 6)

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A 78-year-old man with good past health presented in 2009 with locally advanced prostate cancer with pelvic lymph node metastasis. The PSA level was 91 ng/mL and a TRUS biopsy showed adenocarcinoma (T3N1, Gleason score 4+4 since late 2008).

The patient was treated with an LHRH analogue from February 2009 and his PSA levels decreased rapidly; he underwent an orchiectomy in September 2009 and his PSA level was 1.97 ng/mL the following month. Biochemical failure was noted in February 2010 when his PSA level rose to 3.84 ng/mL, so ADT (including flutamide and bicalutamide) was given and PSA level decreased to 0.44 ng/mL. Biochemical progression was again observed in Aug 2011 (PSA 14 ng/mL); an MRI scan confirmed pelvic lymph node metastases and extra-capsular spread. Because the disease seemed to be confined to the pelvic region, locoregional treatment was given in the form of pelvic radiotherapy to the prostate and pelvic lymph nodes, and was completed in November 2011; the patient's PSA level decreased to 6.5 ng/mL.

Further biochemical progression was detected in March 2012 when his PSA level was found to be 22.6 ng/mL. A PET/CT scan in April showed ^{11}C-acetate uptake at nodes in the left para-aortic, aortocaval and retrocaval regions, and by May 2012, the PSA level had risen to 43.3 ng/mL. Despite his advanced age, the patient agreed to receive docetaxel/prednisolone (at an 85% dose reduction) in May 2012. However, his tolerance for chemotherapy was poor, and he experienced Grade 3 neutropenia and had multiple treatment delays, some of which were due to a perianal abscess. His PSA level decreased to 28.9 ng/mL in September 2012, but by mid-November it was

48.9 ng/mL and it increased further to 95.2 ng/mL in December 2012, at which point chemotherapy was stopped after 10 cycles.

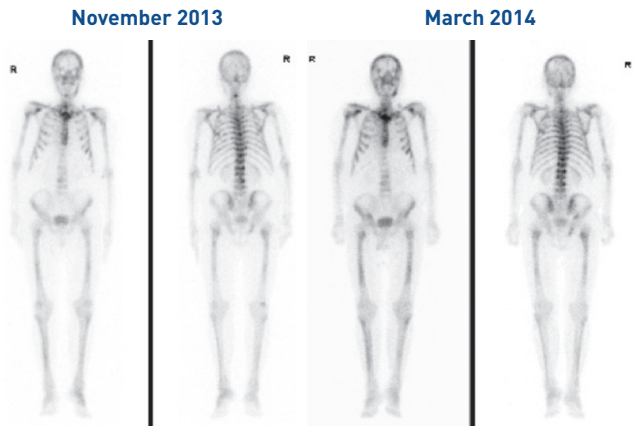
In April 2013, the patient complained of lower back pain; the PSA level had increased to 126 ng/mL. A bone scan showed several discrete foci in both ribs, the thoracic spine, the lower sternum and the left posterior skull and thereafter, a deterioration in his general condition was observed. He had to stay at home and in bed most of the time, had poor pain control and poor appetite, and could only walk with aid. His ECOG performance status was 3. In July 2013 his PSA level was 1,020 ng/mL.

According to Dr Poon, disease progression contributes to poor performance status and reversing the disease burden may improve ECOG status. The toxicity profile of the potential treatment should be taken into account, as should the patient's motivation to continue with further treatment.

In the abiraterone study COU-AA-301, a survival benefit was observed even in patients with ECOG performance status (PS) 2, although this was not statistically significant.[11] A study of outcomes with abiraterone in poor-performance status mCRPC patients showed decreased OS in ECOG PS ≥2 patients, irrespective of whether treatment was given before or after docetaxel.[30] Multivariate analyses showed that ECOG PS was a significant factor for OS (p<0.001), time to PSA progression (p=0.043), and PSA decline (p=0.002). In another study to determine the risk of death of different post-docetaxel treatments according to ECOG PS, when ECOG PS 2 patients were stratified by type of treatment, a reduction in the risk of death was confirmed for abiraterone and enzalutamide (HR, 0.72; p=0.046), but not for chemotherapy (HR, 0.81; p=0.43).[31]

The patient started treatment with abiraterone/prednisolone in August 2013. His bone pain and general condition improved and his ECOG PS improved to 1–2. The PSA level decreased to 472 ng/mL in November 2013, but increased again from December. A bone scan in March 2014 (when the PSA level was 716 ng/mL) showed a similar extent of diffuse bone metastasis, with some improvement in the vertebral column and rib cage, but possible mild worsening in bilateral femoral uptake (Figure 11). Abiraterone was stopped in April 2014 when his PSA level reached 926 ng/mL. The patient was still alive at the last follow-up in October 2014, although he needed repeated admission for transfusions due to pancytopenia.

Figure 11. Bone scans in an 83-year-old man showing changes in radiological uptake after 7 months' treatment with abiraterone and prednisolone



Three radiopharmaceutical agents for targeting bone metastases have been approved: radium-223, strontium-89 (a pure β-particle emitter) and samarium-153 EDTMP (a β- and ϒ-particle emitter). Samarium has been shown to improve pain scores and to reduce daily opioid analgesic use in patients with bone metastases.[32] The benefits of radium-223 extend from pain palliation to improved survival.[14]

Dr Poon concluded that patients with ECOG PS 2–4 can still derive some benefit from treatment. However, the treatment benefit is smaller in poor-performance patients, hence it is important to treat them before their ECOG PS worsens. There is an emerging role for radionuclide treatments, particularly for radium-223. Finally, best supportive care (including palliative radiotherapy and bisphosphonates) should always be considered for patients with poor performance status.

AUA treatment guidelines for Index 6 patients (mCRPC with poor performance status who have received prior docetaxel chemotherapy)[26]

- Clinicians should offer palliative care. Alternatively, for selected patients, clinicians may offer treatment with abiraterone plus prednisone, enzalutamide, ketoconazole plus steroid, or radionuclide therapy. (Expert Opinion)
- Clinicians should not offer systemic chemotherapy or immunotherapy to these patients. (Expert Opinion)

Advantages of a multi-disciplinary approach to treating prostate cancer

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Collaboration between the urologist and the oncologist is of paramount importance in managing prostate cancer. This was confirmed in a study to determine how the treatment approach in a multidisciplinary clinic affects management, compared to treatment by sequential specialists.[33] The proportion of low-risk prostate cancer

patients who underwent a prostatectomy was much higher in the group treated by individual practitioners, while active surveillance was more prevalent amongst patients treated at the multidisciplinary clinic. Consultation at a multidisciplinary clinic was significantly associated with patients' choice to pursue active surveillance.[33]

The Prince of Wales Hospital (PWH) has seen collaboration between the urology and oncology departments since 2009 in terms of bi-monthly case discussions, topic sharing, administrative matters, and research collaboration. Sharing experience contributes to the formulation of patients' management plans for both simple and complicated uro-oncology cases (such as locally advanced bladder cancer, testicular tumours, or cytoreductive surgery for renal cell carcinoma). Joint discussions are held on post-operative radiotherapy for post-prostatectomy cases, and on the early initiation of systemic treatment in patients with metastatic prostate cancer. Patients' tumour pathology and clinical features are also discussed to determine whether adjuvant radiotherapy or hormone therapy would be the most appropriate treatment.

Collaborative research projects at the PWH include studies on stereotactic body radiation therapy versus intensity-modulated radiation therapy in low- to intermediate-risk prostate cancer patients, ADT efficacy, validation of the Chinese version of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, and a comparison between surgery and radiotherapy in high-risk prostate cancer patients.

In summary, the contemporary approach to prostate cancer management should be multi-disciplinary, and close collaboration between the urologist and the oncologist enhances patient management. In this era of promising treatments for metastatic prostate cancer, communication between specialties is essential to providing the optimal treatment sequence for these patients.

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