**A Systematic Review of Clinical Practice Guidelines for Castration-Resistant Prostate Cancer**

Mohamad Javad Foroughi Moghadam, Saeed Taheri and Farzad Peiravian*

*Department of Pharmacoeconomics and Pharmaceutical Management, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

**Abstract**

Cancer constitutes a huge burden on societies in countries with any level of economic development. Prostate cancer is the first most diagnosed cancer of men in developed countries and the forth one in developing countries in terms of incidence rate. It is also the third incident cancer of men in Iran along with a prevalence of about 10,000 cases. Castration-resistant prostate cancer (CRPC) is a severe stage of the disease with a number of newly discovered treatment options. These therapeutic alternatives including abiraterone acetate, enzalutamide, cabazitaxel, immunotherapy with sipuleucel-T, radiopharmaceuticals and bone-targeted therapies (zoledronic acid, denosumab) along with docetaxel have made the decision making process complex and challenging for clinicians. In addition to the challenges of selecting the best-fit treatment, high costs of new pharmaceuticals and technologies necessitates the health policy-makers to develop practice guidelines in adaptation with local resources and limitations. The aim of this paper is to review the clinical guidelines for the management of CRPC. For better comprehension of guideline recommendations, the main clinical trials on new treatments were also identified. The efficacy and safety outcomes including but not limited to overall survival, progression free survival, quality of life and adverse effects were summarized. The guidelines of American Urological Association (AUA), National Comprehensive Cancer Network (NCCN), European Association of Urology (EUA), Spanish Oncology Genitourinary Group (SOGG), Asian Oncology Summit, Saudi Oncology Society-Saudi Urology Association combined guideline, National Institute for Health and Care Excellence (NICE) and Canadian Urological Association-Canadian Urologic Oncology Group (CUA-CUOG) were covered in this paper.

**Keywords:** Treatment Guideline; Hormone-Refractory Prostate Cancer; Health-Related Quality of Life; Cost; Enzalutamide; Abiraterone Acetate; Cabazitaxel.
PCa is the first incident cancer while it is in the fourth place in developing countries with about 353,000 new cases in 2012. In terms of mortality, PCa is the third in developed countries and the sixth ranked in developing countries with about 165,500 deaths in 2012 (2). The incidence and prevalence rates of PCa in the world are presented in Table 1.

In 2015 the number of new case of PCa in Iran was estimated about 4260 with a five-year prevalence of more than 10000 patients (3,4). Prostatic neoplasm is the third most frequently diagnosed visceral cancer among men in Iran (7.75% of all new cancer cases). It is also the fourth reason of cancer-caused mortality in men in Iran. The annual incidence of PCa in Iran (age-adjusted by world standard population) is about 12.59 per 100,000 men, according to 2009 Iran Ministry of Health (MOH) cancer registry book. Incidence rate of this cancer is even higher in capital city of Iran (Tehran) with 22.72 cases per 100,000 men and it is the first frequently diagnosed cancer in men after non-melanoma skin cancer in this city. In comparison with previous released data, PCa shows an increase in incidence rate (Table 2) (5).

PCa is also a principal cause of cancer-related death in men (2). The Disability Adjusted Life Years (DALYs) related to PCa was estimated around 4.8 million globally in 2013, from which 43% was occurred in developing countries, and 57% was in developed countries (6).

Castrate-Resistant Prostate Cancer
“Castrate-resistant prostate cancer (CRPC) is defined by disease progression despite androgen depletion therapy (ADT) and may be presented as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases” (7). When PSA rises whilst patient is under ADT and symptoms of disease progression is proved with bone scanning and CT scanning, CRPC would be possible diagnosis. This stage of PCa consists of wide range of severity including PSA rise with no metastases nor symptoms to a very severe state with metastases to the bones and other tissues (7). CRPC is also the most challenging stage of PCa in terms of treatment strategies. Oncologists and Uro-oncologists have to decide on various options based on patients and tumor characteristics and it is one of the most complicated situations that is medical decision making. In recent years, various treatment options including extensive mechanisms of action have been introduced. Abiraterone acetate, enzalutamide, cabazitaxel, immunotherapy with sipuleucel-T, radionuclide therapy, and bone-targeted therapies (zoledronic acid, denosumab) are the main therapeutic options.

| Year       | Prostate Cancer ASR 2005-2006 (1384) | Prostate Cancer ASR 2006-2007 (1385) | Prostate Cancer ASR 2007-2008 (1386) | Prostate Cancer ASR 2008-2009 (1387) | Prostate Cancer ASR 2009-2010 (1388) |
|------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
|            | 9.22                                 | 9.37                                 | 10.91                                 | 12.8                                 | 12.5                                 |

Source: cancer Registry Book 2009, Iran Ministry of Health, Cancer office
The new treatment options will prolong the survival of patients and consequently their use of health care resources will increase dramatically. Therefore, the diagnostic and therapeutic costs of CRPC will bring about a significant economic burden in near future (9).

**Aim of the Study:** Considering the challenges in the selection and sequencing of the best treatment options and the potential economic burden especially in a developing country with limited resources, the aim of this article is to review the clinical practice guidelines for the management of CRPC and to summarize the recommendations of these guidelines. Furthermore, clinical studies of the existing and emerging medicines will be reviewed to prepare a brief summary of their potential benefits as well as safety concerns. Some suggestions will also be prepared while keeping in mind the economic limitations in health resources in addition to the concept of Health-Related Quality of Life (HRQoL) and patient satisfaction.

**Methods**

The PubMed and Scopus database were systematically searched and the relevant articles and guideline reviews were selected for scrutiny. PubMed database was searched using MeSH database with the following key-words: “Practice Guideline”[Publication Type], “Prostatic Neoplasms”[Mesh], and (“2006/07/13”[PDat]: “2016/07/09”[PDat]). The documents that had been published since 10 years before the search date, including 98 articles, were reviewed for finding the relevant papers. In addition, Scopus database was searched using the following key-word combinations: ( TITLE-ABS-KEY ( guideline ), TITLE-ABS-KEY ( “prostate cancer” ), TITLE-ABS-KEY ( “treatment” or “management” ), TITLE-ABS-KEY ( “castration resistant” or “castration-resistant” or “castrate-resistant” or “castrate resistant” or “hormone resistant” or “hormone-resistant” or “hormone-refractory” or “hormone refractory” or “hormone-insensitive” or “hormone insensitive” ).

The search result included 203 articles. When time limitation was applied (published articles since 2007), 179 articles were accessed. By reviewing the titles and abstracts, 52 relevant articles were found. Since many articles were discussing the same guidelines and considering the last update of each guideline, the authors selected eight leading clinical guidelines from different health care settings among the most and less developed countries. The authors summarized treatment recommendations of each guideline for various risk-groups of patients.

When the most recommended treatment options were identified, the main clinical trials on them were found within PubMed and the Cochrane library. A review on the papers was performed and the results were summarized focusing on overall survival, progression-free survival, HRQoL, time to progression, time to skeletal-related events, and other efficacy and safety outcomes.

**Guidelines review**

The practice guidelines by eight national and international societies and organizations were reviewed which are as follows: American Urological Association (AUA), National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU), Spanish Oncology Genitourinary Group (SOGG), Asian Oncology Summit, Saudi Oncology Society-Saudi Urology Association combined guideline, National Institute for Health and Care Excellence (NICE), and Canadian Urological Association-Canadian Urologic Oncology Group (CUA-CUOG).

1. **American Urological Association** (10, 11)

The final AUA guideline for the treatment of CRPC was published in May 2013 and was updated in April 2014 and then in March 2015 to incorporate relevant newly published literature to provide a better rational basis for the management of patients (Table 3).

**Patient Classification**

- In the AUA guideline, six categories of patients are defined representing the most common scenarios that are faced in clinical practice. These patients groups are categorized based on the presence or absence of metastatic disease, the degree of symptoms, the performance status of patients (defined by the ECOG scale), and
Foroughi Moghadam MJ et al. / IJPR (2018), 17 (Special Issue): 17-37

their previous history of chemotherapy with docetaxel. Index Patient 1: Asymptomatic non-metastatic CRPC.

- Index Patient 2: Asymptomatic or minimally-symptomatic mCRPC, good performance status, no prior docetaxel chemotherapy.
- Index Patient 3: Symptomatic mCRPC, good performance status, no prior docetaxel chemotherapy.
- Index Patient 4: Symptomatic mCRPC, poor performance status, no prior docetaxel chemotherapy.
- Index Patient 5: Symptomatic mCRPC, good performance status, prior docetaxel chemotherapy.
- Index Patient 6: Symptomatic mCRPC, poor performance status, prior docetaxel chemotherapy.

| Index Patient number | Situation | Recommendation/Option/Standard | Evidence Level Grade |
|----------------------|-----------|---------------------------------|----------------------|
| Index Patient 1      | Asymptomatic non-metastatic CRPC | Observation with continued Androgen Deprivation Therapy [Recommendation] | C |
|                      | Patients unwilling to accept observation | 1st generation antiandrogens (Flutamide, Bicalutamide, Nilutamide) or 1st generation Androgen Synthesis Inhibitors (Ketoconazole+Steroid) [Option] | C |
|                      | patients outside the context of a clinical trial | Systemic chemotherapy or immunotherapy should not be used [Recommendation] | C |
|                      | --- | Abiraterone + Prednisone, Enzalutamide / Docetaxel, or Sipuleucel-T [Standard] | A/B |
| Index Patient 2      | Patients who do not want or cannot have one of the standard therapies | 1st generation Anti-androgen therapy, Ketoconazole + Steroid or observation [Option] Manipulation with existing antiandrogen agents, such as Bicalutamide, Nilutamide or Flutamide [Option] | C |
|                      | --- | Abiraterone + Prednisone, Enzalutamide / Docetaxel [Standard] | A/B |
|                      | Patients who do not want or cannot have one of the standard therapies | Ketoconazole + Steroid / Mitoxantrone / Radionuclide therapy [Option] | C/B/C |
|                      | --- | Estramustine or sipuleucel-T should not be used [Recommendation] | C |
| Index Patient 3      | Patients with symptoms from bony metastases and without known visceral disease | 223Ra(Radium) [Standard] | B |
|                      | --- | Abiraterone + prednisone or enzalutamide [Option] | C |
|                      | Patients who are unable or unwilling to receive abiraterone + prednisone or enzalutamide | Ketoconazole+ steroid or radionuclide therapy [Option] | C |
|                      | --- | Estramustine or sipuleucel-T should not be used [Recommendation] | C |
| Index Patient 4      | Select cases, specifically when the performance status is directly related to the cancer | Docetaxel or Mitoxantrone [Expert opinion] | - |
|                      | patients with symptoms from bony metastases and without known visceral disease | 223Ra(Radium) (specifically when the performance status is directly related to symptoms related to bone metastases) [Expert opinion] | - |
|                      | --- | sipuleucel-T should not be used [Recommendation] | C |
### Guidelines for Castrate-Resistant Prostate Cancer

| Index Patient number | Situation | Recommendation/Option/Standard | Evidence Level Grade |
|----------------------|-----------|--------------------------------|----------------------|
| Index Patient 5      | Abiraterone + Prednisone / Cabazitaxel / Enzalutamide [Standard] If the patient received Abiraterone + Prednisone prior to Docetaxel chemotherapy, they should be offered Cabazitaxel or Enzalutamide | A/B/A                |
| Index Patient 6      | Patients who were benefitting at the time of discontinuation (due to reversible side effects) of Docetaxel chemotherapy | Ketconazole + Steroid [Option] | C                    |
| Index Patient 6      | Patients with symptoms from bony metastases and without known visceral disease | $^{223}$Ra(Radium) [Standard] | B                    |
| Bone Health          | Patients with fractures and skeletal related events to CRPC | Preventative treatment (e.g. supplemental calcium, vitamin D) [Recommendation] | C                    |
| Bone Health          | mCRPC patients with bony metastases | Denosumab or Zoledronic acid as preventative treatment for skeletal related events [Option] | C                    |

2. Canadian Urological Association-Canadian Urologic Oncology Group (12) (Table 4).

3. The guideline proposed by Asian Oncology Summit (13) (Table 5).

4. Spanish Oncology Genitourinary Group (14,15) (Table 6).

5. National Institute for Health and Care Excellence (NICE) (16–20) (Table 7).

6. European Association of Urology (22–24) (Table 8).

7. Saudi Oncology Society and Saudi Urology Association (25) (Table 9).

8. The US National Comprehensive Cancer Network (26) (Table 10).

NCCN Clinical Practice Guidelines in Oncology are used extensively in many health care systems even in low and middle-income countries. The NCCN Framework™ has established to define applicable treatment pathways that are suited with available resources. The categories of contexts are defined as basic, core, and enhanced levels. In this paper, the recommendations for systems with basic level of resources are presented. “Basic Resources” is defined as a level which “includes essential services needed to provide basic minimal standard of care” (27).

### Cytotoxic Medicines

**Docetaxel**

The phase 3 TAX327 study compared docetaxel+prednisone versus mitoxantrone plus prednisone, and the results showed 2-4 month median prolongation in survival (HR 0.76, 95% CI 0.62–0.94; $p = 0.009$). Quality of life was measured using FACT-P tool in more than 800 patients and the score was also significantly
Table 4. Canadian Urological Association-Canadian Urologic Oncology Group (12).

| CRPC type       | Patient situation     | Recommendation                                                                 | Level/ Grade |
|-----------------|-----------------------|--------------------------------------------------------------------------------|--------------|
| Non-metastatic  | Rising PSA            | No approved regimen and no standard of care exists. Discontinuation of AA therapy should be considered if patients are receiving these agents. Secondary hormonal treatments (excluding Abiraterone or Enzalutamide) may be attempted. | 3/C          |
| Metastatic      | With symptoms         | Introduction of, or changes to, a first-generation AA or the use of corticosteroids with or without Ketoconazole | 3/C          |
|                 | without symptoms or minimally symptomatic | Abiraterone acetate 1000 mg/day + Prednisone 5 mg bid is recommended as first-line therapy | 1/A          |
|                 |                       | Enzalutamide 160 mg/day is recommended as first-line therapy                      | 1/A          |
|                 |                       | Treatment with Docetaxel 75 mg/m² q3W + 5 mg oral Prednisone bid                 | 1/A          |
|                 |                       | Treatment with Docetaxel 75 mg/m² q3W + 5 mg oral Prednisone bid is recommended | 1/A          |
|                 |                       | For patients with pain due to bone metastases and who do not have visceral metastases 223Ra(Radium) q4W for 6 cycles is recommended | 1/A          |
|                 |                       | For patients who cannot receive or refused Docetaxel, combination of Abiraterone acetate 1000 mg/day + Prednisone 5 mg bid or Enzalutamide 160 mg/day should be considered as first-line therapy (Expert opinion) |            |
|                 |                       | Cabazitaxel (25 mg/m²) + Prednisone (5 mg/day)                                  | 1/A          |
|                 |                       | Abiraterone acetate (1000 mg per day) + Prednisone (5 mg bid)                   | 1/A          |
|                 |                       | Enzalutamide (160 mg/day)                                                      | 1/A          |
|                 |                       | 223Ra(Radium) q4W for 6 cycles                                                  | 1/A          |
|                 |                       | For palliative pain relief Mitoxantrone + Prednisone may be offered (Grade C). | (Expert Opinion) |
|                 |                       | Patients with CRPC and bone metastases Denosumab (120 mg subcutaneous) or Zoledronic acid (4 mg IV) q4W, along with daily calcium and vitamin D supplementation | 1/A          |

improved with docetaxel specifically in prostate-specific subscale (28). The phase 3 SWOG-9916 trial compared docetaxel+estramustine with mitoxantrone+prednisone. The median overall survival was longer in the docetaxel group than in the group given mitoxantrone and prednisone (17.5 months vs. 15.6 months, \( P = 0.02 \)) but pain relief was similar in both groups. High grade neutropenic fevers, nausea and vomiting, and cardiovascular events were more common among patients receiving docetaxel. (29). An extended survival analysis of TAX324 trial proved that
Guidelines for Castrate-Resistant Prostate Cancer

Table 5. Asian Oncology Summit (13).

| CRPC type        | Patient situation                      | Recommendation                                                                 |
|------------------|----------------------------------------|--------------------------------------------------------------------------------|
| Non-metastatic   | Rising PSA                             | Non-steroidal Anti-Androgens / Ketoconazole                                  |
|                  |                                        | Docetaxel (as an standard first-line therapy)                               |
|                  |                                        | Docetaxel + Prednisone or Mitoxantrone + Prednisone can be used             |
| Metastatic       | Progression after Docetaxel-based chemotherapy | Cabazitaxel as an cytotoxic agents                                           |
|                  |                                        | Abiraterone acetate (it is 10 times more potent than Ketoconazole in this regard) |
|                  |                                        | Concurrent Prednisone should be considered                                    |
|                  |                                        | Enzalutamide, $^{223}$Ra (Radium) and sipuleucel-T                          |

Palliative approaches

| Bone protection | To reduce skeletal-related events In patients with metastatic CRPC, Zoledronate and denosumab should be used. |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| Chemotherapy    | In palliating metastatic CRPC patients Mitoxantrone + Prednisone is effective.                           |
|                 | Radionuclide Therapy by the strontium ($^{89}$Sr) as a calcium mimetic preferentially taken into sites of osteoblastic disease can be used. |
|                 | Palliative surgical interventions such as channel transurethral resection of prostate or ureteric stenting can be used. |

For countries with enhanced level of resources, palliative chemotherapy with Docetaxel and Cabazitaxel, and Bone protection with Zoledronic acid or Denosumab are recommended. Third-line hormone therapy—e.g., abiraterone, Enzalutamide, or Ketoconazole and Bone-seeking α-particle therapy or radioisotope therapy and Palliative chemotherapy with Docetaxel and Cabazitaxel, and Bone protection with Zoledronic acid or Denosumab are recommended for countries with maximum level of resources(13).

hat survival of men with mCRPC is significantly longer after treatment with docetaxel+prednisone than with mitoxantrone+prednisone arm. Median survival time was 19.2 months (95% CI, 17.5 to 21.3 months) in the docetaxel arm and 16.3 months (95% CI, 14.3 to 17.9 months) in the mitoxantrone group. More patients survived ≥ 3 years in the docetaxel-receiving patients (16.6% -18.6%) compared with the mitoxantrone arm (13.5%) (30).

In Cochrane review of 47 RCTs on chemotherapy for hormone resistant PCA patients, 6929 patients were included. Drug categories included in this review were estramustine, 5-fluorouracil, cyclophosphamide, doxorubicin, mitoxantrone, and docetaxel. Although the improvement was less than 2.5 months, only docetaxel studies reported a significant improvement in overall survival compared to best standard of care. The mean percentage of patients achieving at least a 50% reduction in PSA compared to baseline was 48% with estramustine, 20% with 5-fluorouracil, 33% with mitoxantrone, 52% with docetaxel and 50% with the only one study on doxorubicin. Pain relief was reported in 35% to 76% of patients receiving either single agents or combination regimens. All cytotoxic treatments were associated with toxicity including mainly myelosuppression, gastrointestinal and cardiac toxicities, neuropathy, and alopecia (31).

**Cabazitaxel**

In the open-label randomized phase 3 TROPIC trial, 755 men with mCRPC who had received but failed to previous docetaxel therapy, were randomized to receive either 12 mg/m2 mitoxantrone along with 10 mg oral prednisone or 25 mg/m2 cabazitaxel along with prednisone. In the cabazitaxel group median survival was 15·1 months (95% CI 14·1–16·3) versus 12·7 months (11·6–13·7) in the mitoxantrone group.
Table 6. Spanish Oncology Genitourinary Group (14,15).

| CRPC type                        | Patient situation               | Recommendation                                                                 | Level/ Grade |
|----------------------------------|---------------------------------|-------------------------------------------------------------------------------|--------------|
| Without metastases or symptoms   | With rising PSA                 | LHRH analogs should be continued in patients with CRPC                        | 3/C          |
|                                  | Antiandrogen withdrawal         | Anti-androgen withdrawal should be considered in patients with CRPC (except in symptomatic patients or in patients who have a rapid and aggressive progression). | 2b/B         |
|                                  | As an option Ketoconazole + Hydrocortisone and Anti-androgen withdrawal in asymptomatic CRPC produces a better response than Anti-androgen withdrawal alone. |                                                               | 2b/B         |
| Metastatic CRPC                  | Asymptomatic or minimally symptomatic patients | Abiraterone for patients without visceral metastases and previously untreated with chemotherapy | 1b/A         |
|                                  | Symptomatic patient and/or with visceral metastases | Docetaxel (75 mg/m² q3W) + Prednisone (5 mg bid) as a standard first-line chemotherapy | 1a/A         |
|                                  | Asymptomatic patients with mCRPC might be treated with the same Docetaxel schedule, particularly if additional factors of poor prognosis are present |                                                               | 1a/A         |
| Patients who progress after Docetaxel chemotherapy | Docetaxel rechallenge should be used only for patients who progressed after Docetaxel response and who did not experience any severe toxicity. |                                                               | -            |
| Metastatic CRPC                  | Patients who progress after Docetaxel chemotherapy | In patients with symptomatic bone metastases and without visceral metastases, after Docetaxel or in those patients who are not eligible for chemotherapy 223Ra (Radium) is a reasonable treatment option. | 1b/A         |
|                                  | Treatment with Abiraterone should be considered for patients with mCRPC following progression with Docetaxel |                                                               | 1b/A         |
|                                  | Cabazitaxel should be considered for the treatment of patients with mCRPC with progressive disease after Docetaxel-based treatment |                                                               | 1b/A         |
|                                  | Alternative treatments after Docetaxel and/or Cabazitaxel and/or Abiraterone include Docetaxel rechallenge, Mitoxantrone, oral Cyclophosphamide or Vinorelbine chemotherapy |                                                               | 2b/B         |

Patients with bone metastases: Bone targeted therapies

- Although Zoledronic acid, 4 mg IV every 3–4 weeks, and Denosumab, 120 mg SC q4w are recommended for the treatment of bone metastases in patients with CRPC to prevent bone complications, Denosumab has demonstrated superiority over Zoledronic acid in a phase III trial (level of evidence: Ib; grade of recommendation: A).
### Table 7. National Institute for Health and Care Excellence (NICE) (16–20).

| Type of prostate cancer | Recommendation |
|-------------------------|----------------|
| **Metastatic prostate cancer** | Offer bilateral orchietomy to all men with metastatic prostate cancer as an alternative to continuous LHRH agonist therapy. |
| | Anti-androgen monotherapy with Bicalutamide (150 mg) can be offered in men with metastatic PCa who are willing to accept the adverse impact on overall survival and gynecomastia in the hope of retaining sexual function. |
| | Begin androgen deprivation therapy and stop Bicalutamide treatment in men with metastatic PCa who are taking Bicalutamide monotherapy and who do not maintain satisfactory sexual function. |
| **Hormone-relapsed metastatic prostate cancer** | Enzalutamide is recommended, as an option for treating metastatic hormone relapsed prostate cancer, in people who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicated. |
| | Docetaxel as a treatment option for men with hormone-refractory prostate cancer is recommended only if their Karnofsky performance-status score is 60% or more. |
| | 223Ra (Radium) as an option for treating adults with hormone relapsed PCa, symptomatic bone metastases and no known visceral metastases is recommended only if they have had treatment with Docetaxel. |
| | Corticosteroids such as Dexamethasone (0.5 mg daily) as third-line hormonal therapy after androgen deprivation therapy and anti-androgen therapy could be used. |
| | Abiraterone in combination with Prednisone or Prednisolone is recommended as an option for the treatment of mCRPC in adults, only if their disease has progressed on or after one Docetaxel-containing chemotherapy regimen. |
| | Cabazitaxel in combination with Prednisone or Prednisolone is recommended as an option for patients whose disease has progressed during or after Docetaxel chemotherapy, only if: |
| | o has an eastern cooperative oncology group (ECOG) performance status of 0 or 1 |
| | o has had 225 mg/m² or more of Docetaxel |
| | o treatment with Cabazitaxel is stopped when the disease progresses or after a maximum of 10 cycles (whichever happens first) |

### Bone-targeted therapies
- Do not offer Bisphosphonates to prevent or reduce the complications of bone metastases in men with hormone-relapsed PCa.
- Bisphosphonates for pain relief may be considered for men with hormone-relapsed PCa when other treatments (including analgesics and palliative radiotherapy) have failed. Choose the oral or IV route of administration according to convenience, tolerability, and cost.
- Strontium-89 should be considered for men with hormone-relapsed PCa and painful bone metastases, especially those men who are unlikely to receive myelosuppressive chemotherapy.

Marketing authorization for sipuleucel-T was withdrawn on 19 May 2015 (21).

The hazard ratio of death for men treated with cabazitaxel was 30% lower compared with mitoxantrone cohort (95% CI 0.59–0.83, p < 0.0001) and median progression-free survival was 1.4 months higher in the cabazitaxel group. The incidence of clinically important adverse events were significantly higher with cabazitaxel compared to mitoxantrone group (neutropenia [82% vs. 58%], diarrhea [6% vs < 1%], febrile neutropenia 8% vs. 1%) (32).

To assess the safety profile and health related quality of life for mCRPC patients treated with cabazitaxel, 112 patients from 12 cancer centers in UK were planned to receive cabazitaxel for
### Table 8. European Association of Urology (22–24)

| Treatment of CRPC | Recommendation |
|-------------------|----------------|
| First-line treatment | Abiraterone acetate + Prednisone is approved for treatment of asymptomatic and mildly symptomatic mCRPC patients |
| | Docetaxel + Prednisone is also recommended as first line therapy for CRPC The most appropriate indication for chemotherapy might be the clinical scenario of symptomatic or extensive metastases, rapid PSA DT, high Gleason score, or short-term response to primary ADT |
| Second-line treatment | Docetaxel rechallenge for patients who might be good candidates for re-exposure |
| | Abiraterone acetate + Prednisone for progressive mCRPC patients who failed Docetaxel-based chemotherapy. |
| | Enzalutamide with 10 times greater affinity to the AR relative to Bicalutamide |
| Bone-targeting and bone-metastasis targeting agents | Zoledronic acid or Denosumab (The median time to first bone metastases will significantly be prolonged by denosumab). |

Currently, there is lack of evidence on a specific sequence of therapy. Therefore, physicians should adhere to the inclusion criteria of the various clinical trials when treating real-world patients with CRPC. Furthermore, the EAU guideline panel on PCa believes that any patient with PCa and especially CRPC is on a clinical trial.

### Table 9. Saudi Oncology Society and Saudi Urology Association (25).

| CRPC type | Patient situation | Recommendation |
|-----------|-------------------|----------------|
| Non-metastatic | Patients who were on LHRH antagonist/agonists | These patients should continue LHRH antagonist/agonists indefinitely. |
| | With rising PSA | Secondary hormonal manipulations may be offered by either adding a Nonsteroidal anti androgen, Antiandrogen withdrawal, Ketoconazole, Steroids, diethylstilbestrol, or other estrogens |
| | Asymptomatic | Abiraterone with Prednisone, systemic chemotherapy, or secondary hormonal manipulations (adding a non-steroidal antiandrogen, or antiandrogen withdrawal) |
| | Symptomatic | Abiraterone + Prednisone (only in mildly symptomatic patients) or systemic chemotherapy. |
| Metastatic | patients with performance status 0-2 (by Eastern Cooperative Oncology Group scale) | Systematic chemotherapy in the form of Docetaxel + Prednisone should be offered only to these patients |
| | Patients who fail Abiraterone | Docetaxel + Prednisone. |
| | Patients who fail Docetaxel | Cabazitaxel with Prednisone, Abiraterone acetate (if not received in chemo-naïve setting), or Enzalutamide. Patients who have disease limited to the bone can also be offered alpharadin (Radium 223) in addition. |
| | Patients with bony metastases | Denosumab therapy q4w (if not available Zoledronic acid can be given) |
### Table 10. The US National Comprehensive Cancer Network (26).

| CRPC type                  | Patient situation | Recommendation                                                                                                                                 |
|----------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| without Signs of Metastasis| -                 | Secondary hormone therapy (anti-androgen, anti-androgen withdrawal, corticosteroid, Ketoconazole with or without hydrocortisone, diethylstilbestrol or other estrogen) for patients with PSADT less than 10 months. Anti-androgen withdrawal should be offered to progressive patients while on combined androgen blockade. |
| Bone metastases            |                   | Zoledronic Acid or Denosumab is recommended for patients without visceral metastases, Radium-223 as a category 1 option to treat symptomatic bone metastases is recommended. |
| Asymptomatic or Minimally Symptomatic |                   | Zoledronic Acid or Denosumab is recommended for patients without visceral metastases, Radium-223 as a category 1 option to treat symptomatic bone metastases is recommended. |
| No Visceral Metastases     |                   | Systemic radiotherapy using Samarium-153 or Strontium-89 for patients that the tumor does not respond to palliative chemotherapy or systemic analgesia and the patient is not a candidate for EBRT. |
| Metastatic                 |                   | Sipuleucel-T is recommended for patients with good performance level (ECOG 0-1), estimated life expectancy more than 6 months and no liver metastases. |
| Visceral Metastases        |                   | Docetaxel + Prednisone can be used in asymptomatic patients when rapid progression or visceral metastases occur. |
| Progression after Enzalutamide or Abiraterone |                   | Docetaxel + Prednisone is the first line therapy for symptomatic metastatic patients (The addition of Estramustine is not recommended because it does not enhance efficiency and increases side effects). |
| Post Cabazitaxel           |                   | Enzalutamide is another category 1 recommendation |
| Progression after Docetaxel |                   | Abiraterone is category 2 recommendation because of lack evidence in these patients. |
| Post Cabazitaxel           |                   | Mitoxantrone is an option for patients who cannot tolerate Docetaxel. |

Some explanations about categorizations of evidences and levels of recommendations by guidelines are prepared in a supplementary file which is available at the journal webpage for this paper.

---

10 cycles. These patients had received docetaxel but showed disease progression before starting cabazitaxel. QoL was recorded at alternate cycles using the EQ-5D-3L questionnaire and visual analogue scale (VAS). Both QoL and VAS scores were improved from 0.7 to about 0.8 but no statistical analysis was performed to prove the significance (33).
Anti-Androgens

Abiraterone Acetate

The efficacy of abiraterone acetate was proved in two landmark controlled trials COU-AA-301 and COU-AA-302 in which abiraterone was tested on mCRPC patients with or without prior docetaxel therapy respectively.

The COU-AA-301 study enrolled 1195 patients at 147 sites in 13 countries. Eligible patient had mCRPC progressing after docetaxel. Patients received either 1000 mg abiraterone acetate once a day plus 5 mg prednisone BD or placebo plus prednisone. The primary endpoint was overall survival. At median follow-up, patients on abiraterone had 4.4 months higher overall survival than placebo group. Median time to PSA progression was also significantly longer with abiraterone. The most common grade 3–4 adverse events including fatigue, anemia, and bone pain did not differ significantly between groups and the incidence rate ranged between 6-10 percent of patients in both groups (34). In patients with clinically significant pain at baseline, abiraterone acetate resulted in significantly more palliation than prednisone alone (40% of patients vs. 28.8% of patients). Significantly faster palliation (median time to palliation 5-6 months vs. 13-7 months, \( p = 0.0018 \)) of pain intensity was resulted by abiraterone than with prednisone alone. Median time to occurrence of first skeletal-related event was significantly longer (25 months vs. 20.3 months) with abiraterone acetate and prednisone than with prednisone alone (35). Along with the demonstrated survival benefit for abiraterone, HRQoL improvement and delay in HRQoL worsening was likewise in favor of Abiraterone group. Abiraterone resulted in significantly better FACT-P outcomes than prednisone, with the exception of the Social/Family Well-Being (SFWB) subscale. Significant improvements in the FACT-P total score were observed in 48% of patients receiving abiraterone versus 32% of patients receiving prednisone (\( p < 0.0001 \)) in COU-AAA-301 trial (36). Abiraterone acetate provides significant clinical benefit in terms of improvements in OS and PSA response rates, post-docetaxel therapy, in patients either with or without baseline visceral disease (37). In mCRPC patients with previous docetaxel chemotherapy, abiraterone acetate improved patient-reported fatigue and time to fatigue improvement compared with prednisone alone. These results were statistically significant and clinically meaningful (38).

In the COU-AA-302 study, 1088 patients were randomly assigned to receive abiraterone acetate plus prednisone or placebo plus prednisone. The median radiographic progression free survival (PFS) was 16.5 months in abiraterone group and 8.3 months in placebo group (\( P < 0.001 \)). After a median follow-up time of 22.2 months, overall survival was improved significantly with abiraterone. Additionally, abiraterone significantly delayed the initiation of chemotherapy and opiate use compared to prednisone alone (39). Since, PFS in metastatic mCRPC trials has not been defined consistently and has poor association with overall survival (OS), a reproducible quantitative definition of radiographic PFS (rPFS) was tested for association with the primary end point of OS in a COU-AA-302 trial. rPFS was highly consistent and highly associated with OS, providing initial prospective evidence on further developing rPFS as an intermediate end point in mCRPC trials (40). With a median follow-up duration of 27.1 months, rPFS improvement was significantly higher with abiraterone versus prednisone (median: 16.5 vs. 8.2 months; \( p < 0.0001 \)). Abiraterone improved OS (median: 35.3 vs. 30.1 months; \( p = 0.0151 \)) but this survival time did not reach the pre-specified efficacy level (41). Median time to progression to median pain intensity, pain interference with daily activities as well as median time to progression of worst pain were longer with abiraterone vs. prednisone alone. All the differences in time to progression of pain were significant except the latter. Median time to HRQoL score deterioration was also significantly longer in abiraterone group (42). In a subgroup analysis of men aged 75 years and older, abiraterone acetate was proved to have clinical benefit and to be well tolerated in elderly and younger men with chemotherapy naïve mCRPC. The subgroup analysis support the use of abiraterone in elderly patients who may not tolerate other therapeutic options with higher toxicity (43).
Enzalutamide

The efficacy and safety of enzalutamide was established in two large randomized controlled trials which were performed on near 3000 metastatic hormone resistant patients with PCa before and after chemotherapy. The first phase III clinical trial (the AFFIRM study) was published in 2012 presenting mainly the overall survival benefit on the patient post docetaxel therapy. The primary analysis of the other leading clinical trial (the PREVAIL study) was published in 2014 focusing on radiographic progression-free survival and overall survival as co-primary endpoints.

AFFIRM (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was a multi-center phase III RCT on enzalutamide in mCRPC patients who had failed or progressed after chemotherapy. From 156 centers in 15 countries 1199 patents were randomly assigned, in a 2:1 ratio, to receive oral enzalutamide 160 mg/day (800 patients) or placebo (399 patients). The median overall survival was 18.4 months in the enzalutamide cohort versus 13.6 months in the control group (HR: 0.63, \( P < 0.001 \)). Enzalutamide was also significantly superior over placebo in secondary endpoints. In enzalutamide group 50% of patients showed at least 50% reduction in PSA level by 50% versus 2% of patients in placebo group (\( P < 0.001 \)). Quality-of-life response rate defined as at least 10 point improvement in global score of FACT-P was significantly better with enzalutamide (43% vs. 18%, \( P < 0.001 \)). Enzalutamide resulted in about 5.3 months longer time to PSA progression compared to placebo. Radiographic progression-free survival was also longer with enzalutamide (8.3 vs. 2.9 months; hazard ratio, 0.40; \( P < 0.001 \)). Additionally, patients on enzalutamide had lower risk to show the first skeletal-related events (16.7 vs. 13.3 months; hazard ratio, 0.69; \( P < 0.001 \)). Adverse events including fatigue, diarrhea, and hot flashes were more frequent in the enzalutamide group and seizure was reported in 0.6% of patients on enzalutamide (44). Exploratory analysis to assess the efficacy outcomes based on differences in patient characteristics specifically the baseline PSA level in the AFFIRM trial, demonstrated that benefits in overall survival and time to PSA progression with enzalutamide is not related to the baseline disease severity (45). Another post hoc analysis of the AFFIRM trial showed that pain palliation, median time to pain progression and median time to HRQoL score deterioration were significantly improved with enzalutamide versus placebo (46). A post hoc subgroup analysis of elderly patients (≥ 75 years) in the AFFIRM study proved the similar efficacy, safety and tolerability of enzalutamide in both subgroups of younger and older patients (47).

In the PREVAIL trial 1717 patients with metastatic PCa who have not received chemotherapy were randomly assigned in two cohorts to receive either enzalutamide 160 mg/day or placebo. Enzalutamide decreased the rate of radiographic progression-free survival 81% relative to placebo (\( P < 0.001 \)). At the cut-off date 72% of patients in enzalutamide were alive compared to 63% in control group (HR of death: 0.71, \( P < 0.001 \)). Enzalutamide was also significantly superior against placebo in all secondary endpoints including the lag time until the progression to the use of chemotherapy, the time until the first skeletal-related event, a complete or partial soft-tissue response, and the time to PSA progression ratio. The PSA decline of at least 50% was observed in 78% of patients in enzalutamide group vs 3% of control patients (48). HRQoL was assessed using FACT-P and EQ-5D and pain was assessed using Brief Pain Inventory Short Form (BPI-SF) in the PREVAIL study. Median time to deterioration in FACT-P total score was 5.7 months longer compared to placebo and 40% of patients in treatment group versus 23% of control patients reported clinically important improvements in FACT-P total score. Median time to progression in BPI-SF pain at its worst also differed significantly in favor of enzalutamide but it was not clinically meaningful (49).

Immunotherapy

Sipuleucel-T

“Sipuleucel-T is an autologous cellular immunotherapy for asymptomatic/minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC)” (50). Sipuleucel-T is the first vaccine for treatment of which received...
FDA approval (51).

The first phase III trial on sipuleucel-T was a placebo-controlled on 127 patients with asymptomatic mCRPC who randomly received three infusions of sipuleucel-T or placebo twice monthly. The patients were followed for 36 months for survival assessment. Median survival with sipuleucel-T was 25.9 months for and 21.4 months for placebo ($P = 0.01$) with a not significant time to disease progression compared to placebo (11.7 vs. 10 weeks, $P = 0.052$) (52).

The same protocol was performed in another phase III RCT on 512 patient (IMPACT study). The recruited patients had an expected survival of at least 6 months. Patients were recruited since August 2003 until November 2007 and by January 2009, 22% reduction in the risk of death was perceived with sipuleucel-T (HR: 0.78; $P = 0.03$). The medial survival was 25.8 vs. 21.7 months but the time to objective disease progression was similar in both groups. Additional therapies after intervention period included docetaxel use which slightly higher in sipuleucel-T group (57% vs. 50%) and the Kaplan–Meier estimate of the median time to docetaxel use was 1.6 months earlier in treatment group. The most frequent adverse events in sipuleucel-T group included chills, fever, headache, influenza-like syndrome, myalgia, hypertension, hyperhidrosis, and groin pain which most of them were improved within 1-2 days (53).

Radiopharmaceuticals

**Strontium-89 and Samarium-153**

Strontium-89 and Samarium-153 are radioisotopes with β-emitting activity that received U.S. FDA approval for pain relief of bone metastatic CRPC patients (54).

In a phase III randomized trial, strontium-89 with a single dose of 10.8 milicurie was compared to placebo in bony metastatic hormone resistant PCa patients who under treatment with local field radiotherapy. Analysis of the survival did not show any significant difference between strontium-89 and placebo. Progression of pain, which was measured by the number of new sites of pain or the necessity radiotherapy, and the Intake of analgesics for control of pain, decreased significantly in treatment group compared to placebo. Over the first four months, tumor markers including PSA and alkaline phosphatase were also reduced significantly in treatment group. Quality of life in terms of physical activity and pain alleviation showed significant improvement in favor of strontium-89. Hematologic toxicities were significantly higher in treatment group in terms of both white blood cell and platelet levels (55). In a systematic review on clinical trials of strontium-89 in the management of pain in the bony metastatic patients with prostate or breast cancer up to 80% of patients showed pain relief and about 10% got pain free. The severity of hemotoxicity was reported as mild in this review (56). In another phase trial of strontium-89 in patients with bone metastases due to prostate, breast, and other types of cancer, pain was considerably improved in 58% of patients in strontium-89 group following by an improved quality of life (57).

In a phase III randomized trial for the efficacy evaluation of samarium-153 (153 Sm)-lexidronam, also referred as samarium-153 EDTMP, 152 men with CRPC and painful bone metastases were enrolled. Patients in two cohorts received either radioactive samarium-153 at a dose of 1 mCi/Kg or non-radioactive samarium-152 both as lexidronam complex. Statistically significant Improvement on measures of pain compared with control within the first 2 weeks and opioid use reduction at weeks 3 to 4 was reported. The only adverse event relating to samarium was mild and transient bone marrow suppression. WBC and platelet counts recovered to baseline at approximately 8 weeks (58). In a clinical trial on 35 patients with bone metastasis arising from various tumor types, pain palliation was observed 80% of the patients and 54% of them reported substantial or complete pain relief. Moderate myelosuppression was reported in one patient (59).

A comparative trial of strontium-89 and samarium-153 proved that the similar pain relief with both radiopharmaceuticals in both prostate and breast cancer patients. The frequency of severe adverse events were also reported as rare with both comparators (60).

**Radium-223**

Radium-223 chloride formerly known as
alpharadin is a first-in-class α-particle-emitting radiopharmaceutical, which provides survival benefit for patients with hormone-resistant prostatic neoplasm which has spread to the bones (61). Radium-223 is a calcium mimetic element with preferential uptake in bone mineral hydroxyapatite. It targets tumor cells near the areas on new bone formation. Ra223 forms complexes with hydroxyapatite and consequently gets integrated in the bony matrix (62). The novel mechanism of action of Ra223 brings about low rates of hematologic adverse events and makes it a potential treatment option in many of symptomatic mCRPC patients before docetaxel challenge (63). The approval of Ra223 in May 15, 2013 by the U.S. Food and Drug Administration (FDA) was based on a randomized, placebo-controlled, international trial (the “ALSYMPCA” trial) (54).

In the ALSYMCA study, 921 castration resistant patients with two or more bone metastases detected on skeletal scintigraphy and no known visceral metastases were recruited. Patients were randomly assigned to receive either Ra223 or placebo along with best standard care. The patients received six periods of Ra223 with dose of 50 kBq/Kg (1.35 microcurie/Kg) or similar placebo as intravenous injection every four weeks. The planned follow-up time was up to 3 years. At the end of study period, overall survival with Ra223 was 3.6 months longer than with placebo along with 30% lower risk of death (median, 14.9 months vs. 11.3 months; HR: 0.70; \( P < 0.001 \)). Radium-223 also prolonged the time to the first symptomatic skeletal event about 5.6 months relative to placebo (median, 15.6 months vs. 9.8 months; HR: 0.66; \( P < 0.001 \)). The times to increase in alkaline phosphatase level as well as PSA level were also significantly prolonged with Ra223. The proportion of patients who had at last one adverse event were similar in both groups (93% vs 96%) and generally no clinically meaningful differences were observed between cohorts in terms of the frequency of grade 3 or 4 adverse events. The treatment seems to be as safe as placebo but the only one report of grade 5 thrombocytopenia in a patient in the treatment group and considered to be related to Ra223. In terms of HRQoL, a higher proportion of patients in treatment group had a meaningful improvement in the FACT-P total score, during the intervention period (25% vs. 16%, \( P = 0.02 \)) (64). The subgroup analysis of ALSYMCA trial for patients with or without previous docetaxel therapy proved the efficacy of Ra223 in both subgroups in terms of overall survival and most of the secondary endpoints. The safety profile however was in favor of patients without previous docetaxel therapy. Patients in Ra223 group and with previous docetaxel therapy had a higher incidence of grade 3-4 thrombocytopenia (65).

**Bone protecting agents**

Denosumab and Zoledronic Acid

Denosumab was compared with zoledronic acid in phase 3 double blind study in men with CRPC metastatic to the bone with no previous exposure to intravenous bisphosphonate. In this multi-center trial, 1904 patients were randomized to receive either denosumab or zoledronic acid in 1:1 ratio. Patients received 120 mg denosumab subcutaneously plus intravenous placebo, or 4 mg intravenous zoledronic acid along with a subcutaneous placebo, Q 4 weeks. Median time to the first skeletal-related event (considering study duration only) was 20.7 months in denosumab group versus 17.1 months in zoledronic acid group (HR for the first and subsequent skeletal-related events: 0.82, \( p = 0.0002 \) for non-inferiority; \( p = 0.008 \) for superiority). More events of hypocalcaemia occurred in the denosumab group (121 [13%]) than in the zoledronic acid group (55 [6%]; \( P < 0.0001 \)). Osteonecrosis of the jaw occurred infrequently (22 [2%] vs. 12 [1%]; \( p = 0.09 \)). The rate more frequent adverse events including anemia, back pain, decreased appetite, nausea, fatigue, constipation, bone pain, asthenia, arthralgia, severe pain and peripheral edema ranged between 18 to 36 percent in both groups with no significant difference. The incidence rate of any adverse events was 97% in each group in addition to no significant difference in serious and fetal adverse events (about 61.5% and 29.5% respectively). Furthermore, the rate of grade 3 or 4 adverse events (72% vs. 66%) and hypocalcemia (13% vs. 6%) were significantly higher with denosumab (66).
1432 non-metastatic CRPC patients at high risk of bone metastasis, denosumab significantly increased bone-metastasis-free survival (median 29.5 months vs. 25.2 months in placebo group; HR: 0.85, P = 0.028). Denosumab similarly delayed the time to first bone metastasis by 3.7 months (HR 0.84, p = 0.032). Overall survival did not differ between treatment and placebo group significantly. Rates of all adverse events and serious ones were nearly the same in both groups with no significant difference. Osteonecrosis of the jaw (5% vs. 0%) and hypocalcaemia (2% vs. < 1%) were significantly higher with denosumab (67).

In a randomized, placebo-controlled, Phase III trial on 422 patients with CRPC, efficacy, and safety of zoledronic acid was compared with placebo. Zoledronic acid significantly palliated pain compared with placebo at 3, 9, 21, and 24 month. The annual incidence of skeletal-related events was also reduced by 49% with zoledronic acid. In patients without pain at the beginning of the study, zoledronic acid delayed the onset of bone pain compared with placebo (68).

A pooled data analysis was performed on the three landmark double-blind phase III studies comparing denosumab with intravenous zoledronic acid in patients with bone metastases from breast cancer, castration-resistant PCa, or other solid tumors. The onset of moderate or severe pain was 6.5 months with denosumab compared to 4.7 months with zoledronic (HR: 0.83; p < 0.001). There was also 17% risk reduction for overall pain interference with denosumab compared to zoledronic acid. HRQoL score improvement, measured by FACT-G, did not show significant difference between treatments. Fewer patients (Absolute Difference: 0.9%-3.4%; Average Relative Difference: 4.1%) on denosumab experienced clinically important decrease from baseline in FACT-G total score in comparison with patients on zoledronic acid (P = 0.005) (69).

The TRAPEZE Randomized Clinical Trial was designed to determine the clinical effectiveness and cost-effectiveness of the combination of docetaxel, zoledronic acid, and Strontium 89, in CRPC metastatic to the bone in terms of bone symptom palliation and survival prolongation in case of docetaxel. A total of 757 were randomized to receive docetaxel alone or with zoledronic acid, Sr89, or both. Clinical PFS and overall survival was not significantly different with either Sr89 or ZA. Time to skeletal-related events was delayed significantly with zoledronic acid. Strontium-89 combined with docetaxel improved Clinical PFS but did not improve OS, SRE-free interval, or total SREs. Zoledronic acid reduced the risk of symptomatic skeletal events by about 50% (70).

**Discussion**

We reviewed the core guidelines and clinical evidences used in treatment of patients suffering from CRPC. All of them are focusing on clinical efficacy without any economical effectiveness concerns. The pattern of treatments and selection of interventions are based on countries' regulation and health sector resources.

This research found that in the field of Anti-Androgens, both enzalutamide and abiraterone are recommended in different stages of treatment by all of the guidelines. Clinical evidences showed their superior efficacy in comparison with their alternatives. These medicines are not accessible in Iran routinely, because of not listing in Iran Drug List.

Focusing on cytotoxic medicines, both docetaxel and cabazitaxel are recommended or suggested in different sequences of disease management. Although docetaxel is available in Iranian market, the newer alternative, cabazitaxel, is an expensive option in cases with treatment failure and it is not still officially accessible by patients.

Sipuleucel-T, which has received FDA approval for CRPC is also recommended by some guidelines but it is not accessible in many countries yet. One of the major hurdles for availability and accessibility of such treatments is that technological infrastructure behind the use of them is very costly and limited in many contexts.

Radium-223 is strictly recommended in patients with bony metastases and its efficacy and safety is proofed through clinical trials. This option is not also available in Iran because of similar limitation which was mentioned for immunotherapy. However, the less effective and
more hazardous alternative, samarium-153, is available in some nuclear medicine centers of Iran.

Finally, in the field of bone protecting agents, denosumab and zoledronic acid are recommended similarly by different guidelines. Although, the level of efficacy slightly favors denosumab, but many guideline except Saudi guideline do not recommend one option against the other. Zoledronic acid is available in Iran in generic and branded forms.

**Conclusion**

Considering the recommendations of various treatment guidelines, it is obvious that some critical treatment options including enzalutamide, abiraterone, cabazitaxel, and Radium-223 which are recommended in all treatment guidelines should be available and accessible in Iran with average level of health-resources. However, there is also a need for economic evaluations in local setting which allows for selecting the cost-effective options, finding the value-based price, and rational allocation of resources. This recommendation is due to the ration of priority setting in health care and the need for equitable access of the majority of patients in all disease categories to their appropriate treatments.

The economic evaluation and budget impact analyses of health technologies and especially pharmaceuticals are currently performed before registration of new entities in Iran. These evaluations have been mandatory for registering the new molecules in Iran formulary list since 2014. The Clinical and pharmacoeconomic assessments are the first steps before registration and market authorization and launching in the pharmaceutical market of Iran. During this process, all medicines are evaluated according to their clinical efficacy and economical effectivenes based on scientific evidences and by scientific committees. After these approvals, the pharmaceutical products have to be registered through issuing CTD (Common Technical Document) to the IFDA (Iran Food and Drug Administration). Consequently, in the pharmaceutical registration process, all technical aspects as well as quality, safety, efficacy, and price are evaluated by expert committees of IFDA.

**Conflict of Interest**

The authors declared no conflict of interest

**References**

(1) Thun MJ, DeLancey JO, Center MM, Jamel A, and Ward EM. The global burden of cancer: priorities for prevention. *Carcinogenesis* (2010): 31: 100–110.
(2) Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, and Jamel A. Global cancer statistics, 2012. *CA. Cancer J. Clin.* (2015): 65: 87–108.
(3) GLOBOCAN. Estimated Number of Prostate Cancer Patients in Iran in 2015.
(4) Atabi F, Mousavi Gargari SL, Hashemi M, and Yaghmaei P. Doxorubicin Loaded DNA Aptamer Linked Myristilated Chitosan Nanogel for Targeted Drug Delivery to Prostate Cancer. *Iran. J. Pharm. Res.* IJPR (2017): 16: 35–49.
(5) *Cancer Registry Book*. Iran Ministry of Health, Office of Cancer (2009).
(6) Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, Allen C, Hansen G, Woodbrooke R, Wolfe C, Hamadeh RR, Moore A, Werdecker A, Gessner BD, Te Ao B, McMahon B, Karimkhani C, Yu C, Cooke GS, Schwobel DC, Carpenter DO, Pereira DM, Nash D, Kazi DS, De Leo D, Plass D, Ukwaja KN, Thurston GD, Yun Jin K, Simard EP, Mills E, Park E-K, Catalá-López F, deVeber G, Gotay C, Khan G, Hosgood HD, Santos IS, Leasher JL, Singh J, Leigh J, Jonas JB, Sanabria J, Beardsley J, Jacobsen KH, Takahashi K, Franklin RC, Ronfani L, Montico M, Naldi L, Tonelli M, Geleijse J, Petzold M, Shrine MG, Younis M, Yonemoto N, Breitborde N, Yip P, Pournak P, Lotfuho PA, Esteghamati A, Hankey GJ, Ali R, Lunevicius R, Malekzadeh R, Dellavalle R, Weintraub R, Lucas R, Hay R, Rojas- Rueda D, Westerman R, Sepanlou SG, Nolte S, Paten S, Weichenthal S, Aberra SF, Fereshtehnejad S-M, Shiue I, Driscoll T, Vasankari T, Alsharif U, Rahimi-Movaghar V, Vlassov V V., Marcenes WS, Mekonnen W, Melaku YA, Yano Y, Artaman A, Campos I, MacLachlan J, Mueller U, Kim D, Trillini M, Eshraihi B, Williams HC, Shibuya K, Dandonia R, Murthy K, … L E. The Global Burden of Cancer 2013. *JAMA Oncol.* (2015): 1: 505.
(7) Saad F, and Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. *J. Can. Urol. Assoc.* (2010): 4: 380–84.
(8) Acar O, Esen T, and Lack NA. New therapeutics to treat castrate-resistant prostate cancer. *ScientificWorldJournal*. (2013): 2013: 379641.
(9) Engel-Nitz NM, Alemayehu B, Parry D, and Nathan F. Differences in treatment patterns among patients with castration-resistant prostate cancer treated by...
oncologists versus urologists in a US managed care population. *Cancer Manag. Res.* (2011): 3: 233–45.

(10) Cookson MS, Roth BJ, Dahm P, Engstrom C, Freedland SJ, Hussain M, Lin DW, Lowrance WT, Murad MH, Oh WK, Penson DF, and Kibel AS. Castration-resistant prostate cancer: AUA Guideline. *J. Urol.* (2013): 190: 429–38.

(11) Cookson MS, Lowrance WT, Murad MH, and Kibel AS. Castration-resistant prostate cancer: AUA guideline amendment. *J. Urol.* (2015): 193: 491–99.

(12) Saad F, Chi KN, Finelli A, and Hotte SJ. The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC). (2015): 9.

(13) Williams S, Chiong E, Lojanapiwat B, Umbas R, and Akaza H. Management of prostate cancer in Asia: resource-stratified guidelines from the Asian Oncology Summit 2013. *Lancet. Oncol.* (2013): 14: e234–34.

(14) Climent MA, León-Mateos L, González del Alba A, Pérez-Valderrama B, Méndez-Vidal MJ, Mellado B, Arranz JA, Sánchez-Hernández A, Cassinello J, Olmos D, and Carles J. Updated recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. *Crit. Rev. Oncol. Hematol.* (2015): 96: 308–18.

(15) Climent MA, Piulats JM, Sanchez-Hernandez A, Arranz JA, Cassinello J, Garcia-Donas J, Gonzalez del Alba A, Leon-Mateos L, Mellado B, Mendez-Vidal MJ, and Perez-Valderrama B. Recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer. *Crit. Rev. Oncol. Hematol.* (2012): 83: 341–52.

(16) Prostate cancer: diagnosis and management (Clinical Guideline 175). National Institute for Health and Care Excellence (2014)https://www.nice.org.uk/guidance/cg175/chapter/1-Recommendations (accessed 24 Sep 2016).

(17) NICE. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen. NICE (2016)

(18) Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. National Institute for Health and Care Excellence (2016)https://www.nice.org.uk/guidance/TA391/chapter/1-Recommendations (accessed 24 Sep 2016).

(19) Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. National Institute for Health and Care Excellence (2016)https://www.nice.org.uk/guidance/TA377/chapter/1-Recommendations (accessed 24 Sep 2016).

(20) Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases. National Institute for Health and Care Excellence (2016)https://www.nice.org.uk/guidance/TA376 (accessed 24 Sep 2016).

(21) Technology appraisal guidance [TA332]: sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer. (2015).

https://www.nice.org.uk/guidance/ta332 (accessed 24 Sep 2016).

(22) Mottet N, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, Schmid HP, van der Kwast T, Wiegel T, Zattoni F, and Heidenreich A. [EAU guidelines on prostate cancer. Part II: treatment of advanced, relapsing, and castration-resistant prostate cancer]. *Actas. Urol. Esp.* (2011): 35: 565–79.

(23) Heidenreich A, Bolla M, Joniau S, Mason MD, Matveev V, Mottet N, Schmid H, Kwast TH Van Der, Wiegel T, and Zattoni F. Guidelines on Prostate Cancer. Update (2011): 53: 31–45.

(24) Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, Mason M, Matveev V, Wiegel T, Zattoni F, and Mottet N. EAU Guidelines on Prostate Cancer. Part II: Treatment of Advanced, Relapsing, and Castration-Resistant Prostate Cancer. *Eur. Urol.* (2014): 65: 467–79.

(25) Rabah D, Abusamara A, Ahmad I, Alghamdi A, Alkhaeteeb S, Alkussa H, Almansour M, Alolayan A, Alotaibh M, Alsharm A, Bazarbashi S, Mahmood R, and Murshid E. Saudi oncology society and urology urology association combined clinical management guidelines for prostate cancer. *Urol. Ann.* (2014): 6: 278.

(26) NCCN Guideline on Prostate Cancer (Basic Resources). (2016)https://www.nccn.org/professionals/physician_gls/f_guidelines.asp

(27) NCCN Framework for Resource Stratification of NCCN Guidelines (NCCN Framework™). https://www.nccn.org/framework/ (accessed 24 Sep 2016).

(28) Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, and Eisenberger MA. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* (2004): 351: 1502–12.

(29) Petrylak DP, Tangen CM, Hussain MHA, Lara Jr PN, Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M, Benson MC, Small EJ, Raghavan D, and Crawford ED. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N. Engl. J. Med.* (2004): 351: 1513–20.

(30) Berthold DR, Pond GR, Soban F, de Wit R, Eisenberger M, and Tannock IF. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer: updated survival in the TAX 327 study. *J. Clin. Oncol.* (2008): 26: 422–45.

(31) Shelley M, Harrison C, Coles B, Stafforth J, Wilt T, and Mason M. Shelley M. Chemotherapy for hormone-refactory prostate cancer. In: Shelley M, editor. *Cochrane Database of Systematic Reviews.* John Wiley & Sons, Ltd: Chichester, UK (2006) doi:10.1002/14651858.CD005247.pub2

(32) de Bonos JS, Oudard S, Ozgueroğlu M, Hansen S, Machiels J-P, Kocak I, Gravis G, Bodrogi I, Mackenzie MJ, Shen L, Roessner M, Gupta S, and Sartor AO. Prednisone plus cabazitaxel or mitoxantrone
for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet (London, England)* (2010): 376: 1147–54.

(33) Bahl A, Masson S, Malik Z, Birtle AJ, Sundar S, Jones RJ, James ND, Mason MD, Kumar S, Bottomley D, Lydon A, Chowdhury S, Wylie J, and de Bono JS. Final quality of life and safety data for patients with metastatic castration-resistant prostate cancer treated with cabazitaxel in the UK Early Access Programme (EAP) (NCT01254279). *BJU Int.* (2015): 116: 880–87.

(34) Fizazi K, Scher HI, Molina A, Logothetis CJ, Chi KN, Jones RJ, Staffurth JN, North S, Vogelzang NJ, Saad F, Mainwaring P, Harland S, Goodman OBJ, Sternberg CN, Li JH, Kheoh T, Haqq CM, and de Bono JS. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet. Oncol.* (2012): 13: 983–92.

(35) Logothetis CJ., Basch E., Molina A., Fizazi K., North SA., Chi KN., Jones RJ., Goodman OB., Mainwaring PN., Sternberg CN., Efstathiou E., Gagnon DD., Rothman M., Hao Y., Liu CS., Kheoh TS., Haqq CM., Scher HI., and de Bono JS. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data from the COU-AA-301 randomised tri. *Lancet. Oncol.* (2012): 13: 1210–17.

(36) Harland S., Staffurth J., Molina A., Hao Y., Gagnon DD., Sternberg CN., Cell a. Fizazi K., Logothetis CJ., Kheoh T., Haqq CM., De Bono JS., and Scher HI. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. *Eur. J. Cancer* (2013): 49: 3648–57.

(37) Goodman OBJ, Flagg TW, Molina A, Mulders PFA, Fizazi K, Suttman H, Li J, Kheoh T, de Bono JS, and Scher HI. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. *Prostate Cancer Prostatic Dis.* (2014): 17: 34–39.

(38) Sternberg CN, Molina A, North S, Mainwaring P, Fizazi K, Hao Y, Rothman M, Gagnon DD, Kheoh T, Haqq CM, Cleeland C, de Bono JS, and Scher HI. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. *Ann. Oncol.* (2013): 24: 1017–25.

(39) Ryan CJ, Smith MR, de Bono JS, Molina A, Logothetis CJ, de Souza P, Fizazi K, Mainwaring P, Piulats JM, Ng S, Carles J, Mulders PFA, Basch E, Small EJ, Saad F, Schrijvers D, Van Poppel H, Mukherjee SD, Suttman H, Gerritsen WR, Flagg TW, George DJ, Yu EY, Efstathiou E, Pantuck A, Winquist E, Higano CS, Taplin M-E, Park Y, Kheoh T, Griffin T, Scher HI, and Rathkopf DE. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N. Engl. J. Med.* (2013): 368: 138–48.

(40) Morris MJ, Molina A, Small EJ, de Bono JS, Logothetis CJ, Fizazi K, de Souza P, Kantoff PW, Higano CS, Li J, Kheoh T, Larson SM, Matheny SL, Naini V, Burzykowski T, Griffin TW, Scher HI, and Ryan CJ. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. *J. Clin. Oncol.* (2015): 33: 1356–63.

(41) Rathkopf DE, Smith MR, de Bono JS, Logothetis CJ, Shore ND, de Souza P, Fizazi K, Mulders PFA, Mainwaring P, Hainsworth JD, Beer TM, North S, Fradet Y, Van Poppel H, Carles J, Flagg TW, Efstathiou E, Yu EY, Higano CS, Taplin M-E, Griffin TW, Todd MB, Yu MK, Park YC, Kheoh T, Small EJ, Scher HI, Molina A, Ryan CJ, and Saad F. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur. Urol.* (2014): 66: 815–25.

(42) Basch E, Autio K, Ryan CJ, Mulders P, Shore N, Kheoh T, Fizazi K, Logothetis CJ, Rathkopf D, Smith MR, Mainwaring PN, Hao Y, Griffin T, Li S, Meyers ML, Molina A, and Cleeland C. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: Patient-reported outcome results of a randomised phase 3 trial. *Lancet Oncol.* (2013): 14: 1193–99.

(43) Smith MR, Rathkopf DE, Mulders PFA, Carles J, Van Poppel H, Li J, Kheoh T, Griffin T, Molina A, and Ryan CJ. Efficacy and Safety of Abiraterone Acetate in Elderly (75 Years or Older) Chemotherapy Naive Patients with Metastatic Castration Resistant Prostate Cancer. *J. Urol.* (2015): 194: 1277–84.

(44) Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flagg TW, Flechon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, and de Bono JS. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* (2012): 367: 1187–97.

(45) Saad F, de Bono J, Shore N, Fizazi K, Loriot Y, Hirmand M, Franks B, Haas GP, and Scher HI. Efficacy outcomes by baseline prostate-specific antigen quartile in the AFFIRM trial. *Eur. Urol.* (2015): 67: 223–30.

(46) Fizazi K, Scher HI, Miller K, Basch E, Sternberg CN, Cella D, Forer D, Hirmand M, and de Bono JS. Effect of enzalutamide on time to first skeletal-related event, pain, and quality of life in men with castration-resistant prostate cancer: results from the randomised, phase 3 AFFIRM trial. *Lancet. Oncol.* (2014): 15: 1147–56.

(47) Sternberg CN, de Bono JS, Chi KN, Fizazi K, Mulders P, Cerbone L, Hirmand M, Forer D, and Scher HI. Improved outcomes in elderly patients with metastatic castration-resistant prostate cancer treated with the androgen receptor inhibitor enzalutamide: results from the phase III AFFIRM trial. *Ann. Oncol.* (2014): 25: 429–34.
(48) Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS, Iversen P, Bhattacharya S, Carles J, Chowdhury S, Davis ID, de Bono JS, Evans CP, Fizazi K, Joshua AM, Kim C-S, Kimura G, Mainwaring P, Mansbach H, Miller K, Noonenberg SB, Perabo F, Phung D, Saad F, Scher HI, Taplin M-E, Venner PM, and Tombal B. Effect of enzalutamide in metastatic prostate cancer before chemotherapy. *N. Engl. J. Med.* (2014): 371: 424–33.

(49) Loriot Y, Miller K, Sternberg CN, Fizazi K, de Bono JS, Chowdhury S, Higano CS, Noonenberg S, Holmstrom S, Mansbach H, Perabo FG, Phung D, Ivancescu C, Skalisa K, m, Beer TM, and Tombal B. Effect of enzalutamide on health-related quality of life, pain, and skeletal-related events in asymptomatic and minimally symptomatic, chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (PREVAIL): Results from a randomised, phase 3 trial. *Lancet Oncol.* (2015): 16: 509–21.

(50) George DJ, Nabhan C, DeVries T, Whitmore JB, and Gomella LG. Survival Outcomes of Sipuleucel-T Phase III Studies: Impact of Control-Arm Cross-Over to Salvage Immunotherapy. *Cancer Immunol. Res.* (2015): 3: 1063–69.

(51) Plosker GL. Sipuleucel-T. Drugs (2011): 71: 101–8.

(52) Small EJ, Schellhammer PF, Higano CS, Redfern CH, Nemunaitis JJ, Valone FH, Verjée SS, Jones LA, and Herschberg RM. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *J. Clin. Oncol.* (2006): 24: 3089–94.

(53) Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, Redfern CH, Ferrari AC, Dreicer R, Sims RB, Xu Y, Frohlich MW, and Schellhammer PF. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N. Engl. J. Med.* (2010): 363: 411–22.

(54) Klutetz PG, Pierce W, Maher VE, Zhang H, Tang S, Song P, Liu Q, Haber MT, Leutzeinger EE, Al-Hakim A, Chen W, Palmyth T, Abebachew E, Sridhara R, Ibrahim A, Justice R, and Pazdur R. Radium Ra 223 dichloride injection: U.S. Food and Drug Administration drug approval summary. *Clin. Cancer Res.* (2014): 20: 9–14.

(55) Porter AT, McEwan AJB, Powe JE, Reid R, McGowan DG, Lukhaa K, Saltyanarayana JR, Yamashita VN, Thomas GM, Erlich LE, Crook J, Gulenchyn KY, Kong KE, Wosolowski C, and Yardley J. Results of a randomized phase-II trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int. J. Radiat. Oncol.* (1993): 25: 805–13.

(56) Robinson RG, Preston DF, Schiebelbein M, and Baxter KG. Strontium 89 therapy for the palliation of pain due to osseous metastases. *JAMA* (1995): 274: 420–24.

(57) Kimura Y, Hamamoto K, Furudate M, Fukuda H, Shishido F, Endo K, Yui N, Kusakabe K, Suzuki K, Kawakami K, Ishii K, Koizumi K, Yokoyama K, Hisada K, Nakagawa T, Kasagi K, Konishi J, Ichiya Y, Masuda K, Nakajo M, Kubo A, and Torizuka K. [Effectiveness of the radioactive strontium (89Sr) chloride agent, SMS.2P for pain palliation in patients with metastatic bone tumor in phase III multicenter clinical trial]. *Kaku Igaku.* (1996): 33: 1347–58.

(58) Sartor O, Reid RH, Hoskin PJ, Quick DP, Ell PJ, Coleman RE, Kotler JA, Freeman LM, and Olivier P. Samarium-153-Lexidronam complex for treatment of painful bone metastases in hormone-refractory prostate cancer. *Urology* (2004): 63: 940–45.

(59) Ahonen A, Joesu H, Hiltunen J, Hännelin M, Heikkila J, Jakobsson M, Jurvelin J, Kairemo K, Kumpulainen E, and Kulmala J. Samarium-153-EDTMP in bone metastases. *J. Nucl. Biol. Med.* (1994): 38: 123–27.

(60) Baczynk M, Czepczynski R, Milecki P, Psarek M, Oleksa R, and Sowinski J. 89Sr versus 153Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. *Nucl. Med. Commun.* (2007): 28: 245–50.

(61) McGann S, and Horton ER. Radium-223 dichloride: a novel treatment option for castration-resistant prostate cancer patients with symptomatic bone metastases. *Ann. Pharmacother.* (2015): 49: 469–76.

(62) Cheetham PJ, and Petrylak DP. Alpha particles as radiopharmaceuticals in the treatment of bone metastases: mechanism of action of radium-223 chloride (Alpharadin) and radiation protection. *Oncology* (2012): 26: 330.

(63) Nilsson S. Radium-223 dichloride for the treatment of bone metastatic castration-resistant prostate cancer: an evaluation of its safety. *Expert Opin. Drug Saf.* (2015): 14: 1127–36.

(64) Parker C, Nilsson S, Heinrich D, Helle S, O’Sullivan JM, Fossa SD, Chodacki A, Wiechno P, Logue J, Seke M, Widmark A, Johannessen DC, Hoskin P, Bottomley D, James ND, Solberg A, Syndikus I, Kliment J, Wedel S, Boehmer S, Dall’Oglio M, Franzen L, Coleman R, Vogelzang NJ, O’Bryan-Tear CG, Staudacher K, Garcia-Vargas J, Shan M, Bruland OJS, and Sartor O. Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer. *N. Engl. J. Med.* (2013): 369: 213–23.

(65) Hoskin P, Sartor O, O’Sullivan JM, Johannessen DC, Helle SI, Logue J, Bottomley D, Nilsson S, Vogelzang NJ, Fang F, Wahba M, Aksnes A-K, and Parker C. Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA. *Lancet. Oncol.* (2014): 15: 1397–1406.

(66) Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Loriot Y, Masuda K, Nakajo M, Kubo A, and Torizuka K. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. *Lancet (London, England)* (2011): 377: 813–22.

(67) Smith MR, Saad F, Coleman R, Shore N, Fizazi K, Tombal B, Miller K, Sieber P, Karsh L, Damiao R,
Tammela TL, Egerdie B, Van Poppel H, Chin J, Morote J, Gomez-Veiga F, Borkowski T, Ye Z, Kupic A, Dansey R, and Goessl C. Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomised, placebo-controlled trial. *Lancet (London, England)* (2012): 379: 39–46.

Saad F, and Eastham J. Zoledronic Acid improves clinical outcomes when administered before onset of bone pain in patients with prostate cancer. *Urology* (2010): 76: 1175–81.

von Moos R, Body J-J, Egerdie B, Stopec A, Brown JE, Damyanov D, Fallowfield LJ, Marx G, Cleeland CS, Patrick DL, Palazzo FG, Qian Y, Braun A, and Chung K. Pain and health-related quality of life in patients with advanced solid tumours and bone metastases: integrated results from three randomized, double-blind studies of denosumab and zoledronic acid. *Support. care cancer* (2013): 21: 3497–3507.

James ND, Pirrie SJ, Pope AM, Barton D, Andronis L, Goranitis I, Collins S, Daunton A, McLaren D, O’Sullivan J, Parker C, Porfiri E, Staffurth J, Stanley A, Wylie J, Beesley S, Birtle A, Brown J, Chakraborti P, Hussain S, Russell M, and Billingham LJ. Clinical Outcomes and Survival Following Treatment of Metastatic Castrate-Refractory Prostate Cancer With Docetaxel Alone or With Strontium-89, Zoledronic Acid, or Both: The TRAPEZE Randomized Clinical Trial. *JAMA Oncol.* (2016): 2: 493–99.

This article is available online at http://www.ijpr.ir