NCCN Guidelines® Insights

Prostate Cancer, Version 1.2014

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Prostate Cancer provide multidisciplinary recommendations on the clinical management of patients with prostate cancer. This report highlights notable recent updates. Radium-223 dichloride is a first-in-class radiopharmaceutical that recently received approval for the treatment of patients with symptomatic bone metastases and no known visceral disease. It received a category 1 recommendation as both a first-line and second-line option. The NCCN Prostate Cancer Panel also revised recommendations on the choice of intermittent or continuous androgen deprivation therapy based on recent phase III clinical data comparing the 2 strategies in the nonmetastatic and metastatic settings. (*JNCCN* 2013;11:1471–1479)

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Disclosures for the NCCN Prostate Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Prostate Cancer Panel members can be found on page 1472.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Describe the current standard of care for the management of patients with prostate cancer
- Discuss the role of adjuvant therapy in the management of prostate cancer

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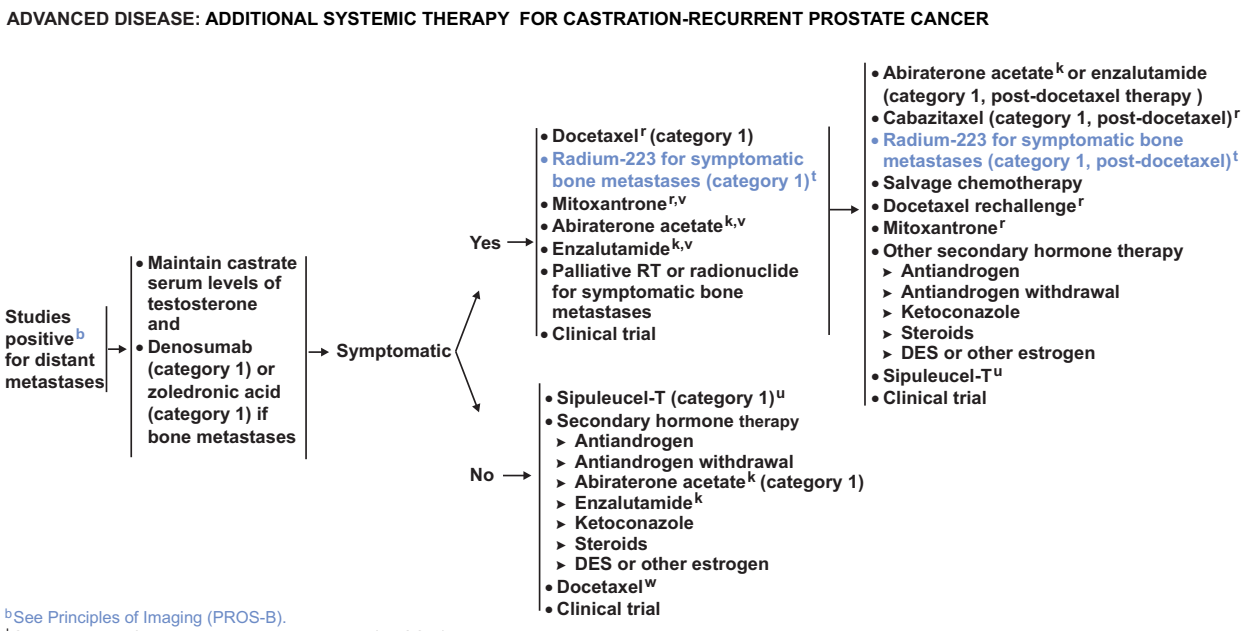

[b] See Principles of Imaging (PROS-B).
[k] See Principles of Androgen Deprivation Therapy (PROS-F).
[r] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[t] Radium-223 is not approved for use in combination with docetaxel or any other chemotherapy. See Principles of Radiation Therapy (PROS-D, page 2 /2).
[u] Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with ECOG performance status 0-1. Sipuleucel-T is not indicated in patients with hepatic metastases or life expectancy <6 months.
[v] For patients who are not candidates for docetaxel-based regimens.
[w] Although most patients without symptoms are not treated with chemotherapy, the survival benefit reported for docetaxel applies to those with or without symptoms. Docetaxel may be considered for patients with signs of rapid progression or hepatic metastases despite lack of symptoms.

PROS-11

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Other than skin cancer, prostate cancer is the most common cancer in men in the United States. In 2013, an estimated 238,590 new cases will be diagnosed, accounting for 28% of new cancer cases.[1] Although most patients are diagnosed early and may be cured with surgery and/or radiation therapy, many eventually experience progression and require further treatment in the form of androgen deprivation therapy (ADT), chemotherapy, or other systemic treatments. Researchers estimate that prostate cancer will account for 29,720 deaths in 2013. ADT is the mainstay initial systemic treatment for advanced prostate cancer. The optimal timing, duration, and schedule of ADT remains an active area of research. Given the many potential side effects of ADT, intermittent administration is becoming an increasingly popular alternative to continuous administration. Recent data from 2 large phase III clinical trials compared the 2

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PRINCIPLES OF RADIATION THERAPY

Post-prostatectomy Radiotherapy

- **Evidence supports offering adjuvant/salvage RT in all men with adverse pathologic features or detectable PSA and no evidence of disseminated disease.**
- **Indications for adjuvant RT include pT3 disease, positive margin(s), Gleason score 8-10, or seminal vesicle involvement. Adjuvant RT is usually given within 1 year after RP and once any operative side effects have improved/stabilized. Patients with positive surgical margins and PSADT >9 mo may benefit the most.**
- **Indications for salvage RT include an untdetectable PSA that becomes detectable and then increases on 2 subsequent measurements. Treatment is most effective when pre-treatment PSA is <1 ng/mL and PSADT is slow.**
- **The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64-70 Gy in standard fractionation.**
- **The defined target volumes include the prostate bed. The pelvic lymph nodes may be irradiated, but pelvic radiation is not necessary.**

Radiopharmaceutical Therapy

- **Radium-223 is an alpha emitting radiopharmaceutical that has been shown to extend survival in men who have CRPC with symptomatic bone metastases, but no visceral metastases. Radium-223 differs from beta-emitting agents, such as samarium-153 and strontium-89, which are palliative and have no survival advantage. Radium-223 causes double-strand DNA breaks and has a short radius of activity. Grade 3-4 hematologic toxicity (2% neutropenia, 3% thrombocytopenia, 6% anemia) occurs at a low risk.**
- **Radium-223 is administered intravenously once a month for 6 months by an appropriately licensed facility, usually in nuclear medicine or radiation therapy departments.**
- **Prior to the initial dose, patients must have absolute neutrophil count ≥1.5 x 10^9/L, platelet count ≥100 x 10^9/L, and hemoglobin ≥10g/dL.**
- **Prior to subsequent doses, patients must have absolute neutrophil count ≥1 x 10^9/L and platelet count ≥50 x 10^9/L (per label, although this may be too low in practice). Radium-223 should be discontinued if a delay of 6-8 weeks does not result in the return of blood counts to these levels.**
- **Non-hematological side effects are generally mild, and include nausea, diarrhea, and vomiting. These symptoms are likely related to the fact that radium-223 is predominantly eliminated by fecal excretion.**
- **At the present time, except on a clinical trial, radium-223 is not intended to be used in combination with chemotherapy due to the potential for additive myelosuppression.**
- **Concomitant use of denosumab or zoledronic acid does not interfere with the beneficial effects of radium-223 on survival.**

Palliative Radiotherapy

- **800 cGy as a single dose should be used instead of 3000 cGy in 10 fractions for non-vertebral metastases.**
- **Widespread bone metastases can be palliated using strontium 89 or samarium 153 with or without focal external beam radiation.**

PROS-D (2 of 2)

approaches in the nonmetastatic and metastatic settings. Unfortunately, almost all patients on ADT eventually experience disease progression. Most patients with castration-recurrent or -resistant prostate cancer (CRPC) die of bone metastases and related complications. The recently approved radium-223 is the first bone-targeting agent to demonstrate a survival benefit in these patients.

NCCN convened a multidisciplinary panel of leading experts at NCCN Member Institutions to develop and continually update guidelines for the treatment of prostate cancer. The latest full guideline, which includes a complete list of updates, is available on the NCCN Web site (NCCN.org). These NCCN Guidelines Insights highlight 2 recent revisions.

Intermittent Versus Continuous ADT

ADT has long been the gold standard for androgen-stimulated metastatic prostate cancer and is used frequently in men who have experienced biochemical failure after local therapy. However, ADT is associated with substantial side effects, including hot flashes, hot flushes, vasomotor instability, osteoporosis, greater incidence of clinical fractures, weight gain, sarcopenia, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease.[2,3] In general, the side effects of continuous ADT increase with the duration of treatment. One proposed approach to alleviate toxicity was an intermittent schedule. Supported by preclinical data and early clinical studies, intermittent ADT is based on the premise that cycles of androgen deprivation followed by re-exposure may delay "androgen independence," reduce treatment morbidity, and improve quality of life.[4,5]

The risk-to-benefit ratio of therapy is very different between asymptomatic patients experiencing an increase in prostate-specific antigen (PSA) and patients with symptomatic metastases. However, past phase III studies were underpowered

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY (ADT)

ADT for Localized Disease

- **Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.**
- **Giving ADT before, during, and/or after radiation prolongs survival in selected radiation managed patients.**
- **Studies of short-term (4-6 mo) and long-term (2-3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary will require further studies.**
- **In the largest randomized trial to date using antiandrogen bicalutamide alone at high dose (150 mg), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.**
- **In one randomized trial, immediate and continuous use of ADT in men with positive nodes following RP resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, such patients should be considered for immediate ADT.**
- **Many of the side effects of continuous ADT are cumulative over time on ADT.**

ADT for Biochemical Failure

- **The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, and the short and long-term side effects of ADT.**
- **Most patients will have a good 15 year prognosis but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy.**
- **Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualized until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier.**
- **Some patients are candidates for salvage after biochemical failure, which may include radiation after failed operation or RP or cryosurgery after failed radiation.**
- **Men with prolonged PSA doubling times (>12 mo) and who are older are candidates for observation.**
- **Men who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm.**

PROS-F (1 of 4)

and did not differentiate between these groups of patients.[6,7] Recently, long-awaited results from 2 phase III noninferiority trials provided valuable insights into each of these settings, although uncertainty remains in the field.

Biochemical Relapse

The Canadian-led PR.7 trial provided the best phase III data to date comparing intermittent and continuous ADT in patients without metastasis. Crook et al[8] randomly assigned 1386 patients with PSA levels greater than 3 ng/mL after radiation therapy to either intermittent ADT or continuous ADT. In the intermittent ADT arm, ADT was given in 8-month cycles followed by off-treatment periods until PSA reached 10 ng/mL. At a median follow-up of 6.9 years, the intermittent approach was noninferior to continuous ADT with respect to overall survival (8.8 vs 9.1 years, respectively; hazard ratio [HR], 1.02; 95% CI, 0.86–1.21). Although more patients died of prostate cancer in the intermittent arm (120 of 690 patients) than the continuous arm (94 of 696 patients), this was balanced by more non–prostate cancer deaths in the continuous ADT arm. The increased mortality from other causes in the continuous group cannot be attributed to any specific type of ADT toxicity. Several quality-of-life factors showed modest improvement in the intermittent ADT group, including physical function, fatigue, urinary problems, hot flashes, libido, and erectile dysfunction.

An unplanned Cox regression analysis of the trial showed that men with Gleason sum greater than 7 in the continuous ADT arm lived 14 months longer than those with the same Gleason sum in the intermittent ADT arm.[8] The caveats to this analysis are that pathology was not centrally reviewed and the study was not powered to detect a small difference based on Gleason sum.

The authors cautioned that these results should not be extrapolated to other treatment schedules.

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Metastatic Disease

- **ADT is the gold standard for men with metastatic prostate cancer.**
- **A phase 3 trial compared continuous ADT to intermittent ADT, but the study was statistically inconclusive for non-inferiority, however, quality of life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months off ADT compared to the continuous ADT arm.**
- **Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs of disease progression.**

Optimal ADT

- **LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.**
- **Combined androgen blockade (medical or surgical castration combined with an antiandrogen) provides modest to no benefit over castration alone in patients with metastatic disease.**
- **Antiandrogen therapy should precede or be coadministered with LHRH agonist and be continued in combination for at least 7 days for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.**
- **Antiandrogen monotherapy appears to be less effective than medical or surgical castration and should not be recommended. The side effects are different but overall more tolerable.**
- **No clinical data support the use of triple androgen blockade (finasteride or dutasteride with combined androgen blockade).**
- **Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/dL) with medical or surgical castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, or steroids), although the clinical benefit remains uncertain. The optimal level of serum testosterone decline has yet to be defined.**

PROS-F (2 of 4)

The test population was heterogenous, and therefore which of these asymptomatic patients benefitted from treatment remains unclear. It is possible that many of these patients could have delayed ADT without harm. The optimal PSA threshold to initiate therapy remains elusive, because the eligibility threshold of PSA level greater than 3 ng/mL was chosen mainly to aid accrual. Furthermore, 59% of deaths in the PR.7 trial were not related to prostate cancer. Because the test population had a low disease burden, a follow-up longer than 6.9 years may be required for disease-specific deaths to outbalance deaths from other causes.

Metastatic Disease

Hussain et al[9] conducted the SWOG 9346 trial to evaluate intermittent and continuous ADT in metastatic patients. Eligibility criteria included a new diagnosis of metastatic, androgen-stimulated prostate cancer; performance status of 0 to 2; and PSA level of 5 ng/mL or higher. After 7 months of induction ADT, 1535 patients whose PSA decreased to 4 ng/mL or below (thereby showing androgen sensitivity) were randomized to intermittent or continuous ADT. In the intermittent group, ADT was reinitiated when the PSA level reached 20 ng/mL, and stopped after 7 months if PSA decreased to 4 ng/mL or below. At a median follow-up of 9.8 years, median survival was 5.1 years for the intermittent ADT arm and 5.8 years for the continuous ADT arm. The HR for death with intermittent ADT was 1.10 with a 90% confidence interval between 0.99 and 1.23, which exceeded the prespecified upper boundary of 1.20 for noninferiority. The authors stated that the survival results were inconclusive, and that a 20% greater mortality risk with the intermittent approach cannot be ruled out. The study showed better erectile function and mental health in patients receiving intermittent ADT at 3 months, but the difference became insignificant thereafter.

In a post hoc stratification analysis of the trial, patients with minimal disease had a median survival of 5.4 years when receiving intermittent ADT versus 6.9 years when receiving continuous ADT (HR, 1.19; 95% CI, 0.98–1.43).[9] The median survival was 4.9 years in the intermittent ADT arm compared with 4.4 years in the continuous ADT arm for patients with extensive disease (HR, 1.02; 95% CI, 0.85–1.22). Subgroup analyses are hypothesis-generating and raise the interesting question of whether men with different disease burdens may respond differently to intermittent versus continuous ADT.

The interpretation of the SWOG 9346 data is further complicated by issues regarding the design and underlying statistics of noninferiority trials.[10] The NCCN Prostate Cancer Panel struggled additionally with differences in the prespecified noninferiority margin between the PR.7 and SWOG trials.[9] The upper limit of HR for death was set at 1.20 in SWOG 9346 and 1.25 in PR.7, translating to an absolute survival difference of 1.0 and 1.8 years, respectively.

NCCN Recommendations

The panel outlined its recommendations based on recent data in the "Principles of Androgen Deprivation Therapy" section of the algorithm (see PROS-F, 1 and 2 of 4; pages 1475 and 1476). In the setting of biochemical relapse after local therapy, one must first determine whether the patient is a candidate for a salvage approach, such as radiation rescue for biochemical failure after surgery, or, less commonly, radical prostatectomy or cryosurgery rescue for biochemical failure after radiation. Men with prolonged PSA doubling times who are older are excellent candidates for observation. Intermittent ADT has been shown to be noninferior to continuous ADT in terms of overall survival, and may improve quality of life for men who choose to initiate ADT.

Patients should be queried about adverse effects related to ADT. Intermittent ADT should be used for patients with metastatic disease who experience significant side effects from ADT. Some men who have no ADT-related morbidity may find the uncertainty of intermittent ADT not worthwhile. Men who have significant pain at the onset may have longer survival with continuous versus intermittent ADT, but this finding is derived from a post hoc analysis. Intermittent ADT requires close monitoring of PSA and testosterone levels, especially during off-treatment periods, and patients may need to switch to continuous therapy on signs of disease progression. Furthermore, the panel continues to believe that not enough emphasis is placed on delaying the initiation of ADT in patients with biochemical relapse after primary and salvage therapy.[11] Even in metastatic disease, intermittent ADT seems appropriate, in that survival is similar to that seen with ADT administered continuously in all studies comparing the 2 strategies thus far, and quality of life is better with intermittent ADT in most studies.[9,12–17]

Radium-223 Dichloride

Bone metastases are a major cause of mortality, morbidity, and poor quality of life in men with CRPC.[18] Although systemic radiopharmaceutical therapy (strontium-89 and samarium-153) has been used to treat these patients, its role has been limited traditionally to palliation of multifocal bone pain.[19,20]

In May 2013, the FDA approved radium-223 dichloride for the treatment of metastatic CRPC in patients with symptomatic bone metastases and no known visceral metastatic disease. This intravenous radioactive agent selectively binds to newly formed bone stroma at the site of bone metastases and induces double-strand DNA breaks in tumor cells.[21,22] Unlike the β-emitting palliative radiopharmaceuticals, radium-223 emits high-energy α particles that have a shorter path, which reduce toxic effects on adjacent tissue.[22]

Approval of radium-223 was based on clinical data from a multicenter, phase III, randomized trial that enrolled 921 men with symptomatic CRPC, 2 or more bone metastases, and no known visceral disease.[23] A total of 57% of the patients received prior docetaxel, and all patients received best supportive care. Patients were randomized in a 2:1 ratio to a total of 6 monthly intravenous injections of radium-223 or placebo. Compared with placebo, radium-223 significantly improved overall survival (median, 14.9 vs 11.3 months; HR, 0.70; 95% CI, 0.058–0.83; $P<.001$) and prolonged time to first skeletal-related event (SRE; median, 15.6 vs 9.8 months). This result rendered radium-223 the first bone-targeting agent to provide a survival advantage; benefits from other agents, such as zoledronic acid

and denosumab, are limited to delay of SREs in the setting of bone metastases.[24,25] The effect on control of existing pain was not reported. In addition, the safety of using chemotherapy after radium-223 has also not been established. Preliminary data suggest that combination with standard doses of docetaxel should not be undertaken.[26]

Radium-223 was well tolerated. Grade 3/4 hematologic toxicity was low (3% neutropenia, 6% thrombocytopenia, and 13% anemia), possibly because of the short range of radioactivity.[23] Fecal elimination of the agent led to generally mild nonhematologic side effects, which included nausea, diarrhea, and vomiting. This favorable toxicity profile and extension of survival renders radium-223 an attractive first-line alternative for patients with symptomatic bone metastases who are too frail to receive docetaxel.

NCCN Recommendations

The panel included recommendations for radium-223 in the treatment of metastatic CRPC, assigning it a category 1 recommendation as a first-line or second-line option for patients with symptomatic bone metastases and no known visceral disease (see PROS-11, page 1473, and PROS-D 2 of 2, page 1474). Hematologic evaluation should be performed according to the FDA label before treatment initiation and before each subsequent dose.[26] Radium-223 given in combination with chemotherapy (such as docetaxel) outside of a clinical trial is not recommended because of the potential for additive myelosuppression.[26] There are no restrictions on combining radium-223 with denosumab or a bisphosphonate.

Given the wide variety of second-line options available to patients with symptomatic metastatic CRPC who have been exposed to chemotherapy, the choice of therapy should be based on clinical considerations, which include patient preferences, prior treatment, presence or absence of visceral disease, and symptoms. Studies on the direct comparison or sequential efficacy of radium-223 with other available agents are warranted.

Conclusions

Important updates to the management of prostate cancer in the NCCN Guidelines for Prostate Cancer are highlighted in these NCCN Guidelines Insights. The NCCN Guidelines are updated at least annually, and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available online at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical data when available and expert consensus of the panel. Independent medical judgment is required to apply these guidelines to individual patients to optimize care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, and consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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Instructions for Completion

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Posttest Questions

1. Which of the following is false regarding the PR.7 trial in patients experiencing biochemical relapse after radiation therapy?
   a. Intermittent ADT was associated with more prostate cancer–specific deaths
   b. Intermittent ADT was associated with improvements in quality-of-life factors
   c. Intermittent ADT was noninferior to continuous ADT in terms of overall survival
   d. More than 90% of patient deaths in the trial were related to prostate cancer
2. True or False: The SWOG 9346 study in patients with metastatic demonstrated noninferiority of intermittent ADT to continuous ADT in terms of overall survival.
3. Radium-223 dichloride is:
   a. An α-emitting radiopharmaceutical
   b. The first bone-targeting agent to provide a survival benefit to patients with CRPC and bone metastases
   c. Not recommended in combination with docetaxel outside of a clinical trial
   d. All of the above