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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Prostate Cancer From the 2016 American Society of Clinical Oncology Genitourinary Cancers Symposium

A Review of Selected Presentations From the 2016 American Society of Clinical Oncology Genitourinary Cancers Symposium

January 7-9, 2016 • San Francisco, California

Special Reporting on:

- Interim Results From ERADICATE: An Open-Label Phase 2 Study of Radium Ra 223 Dichloride With Concurrent Administration of Abiraterone Acetate Plus Prednisone in Castration-Resistant Prostate Cancer Subjects With Symptomatic Bone Metastases
- Challenging Cases Panel Discussion
- Radium-223 (Ra-223) Re-Treatment (Re-tx): First Experience From an International, Multicenter, Prospective Study in Patients (Pts) With Castration-Resistant Prostate Cancer and Bone Metastases (mCRPC)
- Celecoxib With or Without Zoledronic Acid for Hormone-Naïve Prostate Cancer: Survival Results From STAMPEDE (NCT00268476)
- Differential Side Effects Profile in mCRPC Patients Treated With Abiraterone or Enzalutamide: A Meta-Analysis of Randomized Controlled Trials
- Phase II Clinical Study of Radium-223 Chloride (BAY 88-8223) in Japanese Patients With Symptomatic Castration-Resistant Prostate Cancer (CRPC) With Bone Metastases

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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XOFIGO® IS INDICATED *for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.*

Give your patient's standard

BEST STANDARD OF CARE

Defined as[2]:

- Antihormonal agents
- Ketoconazole
- Local external beam radiation therapy (EBRT)
- Treatment with glucocorticoids

PLUS 6 INJECTIONS OF *Xofigo*[1,2]

30%

REDUCED RISK OF DEATH vs PLACEBO PLUS BEST STANDARD OF CARE[2]

- Xofigo is not recommended in combination with chemotherapy

Not an actual doctor. Model used for illustrative purposes only.

Important Safety Information

- **Contraindications:** Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman
- **Bone Marrow Suppression:** In the randomized trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression—notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia—has been reported in patients treated with Xofigo.

  Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure
- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 × 10^9/L and the platelet count ≥50 × 10^9/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care
- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use

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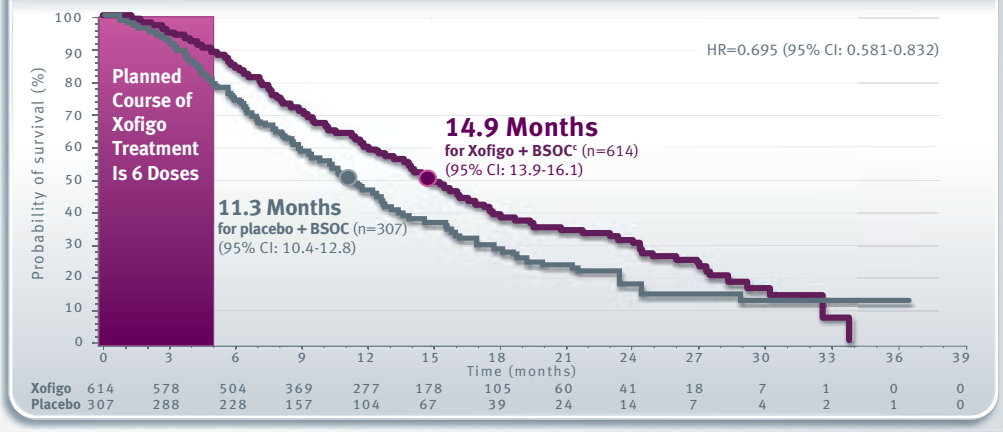
# of care a survival boost[1]

Median Overall Survival (OS) in an Exploratory Analysis[1,2ab]



[a]In the updated analysis.
[b]An exploratory updated OS analysis was performed before patient crossover, incorporating an additional 214 events, resulting in findings consistent with the interim analysis.[1]
[c]Best standard of care.

- Prespecified interim analysis: median OS was 14.0 months for Xofigo (95% confidence interval [CI]: 12.1-15.8) vs 11.2 months for placebo (95% CI: 9.0-13.2)[1]
  - *P*=0.00185; hazard ratio (HR)=0.695 (95% CI: 0.552-0.875)
- BSOC was defined as[2]:
  - Antihormonal agents
  - Ketoconazole
  - Local external beam radiation therapy (EBRT)
  - Treatment with glucocorticoids

of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued

- **Administration and Radiation Protection:** Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations
- **Adverse Reactions:** The most common adverse reactions (≥10%) in the Xofigo arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%). Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in the Xofigo arm (≥10%) vs the placebo arm, respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)

References: 1. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc.; May 2013. **2.** Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.

Please see following pages for brief summary of full Prescribing Information.

Xofigo®
radium Ra 223 dichloride
INJECTION

Xofigo (radium Ra 223 dichloride) Injection, for intravenous use

Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xofigo™ is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

2 DOSAGE AND ADMINISTRATION

2.3 Instructions for Use/Handling

General warning

Xofigo (an alpha particle-emitting pharmaceutical) should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Xofigo are subject to the regulations and/or appropriate licenses of the competent official organization.

Xofigo should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Radiation protection

The administration of Xofigo is associated with potential risks to other persons (e.g., medical staff, caregivers and patient's household members) from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

For drug handling

Follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids to avoid contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water. In the event of spillage of Xofigo, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diamine-tetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care

Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Xofigo or patient fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is expected to be low, because the typical treatment activity will be below 8,000 kBq (216 microcurie). In keeping with the **A**s **L**ow **A**s **R**easonably **A**chievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Xofigo and the detection of contamination with standard instruments.

4 CONTRAINDICATIONS

Xofigo is contraindicated in pregnancy.

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Xofigo is not indicated for use in women. Xofigo is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

In the randomized trial, 2% of patients on the Xofigo arm experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with Xofigo, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Xofigo arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression.

In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) were similar for patients treated with Xofigo and placebo. Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Xofigo. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Xofigo, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Xofigo administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration *[see Adverse Reactions (6)]*.

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration of Xofigo, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Xofigo, the ANC should be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of Xofigo, despite receiving supportive care, further treatment with Xofigo should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

- Bone Marrow Suppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer with bone metastases, 600 patients received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Xofigo and best standard of care and 301 patients received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of patients had received docetaxel in the Xofigo and placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Xofigo and 18 weeks (5 cycles) for placebo.

The most common adverse reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema (Table 3). Grade 3 and 4 adverse events were reported among 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4).

Treatment discontinuations due to adverse events occurred in 17% of patients who received Xofigo and 21% of patients who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Xofigo were anemia (2%) and thrombocytopenia (2%).

Table 3 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 3: Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 4 shows hematologic laboratory abnormalities occurring in ≥ 10% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 4: Hematologic Laboratory Abnormalities

Hematologic Laboratory Abnormalities	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

Laboratory values were obtained at baseline and prior to each 4-week cycle.

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Xofigo and in 2% of patients on placebo. Among patients who received Xofigo, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status

Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia.

Injection Site Reactions

Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo.

Secondary Malignant Neoplasms

Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms *[see Nonclinical Toxicology (13.1)]*. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs. 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow up for patients on the trial.

Subsequent Treatment with Cytotoxic Chemotherapy

In the randomized clinical trial, 16% patients in the Xofigo group and 18% patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy.

7 DRUG INTERACTIONS

No formal clinical drug interaction studies have been performed.

Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Xofigo in the randomized clinical trial.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Category X *[see Contraindications (4)]*

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of Xofigo in pregnancy and Xofigo is not indicated for use in women, maternal use of a radioactive therapeutic agent could affect development of a fetus. Xofigo is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with Xofigo.

8.3 Nursing Mothers

Xofigo is not indicated for use in women. It is not known whether radium-223 dichloride is excreted in human milk. Because many drugs are excreted in human milk, and because of potential for serious adverse reactions in nursing infants from Xofigo, a decision should be made whether to discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Xofigo in pediatric patients have not been established.

In single- and repeat-dose toxicity studies in rats, findings in the bones (depletion of osteocytes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line) and teeth (missing, irregular growth, fibro-osseous lesions in bone socket) correlated with a reduction of osteogenesis that occurred at clinically relevant doses beginning in the range of 20 – 80 kBq (0.541 - 2.16 microcurie) per kg body weight.

8.5 Geriatric Use

Of the 600 patients treated with Xofigo in the randomized trial, 75% were 65 years of age and over and while 33% were 75 years of age and over. No dosage adjustment is considered necessary in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

No dedicated hepatic impairment trial for Xofigo has been conducted. Since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is unlikely to affect the pharmacokinetics of radium-223 dichloride *[see Clinical Pharmacology (12.3)]*. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with mild hepatic impairment. No dose adjustments can be recommended for patients with moderate or severe hepatic impairment due to lack of clinical data.

8.7 Patients with Renal Impairment

No dedicated renal impairment trial for Xofigo has been conducted. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with existing mild (creatinine clearance [CrCl] 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CrCl less than 30 mL/min) due to limited data available (n = 2) *[see Clinical Pharmacology (12.3)]*.

8.8 Males of Reproductive Potential

Contraception

Because of potential effects on spermatogenesis associated with radiation, advise men who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective contraceptive method during and for 6 months after completing treatment with Xofigo.

Infertility

There are no data on the effects of Xofigo on human fertility. There is a potential risk that radiation by Xofigo could impair human fertility *[see Nonclinical Toxicology (13.1)]*.

10 OVERDOSAGE

There have been no reports of inadvertent overdosing of Xofigo during clinical studies.

There is no specific antidote. In the event of an inadvertent overdose of Xofigo, utilize general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity, and consider using medical countermeasures such as aluminum hydroxide, barium sulfate, calcium carbonate, calcium gluconate, calcium phosphate, or sodium alginate.[1]

Single Xofigo doses up to 250 kBq (6.76 microcurie) per kg body weight were evaluated in a phase 1 clinical trial and no dose-limiting toxicities were observed.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of radium-223 dichloride. However, in repeat-dose toxicity studies in rats, osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses 7 to 12 months after the start of treatment. The presence of other neoplastic changes, including lymphoma and mammary gland carcinoma, was also reported in 12- to 15-month repeat-dose toxicity studies in rats.

Genetic toxicology studies have not been conducted with radium-223 dichloride. However, the mechanism of action of radium-223 dichloride involves induction of double-strand DNA breaks, which is a known effect of radiation.

Animal studies have not been conducted to evaluate the effects of radium-223 dichloride on male or female fertility or reproductive function. Xofigo may impair fertility and reproductive function in humans based on its mechanism of action.

17 PATIENT COUNSELING INFORMATION

Advise patients:

- To be compliant with blood cell count monitoring appointments while receiving Xofigo. Explain the importance of routine blood cell counts. Instruct patients to report signs of bleeding or infections.
- To stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo. Instruct patients to report signs of dehydration, hypovolemia, urinary retention, or renal failure / insufficiency.
- There are no restrictions regarding contact with other people after receiving Xofigo. Follow good hygiene practices while receiving Xofigo and for at least 1 week after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers. Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions for patient care such as gloves and barrier gowns when handling bodily fluids to avoid contamination. When handling bodily fluids, wearing gloves and hand washing will protect caregivers.
- Who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective method of birth control during treatment and for 6 months following completion of Xofigo treatment.

Manufactured for:
Bayer HealthCare

Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470

Manufactured in Norway

Revised: 05/2013
6708400BS

Interim Results From ERADICATE: An Open-Label Phase 2 Study of Radium Ra 223 Dichloride With Concurrent Administration of Abiraterone Acetate Plus Prednisone in Castration-Resistant Prostate Cancer Subjects With Symptomatic Bone Metastases

Most men with metastatic prostate cancer who exhibit an initial response to androgen-deprivation therapy or surgical castration progress to castration-resistant disease. More than 90% of patients with metastatic castration-resistant prostate cancer (CRPC) develop bone metastases,[1] which have a major impact by decreasing quality of life, increasing disability, and reducing lifespan. Radium-223 dichloride is an α-emitting radiopharmaceutical and calcium mimetic that selectively binds to areas of increased cellular activity in bone metastases. As a high-energy α-emitter, radium-223 has a short radius of activity. It induces double-stranded DNA breaks within a limited range and thus provides highly localized cytotoxicity. In the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer Patients) trial, radium-223 had a median overall survival of 14.9 months vs 11.3 months with placebo (hazard ratio [HR], 0.70; *P*=.00185) in patients with metastatic CRPC.[2] Radium-223 also increased the median time to the first symptomatic skeletal event by 5.8 months (15.6 vs 9.8 months; HR, 0.66; 95% CI, 0.52-0.83; *P*=.00037) and demonstrated a meaningful improvement in quality of life.[3] Radium-223 treatment was associated with a favorable safety profile, including a low rate of hematologic adverse events (AEs).

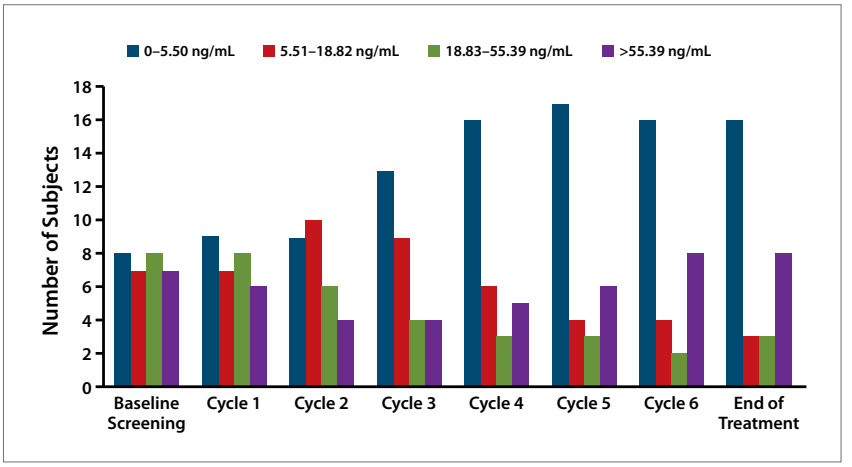


Figure 1. Changes in prostate-specific antigen quartiles among patients in an open-label, phase 2 trial evaluating the combination of abiraterone plus radium-223. Adapted from Shore ND et al. ASCO GU abstract 177. *J Clin Oncol.* 2016;34(suppl 2S).[9]

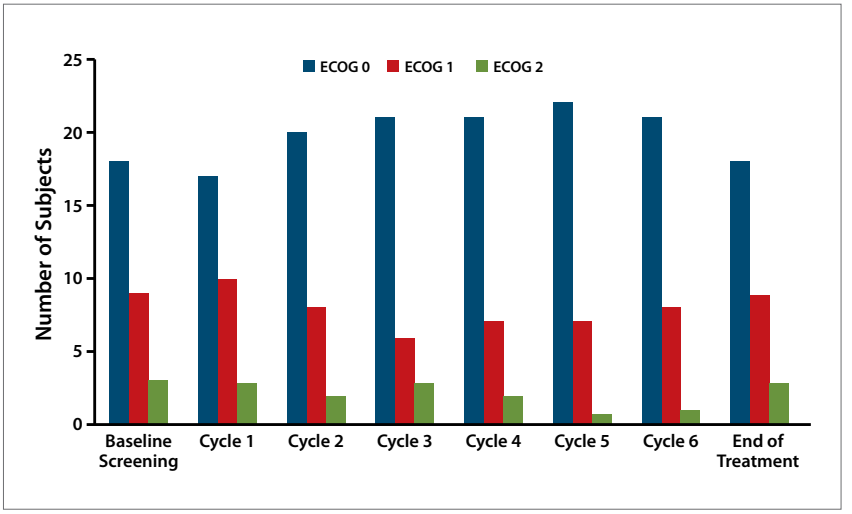


Figure 2. Eastern Cooperative Oncology Group (ECOG) performance status among patients in an open-label, phase 2 trial evaluating abiraterone plus radium-223. Adapted from Shore ND et al. ASCO GU abstract 177. *J Clin Oncol.* 2016;34(suppl 2S).[9]

Abiraterone acetate is a first-in-class inhibitor of cytochrome P450c17/CYP17A1, which catalyzes androgen synthesis.[4] In April 2011, abiraterone in combination with low-dose prednisone was approved by the US Food and Drug Administration for the treatment of metastatic CRPC in men who have received prior treatment with docetaxel.[5,6] The phase 3 COU-AA-302 trial evaluated abiraterone plus prednisone vs prednisone alone in 1088 treatment-naive patients with asymptomatic

ABSTRACT SUMMARY Management of Metastatic Prostate Cancer Patients in First Line: Audit of Real-Life Practices

Docetaxel, abiraterone, and enzalutamide are options for the first-line management of metastatic CRPC patients. An audit of real-world practices among French physicians was conducted to understand trends in first-line management (Abstract 333). An online questionnaire with 22 questions was made available to physicians within the Groupe d'Etude des Tumeurs Urogénitales. From March 2015 to July 2015, more than 100 physicians completed the questionnaire, including 49 medical oncologists, 29 radiation oncologists, 21 urologic surgeons, and 2 other specialists from 22 French regions. Factors leading to the selection of docetaxel as first-line therapy included heavy tumor burden (68.8%), aggressive disease (66.1%), short-term efficacy of castration (66.1%), and the presence of visceral metastases (9.8%). Selection criteria for first-line use of abiraterone or enzalutamide included long-term efficacy of castration (66.1%), increased age (67.9%), low tumor grade (56.9%), and absence of symptoms (54.1%). In patients receiving docetaxel, the first tumor assessment was performed after a median of 3 cycles, with a range of 1 to 6. The PSA level was measured in 96.3%, a CT scan performed in 68.8%, and bone scintigraphy performed in 59.6%. The PSA level was assessed at every treatment cycle in 42.5% of cases and at every third cycle in 39.6%. In patients receiving abiraterone or enzalutamide, tumor assessments occurred after a median 3 months of treatment, with a range of 1 to 6 months. Measures included PSA in 90.8%, CT scan in 61.5%, and bone scintigraphy in 63.3%. PSA level was assessed every 3 months in 49.5% of cases and every month in 29.0%. The findings highlight the heterogeneous practices among physicians and underscore the need for clear management guidelines.

or minimally symptomatic, metastatic CRPC.[7] The median radiographic progression-free survival (PFS) was 16.5 months with abiraterone plus prednisone vs 8.3 months with prednisone alone (HR, 0.53; 95% CI, 0.45-0.62; *P*<.001). After a median follow-up of 49.2 months, the final analysis yielded an improvement in overall survival with abiraterone plus prednisone (34.7 months vs 30.3 months; HR, 0.81; 95% CI, 0.70-0.93; *P*=.003).[8] Results from the COU-AA-302 trial led to the approval of abiraterone plus prednisone for patients with metastatic CRPC who have not received prior chemotherapy.

To provide further treatment options in this setting, an open-label, phase 2 trial was conducted evaluating the combination of abiraterone plus radium-223.[9] The ERADICATE (Open Label Phase Two Trial of Radium Ra 223 Dichloride With Concurrent Administration of Abiraterone Acetate Plus Prednisone in Symptomatic Castration-Resistant [Hormone-Refractory] Prostate Cancer Subjects With Bone Metastasis) trial enrolled 36 patients with CRPC and symptomatic bone metastases but without visceral metastases to receive 6 cycles of treatment with radium-223 dichloride (50 kBq/kg) every 4 weeks, with concurrent abiraterone (1000 mg daily) and prednisone (5 mg twice daily). Interim results were reported for the 30 patients who received the full, 6-cycle course of radium-223. Mean bone pain decreased significantly from baseline (*P*=.014). Significant decreases were observed in the amount of bone pain that interfered with work, general activity, and mood. Quality of life increased, with patients reporting less pain and overall interference as well as improved sleep quality. Mean levels of prostate-specific antigen (PSA) and alkaline phosphatase (ALP) decreased from baseline to the end of treatment, and Eastern Cooperative Oncology Group performance status (ECOG PS) scores remained stable for the population throughout treatment (Figures 1 and 2). A final data analysis is forthcoming.

References

1. Nilsson S. Radionuclide therapies in prostate cancer: integrating radium-223 in the treatment of patients with metastatic castration-resistant prostate cancer. *Curr Oncol Rep*. 2016;18(2):14.
2. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
3. Sartor O, Coleman R, Nilsson S, et al. Effect of radium-223 dichloride on symptomatic skeletal events in patients with castration-resistant prostate cancer and bone metastases: results from a phase 3, double-blind, randomised trial. *Lancet Oncol*. 2014;15(7):738-746.
4. DeVore NM, Scott EE. Structures of cytochrome P450 17A1 with prostate cancer drugs abiraterone and TOK-001. *Nature*. 2012;482(7383):116-119.
5. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
6. Fizazi K, Scher HI, Molina A, et al; COU-AA-301 Investigators. 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(10):983-992.
7. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.
8. Ryan CJ, Smith MR, Fizazi K, et al; COU-AA-302 Investigators. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol*. 2015;16(2):152-160.
9. Shore ND, Tutrone RF, Mariados NF, Nordquist LT, Mehlhaff BA, Harrelson SS. Interim results from ERADICATE: an open-label phase 2 study of radium Ra 223 dichloride with concurrent administration of abiraterone acetate plus prednisone in castration-resistant prostate cancer subjects with symptomatic bone metastases [ASCO GU abstract 177]. *J Clin Oncol*. 2016;34(suppl 2S).

Challenging Cases Panel Discussion: Case #3

The Challenging Cases Panel Discussion included 3 cases on the management of prostate cancer.[1] The panel consisted of Dr Adam Kibel, Dr Silke Gillessen, Dr Neal Shore, Dr Matthew Smith, Dr Peter Hoskin, and Dr Baris Turkbey. Dr Kibel was the moderator, and he presented the third case, which described a 70-year-old patient with stage T1c prostate cancer, a Gleason score of 8, and a PSA level of 4.2 ng/mL. After a radical retropubic prostatectomy, the patient's disease became stage T3a with negative margins, his Gleason score decreased to 4+3, and his PSA was undetectable. Two years later, his PSA level rose to 0.4 ng/mL. The patient responded to treatment with radiation therapy. Five years later, the patient's PSA level rose to 5.2 ng/mL. At this point, the patient began treatment with androgen-deprivation therapy, despite the absence of metastatic disease. His disease initially responded, but then the PSA level again increased. At 9 years, his PSA level was 6.3 ng/mL. Results from bone scans and computed tomography (CT) were negative.

Dr Kibel commented that these results demonstrated the limitations of basing treatment decisions on sodium fluoride bone scans. Dr Hoskin suggested that more sophisticated imaging would be appropriate for this patient, who might have oligometastatic disease eligible for radical treatment. Other panelists commented that accessibility and reimbursement of diagnostic modalities is generally limited in the United States, confining options to a technetium-99m bone scan or multislice CT. Some in the audience thought that enzalutamide, abiraterone, or docetaxel might be appropriate for this patient based on his rising PSA. Dr Gillessen disagreed with this approach. She and Dr Kibel suggested that this patient would be a candidate for a clinical trial evaluating new antiandrogen therapies.

By 10 years, the patient's PSA level had risen to 16.8 ng/mL, but he was still asymptomatic. A CT scan was negative for soft tissue disease, but confirmed the presence of bone metastases, which had been observed via a bone scan. Dr Kibel asked the panel if there was an optimal treatment for this patient, and whether radium-223 would be a reasonable choice if the patient were symptomatic. Dr Smith commented that the patient had relatively indolent disease, having been diagnosed many years earlier, and was therefore likely to respond to treatment with abiraterone or enzalutamide. If the patient had symptoms, Dr Smith said he still would not prioritize radium-223; he considers radium-223 for second-line therapy at progression. The reason for not recommending radium-223 treatment was that the treatment duration is finite, consisting of 6 injections given 1 month apart. With this in mind, radium-223 would be appropriate for a patient who progresses on abiraterone or enzalutamide but who does not yet require chemotherapy.

Dr Shore asked whether radium-223 treatment would be appropriate for a patient with no symptomatic or radiographic progression, but with voluminous disease and a PSA level that was reduced by approximately 30% with antiandrogen treatment before rising again. This patient did not have primary resistance, and yet his PSA level inexorably drifted upward. A treatment scenario was proposed whereby the patient would first receive the full course of treatment with radium-223, which could be followed by

ABSTRACT SUMMARY Radium-223 in Metastatic Castration Resistant Prostate Cancer: Progression Free Survival and Pain Scores—Real-World Single-Institution Experience

Real-world experience was reported for 36 patients with metastatic CRPC treated with radium-223 (Abstract 250). Planned treatment consisted of 6 injections of radium-223 (50 kBq/kg), with 1 injection given every 4 weeks. Patients' median age was 79 years (range, 59-89 years). ECOG PS was 0 or 1 in 66% of patients. The median pain level was 6 based on the visual analogue scale. The median albumin level was 34 g/L (range, 25-47 g/L), the median PSA level was 197 µg/L (range, 2.5-1969 µg/L), and the median serum ALP level was 169 U/L (range, 46-2260 U/L). Previous treatment with docetaxel was reported in 53% of patients. Disease progression led to treatment discontinuation in 18 patients (50%). Among the 18 patients with prior exposure to docetaxel, 12 (67%) discontinued treatment. A discontinuation rate of 43% was observed in patients with a serum albumin level below 34 g/L. Seven patients (19%) required blood transfusion during the course of treatment. A significant reduction in pain scores was observed after treatment cycles 1 and 6 compared with baseline ($P<.05$ and $P<.001$, respectively). The median PFS was 6.1 months. It was significantly longer in patients who completed 6 cycles of treatment (10.97 vs 5.2 months; $P<.0001$) and in patients with a serum ALP level below 220 U/L (10.33 vs 6.4 months; $P<.0001$). A trend was observed for increased PFS among patients with no prior docetaxel treatment, but the difference did not reach significance (10.33 vs 6.5 months; $P=.05$). A similar trend was observed in patients with a serum albumin level greater than 34 g/L (8.9 vs 6.4 months; $P=.06$).

ABSTRACT SUMMARY Phase Ib Trial of Docetaxel, Prednisone, and Pazopanib, in Men with Metastatic Castration Resistant Prostate Cancer (mCRPC)

Pazopanib is a multitargeted tyrosine kinase inhibitor of VEGF receptors that is approved for the treatment of kidney cancer and sarcoma. The combination of pazopanib, docetaxel, and prednisone was investigated in a phase 1b study of men with metastatic CRPC (Abstract 275). Oral pazopanib was administered once daily at a dose of 400 mg, 600 mg, or 800 mg in combination with docetaxel (60 mg/m^2 or 75 mg/m^2 every 3 weeks) plus prednisone (5 mg twice daily). Thirty-six patients were treated with 6 combination dose levels using a 3+3 design. Pegfilgrastim was added to the regimen to control myelosuppression. The maximum tolerated dose was reached with a regimen of pazopanib at 800 mg daily, docetaxel at 75 mg/m^2 every 3 weeks, and prednisone at 5 mg daily. The most common AEs of any grade were alopecia (86%), fatigue (67%), diarrhea (53%), and nausea (53%). The most common grade 3 to 5 AEs were neutropenia (33%) and leukopenia (19%). Three deaths occurred that were attributed to study treatment, including 1 each from pneumonitis, respiratory failure, and intracranial hemorrhage. The entire study population yielded a median radiographic PFS of 14.1 months (95% CI, 7.1-22.2) and a median overall survival of 18.6 months (95% CI, 11.8-22.2). Comparison with historical data suggests that the combination of pazopanib, docetaxel, and prednisone warrants further investigation.

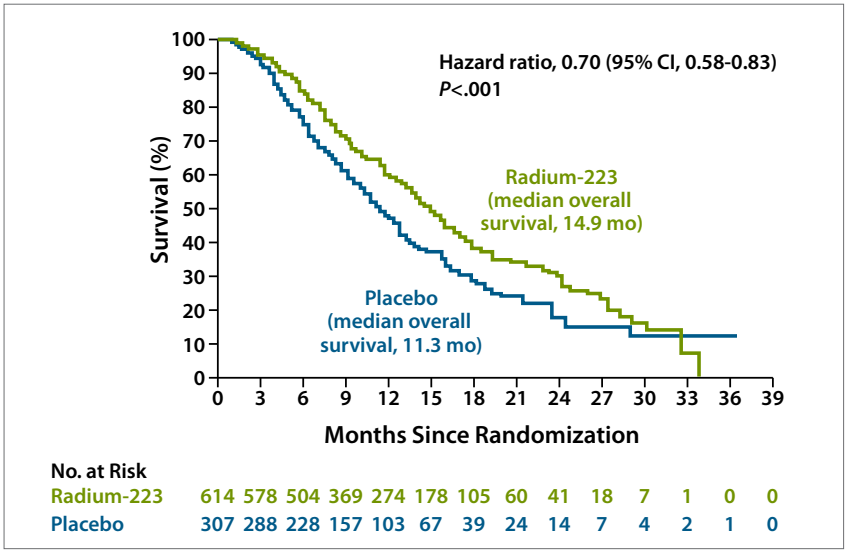


Figure 3. Overall survival in the ALSYMPCA trial, which evaluated radium-223 in combination with the best standard of care. ALSYMPCA, Alpharadin in Symptomatic Prostate Cancer Patients. Adapted from Parker C et al. *N Engl J Med.* 2013;369(3):213-223.[3]

chemotherapy in the event of disease progression. Dr Smith agreed that a patient with PSA progression, but not symptomatic or radiographic progression, is an excellent candidate for initial treatment with radium-223. However, he suggested that androgen-receptor targeted therapy would be a good choice if the disease progressed, and it could be followed by a switch to docetaxel if necessary. He also mentioned osteoclast-targeted therapy as an option based on the extensive burden of bone disease, and said that either denosumab or zoledronic acid would be a reasonable choice.

Dr Kibel asked the panel how to gauge response to treatments, including sipuleucel-T and radium-223, given that PSA levels do not correlate well with overall disease response. Dr Shore underscored the value of ALP as a biomarker for disease response in patients treated with radium-223. Dr Shore uses radium-223 in combination with other agents, an approach that is supported by study data (Figure 3).[2,3] Dr Gillessen proposed that the combination of radium-223 plus an antiandrogen agent is best tested in clinical trials to determine whether the combination truly provides a benefit over sequential monotherapy. There was general consensus "not to treat the biochemistry," but rather to treat the patient based on symptoms and imaging results. Observation is a reasonable option for patients who are maintaining their performance status and quality of life, as well as for patients with modest increases in biochemistry panel results. In the event of bone pain, it is important not only to treat the pain, but also to evaluate the bones for any potential fracturing.

References

1. Gillessen S, Hoskin P, Kibel AS, et al. Challenging Cases Panel Discussion. Presented at: the 2016 ASCO Genitourinary Cancers Symposium; January 7-9, 2016; San Francisco, CA.
2. Shore ND, Tutrone RF, Mariados NF, Nordquist LT, Mehlhaff BA, Harrelson SS. Interim results from ERADICATE: an open-label phase 2 study of radium Ra 223 dichloride with concurrent administration of abiraterone acetate plus prednisone in castration-resistant prostate cancer subjects with symptomatic bone metastases [ASCO GU abstract 177]. *J Clin Oncol.* 2016;34(suppl 2S).
3. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.

Radium-223 (Ra-223) Re-Treatment (Re-tx): First Experience From an International, Multicenter, Prospective Study in Patients (Pts) With Castration-Resistant Prostate Cancer and Bone Metastases (mCRPC)

Radium-223 dichloride treatment is indicated for patients with CRPC and symptomatic bone metastases with no visceral metastases.[1] The approved regimen consists of 1 injection of radium-223 (50 kBq/kg) given every 4 weeks for up to 6 injections. Regimens involving a higher number of injections or repeated treatment have not been previously explored. The favorable safety profile observed in the phase 3 ALSYMPCA trial suggests that treatment beyond the standard regimen may be feasible.[2] To evaluate the safety and efficacy of retreatment with radium-223, an international, multicenter, open-label, phase 1/2 trial was conducted in patients with CRPC and at least 2 bone metastases.[3] Eligible patients had completed 6 injections of radium-223 and had no bone progression during the first course of treatment. They had experienced radiographic or clinical progression after treatment. All patients had an ECOG PS of 0 to 2 and adequate hematologic laboratory values. Enrollment was barred to patients with visceral metastases measuring 1 cm or larger in diameter or with lymphadenopathy consisting of nodes sizes 6 cm or larger. Eligible patients had not received chemotherapy after the initial course of radium-223.

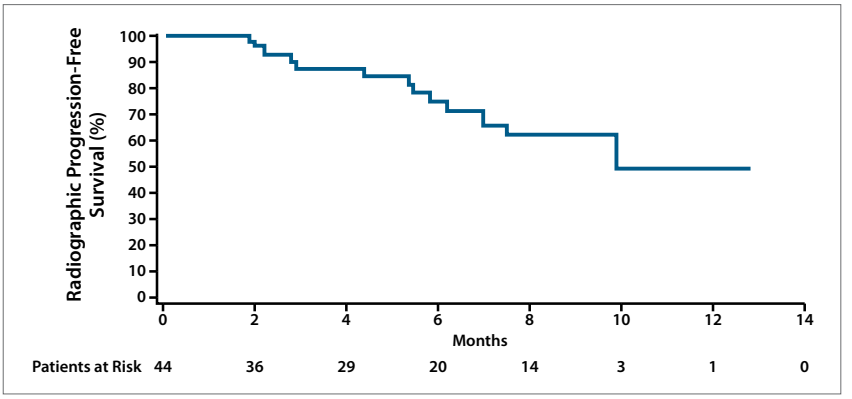


Figure 4. Radiographic progression-free survival in a trial evaluating retreatment with radium-223. Adapted from Sartor AO et al. ASCO GU abstract 197. *J Clin Oncol.* 2016;34(suppl 2S).[3]

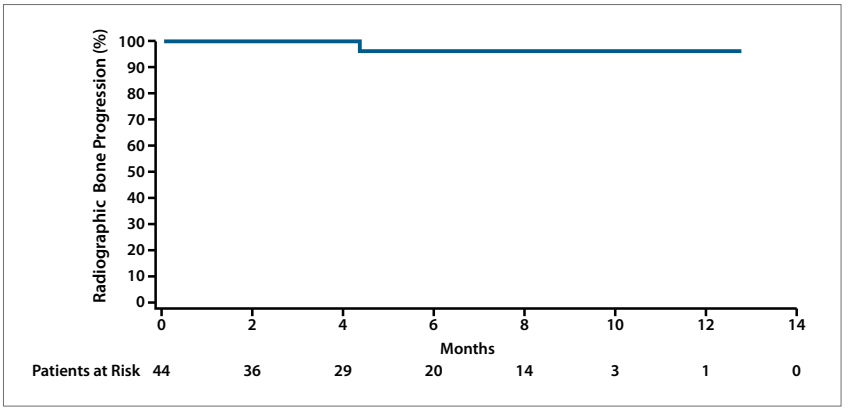


Figure 5. Time to radiographic bone progression in a trial evaluating retreatment with radium-223. Adapted from Sartor AO et al. ASCO GU abstract 197. *J Clin Oncol.* 2016;34(suppl 2S).[3]

The 44 enrolled patients had a median age of 71 years (range, 52-91 years). More than half of patients had 6 or more bone metastases. The most common prior treatments other than radium-223 were abiraterone (61%), denosumab (48%), and docetaxel (45%). All patients had received 2 or more prior hormonal regimens, and 73% had failed previous treatment with abiraterone or enzalutamide. Patients had a median PSA level of 68 µg/L (range, <1-2349 µg/L) and a median total ALP level of 85 U/L (range, 29-705 U/L). These values were lower than those of the 614 patients in the ALSYMPCA trial, who had a median PSA level of 146 µg/L (range, 4-6026 µg/L) and a median total ALP level of 211 U/L (range, 32-6431 U/L).

Twenty-nine patients (66%) completed retreatment with radium-223. The median time from the end of the initial treatment course to enrollment was 6 months. The incidence of treatment-emergent AEs was similar to that in the ALSYMPCA trial, with only 2 retreated patients experiencing grade 3 hematologic treatment-emergent AEs. No grade 4 or 5 treatment-emergent

AEs were reported. Hematologic treatment-emergent AEs of any grade included anemia (14%), thrombocytopenia (2%), and leukopenia (2%). In the overall population, levels of neutrophils, platelets, and hemoglobin remained relatively stable through the end of treatment. The most common nonhematologic treatment-emergent AEs of any grade were fatigue (27%), nausea (25%), and diarrhea (21%). Two patients reported serious ocular treatment-emergent AEs, and 5 patients reported nonserious ocular treatment-emergent AEs. Only 1 episode of grade 1 photopsia was considered related to treatment. The median time to radiographic PFS was 9.9 months, with the majority of events occurring in soft tissue (Figure 4). Among the 13 patients with radiographic progression events, 8 had soft tissue progression, 2 had radiographic progression from disposition that was not documented in the radiographic tumor assessment, 2 died, and 1 had confirmed radiographic bone progression. The median time to bone progression was not reached (Figure 5). A larger prospective study will address expanded dosing and extended duration of treatment with radium-223.

References

1. Xofigo [prescribing information]. Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc; 2013.
2. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
3. Sartor AO, Heinrich D, Mariados N, et al. Radium-223 (Ra-223) re-treatment (Re-tx): first experience from an international, multicenter, prospective study in patients (Pts) with castration-resistant prostate cancer and bone metastases (mCRPC) [ASCO GU abstract 197]. *J Clin Oncol*. 2016;34(suppl 2S).

Celecoxib With or Without Zoledronic Acid for Hormone-Naïve Prostate Cancer: Survival Results From STAMPEDE (NCT00268476)

The STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial was designed to test the hypothesis that adding other drugs to standard hormone treatment at the time of diagnosis would improve outcomes in men with high-risk prostate cancer. The trial enrolled men with high-risk, locally advanced, metastatic or recurrent prostate cancer who were starting first-line long-term hormone therapy. The additional therapies were zoledronic acid, docetaxel, and celecoxib, alone or in combination. Enrolled patients were either newly diagnosed or had relapsed after treatment. Newly diagnosed patients had metastatic disease and 2 of the following characteristics: stage T3 or T4 disease, a PSA level of at least 40 ng/mL, and a Gleason score of 8 to 10. Patients with relapsed prostate cancer had high-risk disease and had received prior treatment with radical surgery, radiotherapy, or both.

Results from 3 arms of the trial have been published.[1] All experimental therapies evaluated in the STAMPEDE trial were administered in combination with the standard of care, which included hormone therapy with or without radiotherapy. All outcomes for the experimental arms were compared with the control arm. The addition of zoledronic acid to standard-of-care therapy did not improve survival over the standard of care alone (HR, 0.94; 95% CI, 0.79-1.11; *P*=.450). In contrast, docetaxel given at the initiation of long-term hormone therapy improved overall survival vs the control arm (HR, 0.78; 95% CI, 0.66-0.93; *P*=.006). Rates of AEs increased with the addition of docetaxel. Patients treated with a combination of zoledronic acid and docetaxel achieved a superior overall survival vs

ABSTRACT SUMMARY To Assess the Clinical Effect of Radium 223 (Ra223) in Patients With Progressive Symptomatic Bone Metastases on a Background of Metastatic Castrate Resistant Prostate Cancer (mCRPC)

A retrospective study was conducted to evaluate the efficacy and safety of radium-223 in patients with metastatic CRPC (Abstract 347). The study included 58 patients, and the median follow-up was 11.6 months (range, 1.0-18.1 months). The median age was 71 years (range, 54-84 years). Patients had received a median 5 injections of radium-223 (50 kBq/kg), and a median of 3 prior treatments (range, 1-6). There were no treatment-related deaths. Grade 3/4 AEs occurred in 5% of patients, and included neutropenia (3%) and anemia (2%). Skeletal-related AEs occurred in 5% of patients, and they developed at a median 218 days after completion of treatment with radium-223. Half of patients had a clinical response. The median PSA level increased from 225 µg/L at baseline to 418 µg/L after treatment (*P*<.0001). The median ALP level decreased from 292 U/L at baseline to 138 U/L after treatment (*P*<.0001). The decrease in ALP level was greater in patients who experienced a clinical benefit. After initiation of radium-223, the median overall survival was 8.33 months (95% CI, 5.65-13.50 months), and the median PFS was 7.23 months (95% CI, 5.73-7.93 months).

the standard of care only (HR, 0.82; 95% CI, 0.69-0.97; *P*=.022). However, outcomes in this arm were comparable to treatment with docetaxel alone added to the standard of care. The authors recommended that docetaxel should be added to the standard of care in men who are beginning long-term hormone therapy and are adequately fit.

Dr Nicholas James presented results from patients who received celecoxib with or without zoledronic acid as part of the STAMPEDE trial.[2,3] Zoledronic acid is a bisphosphonate that inhibits bone resorption, thereby preventing or delaying skeletal events in CRPC patients with bone metastases. Celecoxib is a selective COX-2 inhibitor and nonsteroidal anti-inflammatory drug. COX-2 is induced by various mitogens and cytokines. Its expression is upregulated in prostate cancer, and in vitro studies have demonstrated that inhibition of COX-2 reduces the growth and invasiveness of prostate cancer cell lines.[4] Celecoxib induces apoptosis in prostate cancer cell lines without affecting the normal prostate epithelium. Epidemiologic studies suggest that long-term use of nonsteroidal anti-inflammatory drugs can protect against prostate cancer and other cancers.[5]

The analysis presented by Dr James included 622 patients who received the standard of care only, 312 who received celecoxib, and 311 who received zoledronic acid plus celecoxib. Before randomization, patients were stratified based on metastatic disease, World Health Organization performance status, age, and planned treatment with either radiotherapy or luteinizing hormone-releasing hormone. Patients had a median age of 65 years (range, 37-94 years). Among the 61% of patients with metastatic disease, 52% had metastasis to the bone. World Health Organization performance status was 0 in 77% of patients. The median follow-up was 63 months. During follow-up, 36% of patients died from prostate cancer and 9% from other causes.

The initial results of the celecoxib arm showed no improvement in failure-free survival with the addition of celecoxib to the standard of care vs the control arm (HR, 0.94; 95% CI, 0.74-1.20; Figure 6).[2] Updated failure-free survival data continued to show similarity for the 2 arms (HR, 0.88; 95% CI, 0.77-1.04; *P*=.122), and overall survival was also similar (HR, 1.00; 95% CI, 0.82-1.22; *P*=.986). Based on preplanned analysis of patients with vs without metastases, no difference in overall survival emerged. However, patients with metastases appeared to have a possible advantage in failure-free survival compared with the control arm, as evidenced by clearly separated Kaplan-Meier curves, but the difference did not reach significance (HR, 0.86; 95% CI, 0.71-1.05; *P*=.130).

The combination of zoledronic acid and celecoxib also failed to demonstrate a difference in failure-free survival (HR, 0.85; 95% CI, 0.72-1.01; *P*=.058) or overall survival vs the control arm. However, a preplanned analysis demonstrated a difference in outcomes for patients with metastases (HR, 0.77; 95% CI, 0.63-0.93; *P*=.008). No difference in failure-free survival emerged for nonmetastatic patients (HR, 1.05; 95% CI, 0.77-1.43; *P*=.761). A heterogeneity analysis confirmed the difference in outcomes for metastatic vs nonmetastatic patients (*P*=.086). Furthermore, a difference in overall survival also emerged from a preplanned analysis in patients with metastases treated with zoledronic acid and celecoxib added to the standard of care vs the control arm (HR, 0.78; 95% CI, 0.62-0.99; *P*=.040), but not in nonmetastatic patients (HR, 1.25; 95% CI, 0.81-1.93; *P*=.318). Heterogeneity analysis again confirmed the difference in outcomes for metastatic vs nonmetastatic patients (*P*=.065).

The target dose of celecoxib was 400 mg twice daily, for up to 1 year or until disease progression. At 1 year, 60% of

ABSTRACT SUMMARY A Multicenter Phase I Study of Cabazitaxel, Mitoxantrone, and Prednisone for Chemotherapy-Naive Patients With Metastatic Castration-Resistant Prostate Cancer

Second-line treatment with cabazitaxel plus prednisone has demonstrated antitumor activity and prolonged survival among patients with metastatic CRPC who received first-line treatment with docetaxel (de Bono JS et al. *Lancet.* 2010;376[9747]:1147-1154). Mitoxantrone has also demonstrated antitumor activity in combination with prednisone, and it is approved for pain palliation. Mitoxantrone differs from cabazitaxel in mechanism of action and toxicity profile. A multicenter, dose-escalation, phase 1 trial with an accelerated titration design was conducted to determine the maximum tolerated doses and recommended phase 2 doses of mitoxantrone and cabazitaxel plus prednisone (Abstract 202). The trial enrolled 24 chemotherapy-naive patients with metastatic CRPC. Patients' median age was 67 years (range, 51-78 years). The baseline median PSA level was 62.5 µg/L (range, 3-791.2 µg/L). There were 2 dose-limiting toxicities—sepsis and febrile neutropenia—among the 4 patients treated with 25 mg/m^2 of cabazitaxel plus 10 mg/m^2 of mitoxantrone. Cabazitaxel at 20 mg/m^2 plus mitoxantrone at 12 mg/m^2 was associated with 2 dose-limiting toxicities of febrile neutropenia among 11 patients treated. The recommended phase 2 dose and maximum tolerated dose was established as 20 mg/m^2 for cabazitaxel plus 12 mg/m^2 for mitoxantrone. The most common treatment-related AEs of grade 3 or higher were hematologic, and no cardiac AEs were observed. Patients received a median 7.5 treatment cycles (range, 2-16). In 13 of 21 evaluable patients (62%), the PSA level declined by at least 50% from baseline. Objective tumor responses were observed in 4 of 6 patients (67%) with measurable disease. The median duration of response was not reached (range, 4.9-10.0+ months).

patients were progression-free, and many patients had stopped treatment for reasons other than progression. The target dose of zoledronic acid was 4 mg every 3 weeks for up to 18 weeks, then every 4 weeks for up to 2 years or until disease progression. Overall, compliance was superior for zoledronic acid compared with celecoxib. Rates of severe AEs were similar in the safety populations of the 3 arms, with the most common events in the control, celecoxib, and zoledronic acid/celecoxib arms being endocrine disorders (14%, 11%, 10%), musculoskeletal events (7%, 8%, 5%), and renal events (6%, 4%, 5%). Cardiotoxicity was low, at 3% per arm, but the trial deliberately excluded patients with a history of heart problems. The time to first subsequent therapy of any type was similar for the 3 arms, as was time to the need for life-prolonging therapy.

In summary, the addition of zoledronic acid alone to the standard of care did not improve failure-free survival or overall survival in patients with CRPC.[1] Adding celecoxib alone to the standard of care did not improve failure-free survival or overall survival. The addition of both zoledronic acid and celecoxib to the standard of care improved failure-free survival and overall survival in patients with metastatic disease, but not in the general study population.

References

1. James ND, Sydes MR, Clarke NW, et al; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial [published online December 21, 2015]. *Lancet*. doi:10.1016/S0140-6736(15)01037-5.
2. James ND, Sydes MR, Clarke W, et al. Celecoxib with or without zoledronic acid for hormone-naïve prostate cancer: survival results from STAMPEDE (NCT00268476) [ASCO GU abstract 162]. *J Clin Oncol*. 2016;34(suppl 2S).
3. James ND, Sydes MR, Mason MD, et al; STAMPEDE investigators. Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer: first results from the STAMPEDE multiarm, multistage, randomised controlled trial. *Lancet Oncol*. 2012;13(5):549-558.
4. Harris RE. Cyclooxygenase-2 (cox-2) blockade in the chemoprevention of cancers of the colon, breast, prostate, and lung. *Inflammopharmacology*. 2009;17(2):55-67.
5. Liu Y, Chen JQ, Xie L, et al. Effect of aspirin and other non-steroidal anti-inflammatory drugs on prostate cancer incidence and mortality: a systematic review and meta-analysis. *BMC Med*. 2014;12:55.

ABSTRACT SUMMARY Imaging Response During Therapy (tx) With Radium-223 (Ra-223) for Castrate Resistant Prostate Cancer (CRPC) With Bone Metastases (BM)

A study was conducted to determine the imaging response in CRPC patients with bone metastases receiving standard treatment with radium-223 (Abstract 282). The 51 enrolled patients had a median age of 72 years. Prior treatment included docetaxel in 59%, and 47% had received concomitant treatment with enzalutamide or abiraterone. Approximately three-quarters of patients received the full, 6-injection treatment course of radium-223. As measured by improvement of skeletal pain and performance status, a clinical benefit was observed in 67% of patients. ALP levels decreased in 53% of patients. At 3 months, bone metastatic disease was improved in 22% of patients, was stable in 53%, and had progressed in 25%. Progression of extraskeletal sites, including the lymph nodes, lungs, liver, and adrenal glands, occurred in 35% of patients. Factors associated with superior response to radium-223 included PSA level doubling time of at least 3 months (odds ratio, 2.62; *P*=.02) and concomitant treatment with enzalutamide or abiraterone (odds ratio, 3.3; *P*=.04). A trend toward improved outcome was seen with stable or decreasing levels of lactate dehydrogenase (odds ratio, 2.9; *P*=.05). A CT scan at 3 months to assess bone metastases may be warranted in patients at high risk of progression.

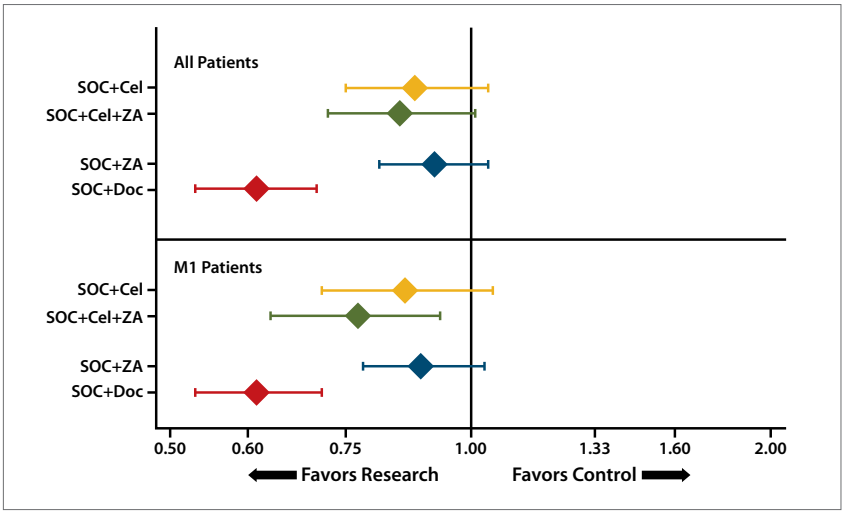


Figure 6. Failure-free survival among patients receiving standard hormone treatment and celecoxib with or without zoledronic acid in the STAMPEDE trial. Cel, celecoxib; Doc, docetaxel; SOC, standard of care; STAMPEDE, Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; ZA, zoledronic acid. Adapted from James ND et al. ASCO GU abstract 162. *J Clin Oncol*. 2016;34(suppl 2S).[2]

Differential Side Effects Profile in mCRPC Patients Treated With Abiraterone or Enzalutamide: A Meta-Analysis of Randomized Controlled Trials

ABSTRACT SUMMARY Impact of Single Agent Daily Prednisone on Survival and Toxicities in Post-Docetaxel Men With Metastatic Castration-Resistant Prostate Cancer (mCRPC): An Analysis of 2 Phase III Trials

A pooled analysis of randomized controlled trials was conducted to determine the efficacy and toxicity of prednisone in men with metastatic CRPC (Abstract 213). The analysis included patient data from the control arms of 2 phase 3 trials: COU-AA-201 (de Bono JS et al. *N Engl J Med*. 2011;364[21]:1995-2005) and CA184-043 (Kwon ED et al. *Lancet Oncol*. 2014;15[7]:700-712). In both trials, patients had metastatic CRPC and had received previous treatment with docetaxel. Patients in COU-AA-201 (n=394) received prednisone plus placebo whereas patients in CA184-043 (n=400) received placebo only. Prednisone plus placebo did not show an improvement in overall survival vs placebo alone (HR, 0.89; 95% CI, 0.72-1.10; *P*=.27). In multivariate analyses, however, prednisone was associated with a higher incidence of treatment-related AEs of grade 3 or higher (HR, 1.48; 95% CI, 1.03-2.13; *P*=.034). Baseline characteristics associated with an elevated risk of grade 3 or higher AEs included ECOG PS of 1 or greater, hypoalbuminemia, and elevated lactate dehydrogenase. Corticosteroid use may have confounded results of the analysis.

Enzalutamide is an oral androgen receptor inhibitor thought to have several mechanisms of action, including disruption of nuclear translocation by the androgen receptor and DNA binding of hormone response elements.[1] Abiraterone inhibits the enzymatic activity of P450c17/CYP17A1, a key regulator of steroid production. With their distinct mechanisms of action, these 2 therapies may also have different toxicity profiles.

A meta-analysis of randomized, controlled, phase 3 trials was conducted to characterize the risk of AEs associated with abiraterone vs enzalutamide in patients with metastatic CRPC.[2] Publications listed on PubMed and published between January 1, 1966 to July 31, 2015 and abstracts presented at meetings of the American Society of Clinical Oncology from 2004 through 2015 were included.[3-6] Two meta-analyses were performed: one for abiraterone plus prednisone vs placebo plus prednisone, which included 2283 patients, and one for enzalutamide vs placebo, which included 2914 patients. Enzalutamide was associated with an increased risk of fatigue of any grade (relative risk [RR], 1.29; 95% CI, 1.15-1.44; Table 1). Enzalutamide was not associated with an increased risk of cardiovascular events of any grade (RR, 1.06; 95% CI, 0.67-1.65) or grade 3 or higher (RR, 0.81; 95% CI, 0.28-2.33). Abiraterone increased the risk of cardiovascular events of any grade (RR, 1.28; 95% CI, 1.06-1.55) or grade 3 or higher (RR, 1.76; 95% CI, 1.12-2.75). Abiraterone was not associated with an increased risk of fatigue of any grade (RR, 0.85; 95% CI, 0.58-1.23) or grade 3 or higher (RR, 1.07; 95% CI, 0.97-1.19).

Table 1. Adverse Events in a Meta-Analysis of Trials of Enzalutamide and Abiraterone

Study	Treatment Arms	Patients (N)	Grade 3 or Higher Fatigue (n, %)	Any Cardiac Events (n, %)	Grade 3 or Higher Cardiac Events (n, %)
Beer TM et al. *N Engl J Med*. 2014[3]	Enzalutamide	871	16 (1.8)	88 (10.1)	24 (2.8)
	Placebo	844	16 (1.9)	66 (7.8)	18 (2.1)
Scher HI et al. *N Engl J Med*. 2012[6]	Enzalutamide	800	50 (6.3)	49 (6.1)	7 (0.9)
	Placebo	399	29 (7.3)	30 (7.6)	8 (2.0)
de Bono JS et al. *N Engl J Med*. 2011[4]	Abiraterone plus prednisone	797	66 (8.3)	106 (13.3)	33 (4.1)
	Prednisone	398	39 (9.8)	42 (10.6)	9 (2.3)
Ryan CJ et al. *N Engl J Med*. 2013[5]	Abiraterone plus prednisone	546	NR	133 (24.4)	31 (5.7)
	Prednisone	542	NR	102 (18.8)	18 (3.3)

NR, not reported.
Adapted from Moreira R et al. ASCO GU abstract 73. *J Clin Oncol*. 2016;34(suppl 2S).[2]

References

1. Crawford ED, Higano CS, Shore ND, Hussain M, Petrylak DP. Treating patients with metastatic castration resistant prostate cancer: a comprehensive review of available therapies. *J Urol*. 2015;194(6):1537-1547.
2. Moreira R, Debiasi M, Maluf FC, et al. Differential side effects profile in mCRPC patients treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials [ASCO GU abstract 73]. *J Clin Oncol*. 2016;34(suppl 2S).
3. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
4. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
5. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.
6. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.

Phase II Clinical Study of Radium-223 Chloride (BAY 88-8223) in Japanese Patients With Symptomatic Castration-Resistant Prostate Cancer (CRPC) With Bone Metastases

The ALSYMPCA study evaluated radium-223 dichloride in patients with CRPC and symptomatic bone metastases. The trial met its primary endpoint by demonstrating an overall survival of 14.9 months with radium-223 vs 11.3 months with best standard of care (P<.001).[1] In a post-hoc analysis of 708 patients from the ALSYMPCA trial, higher baseline total ALP was associated with an increased risk of death (P<.0001).[2] At 12 weeks, total ALP decreased relative to baseline in 87% of patients treated with radium-223 vs 23% who received placebo. Mean total ALP levels decreased by 32% with radium-223 and increased by 37% with placebo (P<.001).

A phase 2 trial was conducted in Japanese patients with metastatic CRPC to evaluate the relationship between radium-223 treatment and ALP levels.[3] The single-arm trial included patients with CRPC, at least 2 bone metastases, and no visceral metastases. Patients received 1 injection of radium-223 (50 kBq/kg) every 4 weeks for a total of 6 injections. The primary endpoint was the change in total ALP from baseline to 12 weeks. The efficacy and safety population consisted of 49 patients. The median age was 74 years (range, 61-83 years), and 96% had an ECOG PS of 0 or 1. The median Gleason score was 9 (range, 6-10). Only 6.1% of patients had fewer than 6 metastases. Over half of patients had more than 20 lesions but did not reach superscan status (ie, lesions in >75% of the ribs, vertebrae, and pelvic bones). Prior docetaxel treatment was noted in 55.1% of patients.

Patients received a median 6 injections of radium-223 (range, 1-6 injections). Treatment was discontinued in 42.9%, and 63.3% of patients used bone-modifying agents during treatment with radium-223. At 12 weeks, the mean total ALP level decreased from baseline by 19.3% (95% CI,

ABSTRACT SUMMARY A Phase 2 Study of BIND-014 (PSMA-Targeted Docetaxel Nanoparticle) Administered to Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer (mCRPC)

BIND-014 is a novel polymeric nanoparticle that contains docetaxel and is targeted to the prostate-specific membrane antigen. This novel agent has been developed with the goal of increasing the intratumoral concentration and duration of exposure to docetaxel. In a phase 1 study, BIND-014 was generally well-tolerated and displayed antitumor activity in multiple tumor types, including 2 patients with chemotherapy-naive metastatic CRPC (Von Hoff D et al. *Clin Cancer Res*. Published online February 4, 2016; doi:10.1158/1078-0432.CCR-15-2548). To further elucidate its activity in this setting, BIND-014 was evaluated in a phase 2 study of patients with chemotherapy-naive, metastatic CRPC (Abstract 233). Patients received a 60-minute infusion of BIND-014 (60 mg/m^2) on day 1 of a 21-day cycle in combination with prednisone (5 mg twice daily). Prior treatments included abiraterone (48%), enzalutamide (12%), and both (14%). The study enrolled 42 patients who received a median 6 infusions of BIND-014 (range, 1-21 infusions). Median radiologic PFS was 7.1 months (95% CI, 2.6-9.9 months), and 78% of patients reached a radiographic PFS of 6 months or longer. A reduction in the PSA level of 50% or higher from baseline was observed in 30% of 40 patients. Circulating tumor cell conversion, defined as fewer than 5 cells per 7.5 mL of blood after treatment, occurred in 50% of 26 patients. Among the patients with measurable disease (n=19), the response rate was 21% and included 1 confirmed complete response and 3 confirmed partial responses. Estimated median overall survival was 13.4 months (95% CI, 9.9-18.6 months). The majority of treatment-related AEs were grade 1/2. The most common treatment-related hematologic grade 3/4 AEs were lymphopenia (11.9%) and anemia (7.1%). The most common treatment-related nonhematologic grade 3/4 AEs were fatigue (4.8%), nausea (4.8%), dyspnea (2.4%), and decreased appetite (2.4%).

ABSTRACT SUMMARY A Randomized Trial of Abiraterone Acetate (AA) Administered With 1 of 4 Glucocorticoid (GC) Regimens in Metastatic Castration-Resistant Prostate Cancer (mCRPC) Patients (pts)

Abiraterone inhibits androgen synthesis but frequently leads to an increase in mineralocorticoid hormones and associated AEs. To prevent these AEs, abiraterone is approved in combination with prednisone for the treatment of metastatic CRPC. An open-label, multicenter, phase 2 study was conducted to evaluate lower glucocorticoid doses in patients with asymptomatic, chemotherapy-naive, metastatic CRPC (Abstract 261). Patients were randomly assigned to 1 of 4 treatment arms: 24 weeks of abiraterone plus either prednisone at 5 mg twice daily, 5 mg once daily, or 2.5 mg twice daily; or dexamethasone at 0.5 mg daily. Treatment-emergent AEs associated with mineralocorticoid excess were observed in 79.4%, 45.9%, 62.9%, and 75.7% of patients, respectively. The most frequent treatment-emergent AE associated with mineralocorticoid excess was hypertension. No grade 4 hypokalemia or hypertension was reported. A post hoc predictor analysis suggested that AEs associated with mineralocorticoid excess were more likely in patients with higher systolic blood pressure, hypertension, and higher sodium levels at baseline. The most favorable outcome was seen in the treatment arm of prednisone at 5 mg once daily, but this finding may have been confounded by the fact that this arm had the highest proportion of patients with grade 2 hypertension at baseline.

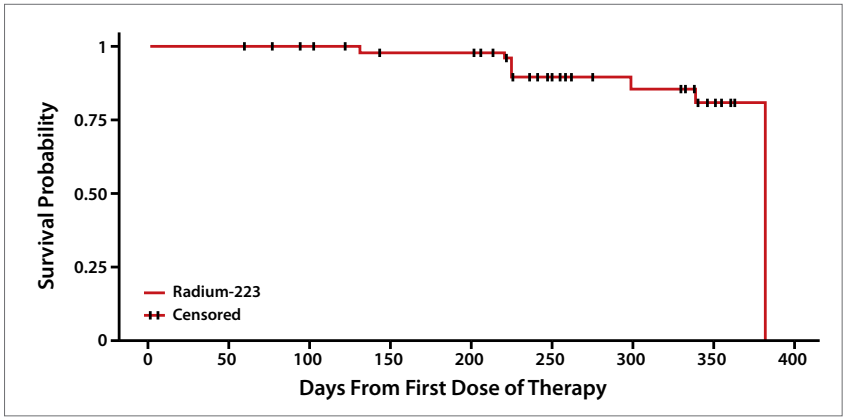


Figure 7. Overall survival in a phase 2 trial of radium-223 chloride in Japanese patients. Adapted from Uemura H et al. ASCO GU abstract 167. *J Clin Oncol.* 2016;34(suppl 2S).[3]

28.0%-10.7%). The upper limit of the 95% CI at 12 weeks was less than 0, demonstrating similarities in ALP reduction in the phase 2 study and the phase 3 ALSYMPCA study.[2] At 12 weeks, the reduction in total ALP was at least 30% in 36.7% of patients and at least 50% in 10.2% of patients. At the end of treatment, a reduction of at least 30% was seen in 34.7%, and a reduction of at least 50% was observed in 14.3%. The median time to total ALP progression was not reached. The PFS rate at 1 year was 59%.

The mean change in PSA from baseline was 97.4% (95% CI, 50.1%-144.8%) at 12 weeks and 280.5% (95% CI, 136.7%-424.4%) at the end of treatment. Median overall survival was 381 days, and the overall survival rate at 1 year was 78% (Figure 7). The most common treatment-emergent AEs of any grade were anemia (32.7%), reduced lymphocyte count (28.6%), and decreased appetite (26.5%). Increased bone pain was reported in 20.4% of patients. The most common treatment-emergent AEs of grade 3 or higher were anemia (14.3%), decreased lymphocyte count (14.3%), decreased appetite (10.2%), and bone pain (10.2%). Three patients (6.1%) experienced a treatment-emergent AE leading to permanent discontinuation of radium-223, and 2 of these discontinuations were considered related to the study drug. Radium-223 treatment was generally well tolerated, and the reduction in total ALP concentration was similar to that observed in the ALSYMPCA trial.

References

1. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369(3):213-223.

2. Sartor AO, Amariglio R, Wilhelm S, et al. Correlation between baseline variables and survival in the radium-223 dichloride (Ra-223) phase III ALSYMPCA trial with attention to total ALP changes [ASCO GU abstract 5080]. *J Clin Oncol.* 2013;31(suppl).

3. Uemura H, Nagamori S, Wakumoto Y, et al. Phase II clinical study of radium-223 chloride (BAY 88-8223) in Japanese patients with symptomatic castration-resistant prostate cancer (CRPC) with bone metastases [ASCO GU abstract 167]. *J Clin Oncol.* 2016;34(suppl 2S).

Highlights in Metastatic Prostate Cancer From the 2016 American Society of Clinical Oncology Genitourinary Cancers Symposium: Commentary

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Several abstracts presented at the 2016 American Society of Clinical Oncology Genitourinary Cancers Symposium provided insight into the management of metastatic prostate cancer. Studies evaluated therapies such as radium-223, abiraterone acetate, glucocorticoids, and celecoxib. Data from real-world analyses were also presented.

Studies of Radium-223

A real-world study assessed the on-label use of radium-223 in 36 patients with metastatic castration-resistant prostate cancer (CRPC) and bone metastases at a single institution in the United Kingdom.[1] This analysis included a higher percentage of patients older than 75 years as compared with the ALSYMPCA (Alpharadin in Symptomatic Prostate Cancer) trial.[2] The study found that radium-223 was safe, well-tolerated, and effective. Elderly patients did well. Completion of the entire 6-cycle course of radium-223 therapy was associated with a significantly higher progression-free survival. A higher discontinuation rate was seen among patients who had received previous treatment with docetaxel and those who had a low albumin level (which suggests poor nutritional status). The authors concluded that these findings could help guide sequencing of therapies. It may be beneficial to start radium-223 earlier in a patient who might be unfit for chemotherapy or who has minimal symptomatology.

I presented interim results from the first well-documented, rigorously interrogated, prospective evaluation of combinatorial therapy with abiraterone acetate and radium-223.[3] There have been some previous retrospective data from expanded access programs, but none with a planned methodology. These 2 treatments have distinct mechanisms of action. This interim analysis reported on 30 patients who received 6 cycles of radium-223 with concurrent abiraterone. At the end of treatment, patients reported decreases in bone pain, as well as improvement in Eastern Cooperative Oncology Group performance status and quality of life, as compared with baseline. There were no new tolerability or safety signals. Expected decreases in levels of prostate-specific antigen and alkaline phosphatase were seen. There were no clinically significant changes in serologic parameters. The final analysis of this study will compare computed tomography and bone scans at baseline with those taken after 4 months of treatment and at the end of the study. We will also report on patients' concomitant medications, such as denosumab and zoledronic acid, as well as the use of sipuleucel-T before therapy.

Dr Oliver Sartor presented results of an international, prospective, open-label phase 1/2 study of retreatment with radium-223.[4] Radium-223 is currently approved for a single 6-injection course of therapy by the US Food and Drug Administration. This important study is the first to report on retreatment. Enrolled patients had completed a full, 6-cycle course of radium-223 and developed radiographic or clinical progression. Many patients had also received treatment with therapies such as docetaxel (in 45%), abiraterone (in 61%), and enzalutamide (in 30%). Among the 44 patients in the study, 29 completed another full course of radium-223. The second course of radium-223 controlled disease progression with a minimal number of hematologic toxicities. Radiographic bone progression was rare, and progression was confined to the soft tissue. The rare hematologic toxicities were limited to anemia, thrombocytopenia, and leukopenia, which occurred in the low single digits.

A phase 2 trial examined the use of radium-223 among patients with CRPC and bone metastases in Japan.[5] There is an important history of studying new therapies in Japan. It has been postulated that Japanese patients might differ from the Western population in factors such as body mass index and genomic tolerability, which could impact response to treatment. This multicenter study found good tolerability and response that was consistent with the ALSYMPCA trial.[2] Reductions in levels of total alkaline phosphatase were also similar.

A study by Dr Daniel Keizman evaluated computed tomography scans and bone scans to determine imaging response during therapy with radium-223 among patients with CRPC and bone metastases.[6] Progression of bone metastases during radium-223 therapy was uncommon. Flares that appear on early scans within the first 3 months of treatment should not be confused with progression of bone

metastases. Clinicians should consider repeating a computed tomography scan at 3 months among patients with a worsening symptomatology, a short pretreatment prostate-specific antigen doubling time, or a significant increase in lactate dehydrogenase, to exclude extraskeletal metastatic disease progression.

Other Clinical Trials

Dr Gerhardt Attard presented initial results of a randomized trial in patients with metastatic CRPC that combined abiraterone at 1000 mg daily with 1 of 4 glucocorticoid regimens: prednisone at 5 mg once daily, 2.5 mg twice daily, or 5 mg twice daily; or dexamethasone at 0.5 mg once daily.[7] A frequent question is whether the ideal dosage of prednisone is 5 mg twice daily when used in combination with abiraterone. Some physicians believe that a lower dosage of 5 mg/day might be sufficient. A dosage of 2.5 mg twice daily might be more physiologic. Treatment-emergent adverse events associated with mineralocorticoid excess were adequately controlled with the regimens containing prednisone 5 mg twice daily and dexamethasone 0.5 mg once daily. A post-hoc predictor analysis suggested that mineralocorticoid excess was associated with higher systolic blood pressure, preexisting hypertension, and higher sodium at baseline. This information about safety, tolerance, and compliance is important because it can be used to help avoid the long-term challenges associated with the chronic use of corticosteroids.

A multicenter, phase 1 study evaluated cabazitaxel, mitoxantrone, and prednisone in chemotherapy-naive patients with metastatic CRPC.[8] Cabazitaxel is approved only for use after chemotherapy. Mitoxantrone is a long-standing chemotherapeutic agent approved only for palliation. This study is the first to combine these therapies. Two doses of cabazitaxel were evaluated: 20 mg/m^2 and 25 mg/m^2. Mitoxantrone was evaluated at escalating doses starting at 4 mg/m^2. The study found that mitoxantrone at the approved dose (12 mg/m^2) was safely combined with cabazitaxel at 20 mg/m^2. The lower dose of cabazitaxel appeared to be associated with less hematologic toxicity than the higher dose. In general, patients stayed on therapy for a reasonably long period. More studies will be required to confirm a synergy between mitoxantrone and cabazitaxel in chemotherapy-naive patients.

A phase 2 study evaluated BIND-014, a nanoparticle that targets prostate-specific membrane antigen (PSMA) and contains docetaxel.[9] An interesting aspect of this study is that it used PSMA-targeted scanning to better define evidence of radiographic disease. PSMA-targeted scanning has been used for diagnosis, and this study suggests that it may have a therapeutic role. By 6 months, 78% of patients reached radiographic progression-free survival. The overall response rate was 21%. This early study will require additional validation with larger numbers of patients.

A multicenter study examined survival and toxicities associated with daily, single-agent prednisone in men with metastatic CRPC who had progressed on docetaxel.[10] The study found no improvement with prednisone compared with placebo. Patients receiving prednisone had more toxicities.

Dr Nicholas James presented data from the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) trial of patients with androgen-sensitive advanced or metastatic disease.[11] There were 3 study arms: standard-of-care androgen-deprivation therapy, standard-of-care therapy plus celecoxib, and standard-of-care therapy plus celecoxib and zoledronic acid. The addition of celecoxib and zoledronic acid to standard-of-care therapy improved failure-free survival and overall survival among men with metastatic CRPC receiving hormone therapy for the first time. The mechanisms of action and synergy potential are unclear. Celecoxib may be associated with cardiovascular toxicity. However, the use of celecoxib with zoledronic acid and androgen-deprivation therapy may have potential when chemotherapy is not an option, specifically for patients with androgen-sensitive metastatic disease.

Adverse Events With Enzalutamide and Abiraterone Acetate

A meta-analysis evaluated the differential adverse events associated with enzalutamide and abiraterone in 4 randomized, controlled trials: COU-AA-301 (Abiraterone Acetate in Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy), COU-AA-302 (Abiraterone Acetate in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer), PREVAIL (A Safety and Efficacy Study of Oral MDV3100 in Chemotherapy-Naive Patients With Progressive Metastatic Prostate Cancer), and AFFIRM (Safety and Efficacy Study of MDV3100 in Patients With Castration-Resistant Prostate Cancer Who Have Been Previously Treated With Docetaxel-Based Chemotherapy).[12-16] These trials led to the approval of these therapies. The meta-analysis showed that abiraterone was associated with an increased risk of cardiovascular adverse events, all grade. Enzalutamide was associated with an increased risk of all-grade fatigue. These therapies share a similar mechanism of action and have comparable efficacy. Therefore, a better understanding of their differential side effects is critical. I look forward to participating in head-to-head trials of enzalutamide and abiraterone that will aim to discern real-world safety and tolerability issues, which could further inform sequencing.

Other Real-World Studies

A French study sought to provide insight into the real-life management of patients with metastatic CRPC.[17] More than 100 physicians completed an online questionnaire consisting of 22 questions on topics such as first-line therapy

of metastatic CRPC and the choice of docetaxel over novel hormonal therapies. Approximately half of the physicians were medical oncologists, and the other half were divided between urologists and radiation oncologists. The choice of docetaxel was associated with patient characteristics such as visceral metastases, heavy tumor burden, short courses of androgen-deprivation therapy before progression to CRPC, and symptomatology. The selection of a novel hormone as opposed to chemotherapy was associated with longer periods of time on androgen-deprivation therapy before progressing, lack of symptoms, lower tumor burden, and lack of visceral metastases.

The CAPRO study from Spain examined the use of second-line management after docetaxel in real-world clinical settings.[18] In Spain, docetaxel is a common first-line therapy in patients with CRPC. Enzalutamide is not yet approved, and radium-223 is still being introduced. Unsurprisingly, the CAPRO trial found that the most frequent second-line therapy was abiraterone. In a small percentage of patients, cabazitaxel was the second-line choice. As therapies such as abiraterone, enzalutamide, and radium-223 become more common worldwide, physicians will likely incorporate them into management based on their overall safety and tolerability. Clearly, the goal is to give the right therapy to the right patient at the right time.

Disclosure

Dr Shore has served as an advisor or consultant for Astellas Pharma, Bayer HealthCare Pharmaceuticals, Dendreon Corporation, Ferring Pharmaceuticals, Janssen Pharmaceuticals, Medivation, Millennium Pharmaceuticals, and Sanofi.

References

1. Challapalli A, Hilman S, Cowley S, et al. Radium-223 in metastatic castration resistant prostate cancer: progression free survival and pain scores—real-world single-institution experience [ASCO GU abstract 250]. *J Clin Oncol*. 2016;34(suppl 2S).
2. Parker C, Nilsson S, Heinrich D, et al; ALSYMPCA Investigators. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-223.
3. Shore ND, Tutrone RF, Mariados NF, Nordquist LT, Mehlhaff BA, Harrelson SS. Interim results from ERADICATE: an open-label phase 2 study of radium Ra 223 dichloride with concurrent administration of abiraterone acetate plus prednisone in castration-resistant prostate cancer subjects with symptomatic bone metastases [ASCO GU abstract 177]. *J Clin Oncol*. 2016;34(suppl 2S).
4. Sartor AO, Heinrich D, Mariados N, et al. Radium-223 (Ra-223) re-treatment (Re-tx): first experience from an international, multicenter, prospective study in patients (Pts) with castration-resistant prostate cancer and bone metastases (mCRPC) [ASCO GU abstract 197]. *J Clin Oncol*. 2016;34(suppl 2S).
5. Uemura H, Nagamori S, Wakumoto Y, et al. Phase II clinical study of radium-223 chloride (BAY 88-8223) in Japanese patients with symptomatic castration-resistant prostate cancer (CRPC) with bone metastases [ASCO GU abstract 167]. *J Clin Oncol*. 2016;34(suppl 2S).
6. Keizman D, Peer A, Neumann A, et al. Imaging response during therapy (tx) with radium-223 (Ra-223) for castrate resistant prostate cancer (CRPC) with bone metastases (BM) [ASCO GU abstract 282]. *J Clin Oncol*. 2016;34(suppl 2S).
7. Attard G, Merseburger AS, Sternberg CN, et al. A randomized trial of abiraterone acetate (AA) administered with 1 of 4 glucocorticoid (GC) regimens in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) [ASCO GU abstract 261]. *J Clin Oncol*. 2016;34(suppl 2S).
8. Dhawan MS, Lee M, Bryce AH, et al. A multicenter phase I study of cabazitaxel, mitoxantrone, and prednisone for chemotherapy-naïve patients with metastatic castration-resistant prostate cancer [ASCO GU abstract 202]. *J Clin Oncol*. 2016;34(suppl 2S).
9. Autio KA, Garcia JA, Alva AS, et al. A phase 2 study of BIND-014 (PSMA-targeted docetaxel nanoparticle) administered to patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) [ASCO GU abstract 233]. *J Clin Oncol*. 2016;34(suppl 2S).
10. Sonpavde G, Pond GR, Templeton AJ, et al. Impact of single agent daily prednisone on survival and toxicities in post-docetaxel men with metastatic castration-resistant prostate cancer (mCRPC): an analysis of 2 phase III trials [ASCO GU abstract 213]. *J Clin Oncol*. 2016;34(suppl 2S).
11. James ND, Sydes MR, Clarke W, et al. Celecoxib with or without zoledronic acid for hormone-naïve prostate cancer: survival results from STAMPEDE (NCT00268476) [ASCO GU abstract 162]. *J Clin Oncol*. 2016;34(suppl 2S).
12. Moreira R, Debiasi M, Maluf FC, et al. Differential side effects profile in mCRPC patients treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials [ASCO GU abstract 73]. *J Clin Oncol*. 2016;34(suppl 2S).
13. de Bono JS, Logothetis CJ, Molina A, et al; COU-AA-301 Investigators. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
14. Ryan CJ, Smith MR, de Bono JS, et al; COU-AA-302 Investigators. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.
15. Beer TM, Armstrong AJ, Rathkopf DE, et al; PREVAIL Investigators. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-433.
16. Scher HI, Fizazi K, Saad F, et al; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med*. 2012;367(13):1187-1197.
17. Turpin A, Lemoine L, Berdah JF, et al. Management of metastatic prostate cancer patients in first line: audit of real-life practices [ASCO GU abstract 333]. *J Clin Oncol*. 2016;34(suppl 2S).
18. Puente J, Gonzalez del Alba A, Sala N, et al. Novel agents' sequencing following first-line docetaxel in mCRPC patients: CAPRO study [ASCO GU abstract 229]. *J Clin Oncol*. 2016;34(suppl 2S).


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