When metastatic castration-resistant prostate cancer progresses to symptomatic bone metastases and no known visceral metastases on an androgen receptor pathway inhibitor,[1]

Your treatment needs to be AGGRESSIVE to fight the cancer, and your patients want a treatment with a well-established SAFETY profile.[1,2]

- Median overall survival was 14.0 months (95% CI: 12.1-15.8) for Xofigo® + best standard of care (BSOC) vs 11.2 months for placebo + BSOC (95% CI: 9.0-13.2). Hazard ratio=0.695 (95% CI: 0.552-0.875) *P*=0.00185[1]
- Evaluated in the ALSYMPCA trial: double-blind, randomized, placebo-controlled, phase III study of 921 patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease[1,2]
- In ALSYMPCA, BSOC was defined as antiandrogens, local external-beam radiation therapy, ketoconazole, estrogens, estramustine, or treatment with glucocorticoids[2]

- Xofigo is associated with serious risks, including bone marrow suppression, increased fractures and mortality in combination with abiraterone plus prednisone/prednisolone, and embryo-fetal toxicity[1]
- In clinical trials, 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 3-4 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%)[1]

CI=Confidence Interval.

Please see additional Important Safety Information throughout and full Prescribing Information.

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions:

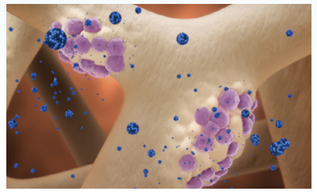
- **Bone Marrow Suppression:** In the phase 3 ALSYMPCA trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure.

Xofigo® radium Ra 223 dichloride INJECTION

OVERALL SURVIVAL
SYMPTOMATIC SKELETAL EVENTS
SAFETY
PATIENT ID

Treat the cancer where it lives[1,3-5]

XOFIGO® IS THE ONLY FDA-APPROVED TARGETED ALPHA THERAPY THAT EXERTS AN ANTI-TUMOR EFFECT ON BONE METASTASES IN CASTRATION-RESISTANT PROSTATE CANCER[1,3]

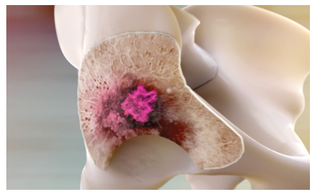


XOFIGO MIMICS CALCIUM

By mimicking calcium, Xofigo has a greater affinity for areas of increased bone turnover, such as bone metastases[1,3]

ANTITUMOR EFFECT ON BONE METASTASES

Xofigo emits alpha particles that induce double-strand DNA breaks. These hard-to-repair DNA breaks result in cell death within the tumor and its microenvironment[1,3]



LIMITED DAMAGE TO NORMAL TISSUE

The short range of alpha particles emitted by Xofigo (<10 cell diameters) limits damage to surrounding normal tissue[1,4]

Xofigo can be absorbed by organs other than bone, primarily the bone marrow and gastrointestinal system, which can result in side effects in those healthy tissues.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

- **Bone Marrow Suppression** (cont'd): 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

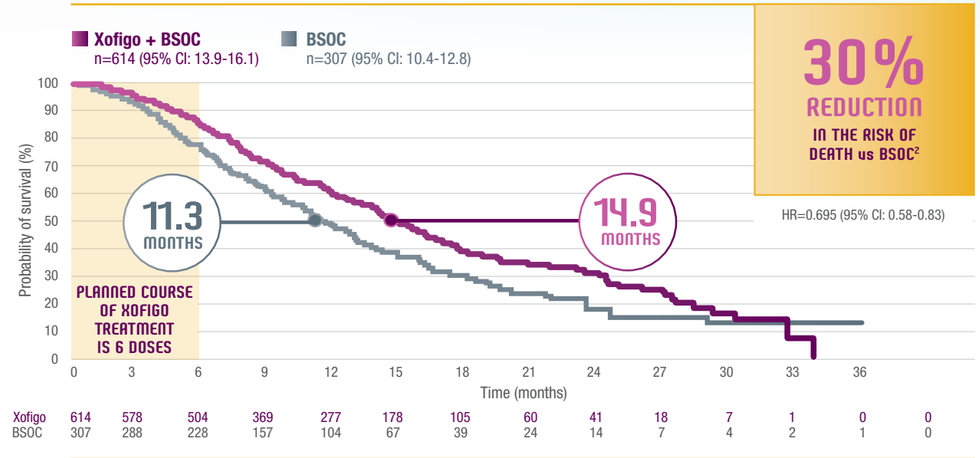
Please see additional Important Safety Information throughout and full Prescribing Information.

Xofigo significantly extends overall survival (OS)[1,2]

Prespecified interim OS analysis

Median OS was 14.0 months (95% CI: 12.1-15.8) for Xofigo + best standard of care (BSOC) vs 11.2 months for BSOC (95% CI: 9.0-13.2). Hazard ratio (HR)=0.695 (95% CI: 0.552-0.875) *P*=0.00185.[1,2]

MEDIAN OS IN AN UPDATED EXPLORATORY ANALYSIS[1,2]



- Evaluated in the ALSYMPCA trial: double-blind, randomized, placebo-controlled, phase III study of 921 patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease[1,2]
- At the preplanned interim analysis, 809 patients were randomized to receive Xofigo 55 kBq (1.49 microcurie)/kg intravenously every 4 weeks for 6 cycles (n=541) + BSOC or BSOC (n=268); statistically significant improvement seen in interim analysis[1]
- An exploratory updated analysis was performed before patient crossover, incorporating an additional 214 events, resulting in findings consistent with the interim analysis[1]
- BSOC was defined as antiandrogens, local external-beam radiation therapy, ketoconazole, estrogens, estramustine, or treatment with glucocorticoids[2]

CI=Confidence Interval.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

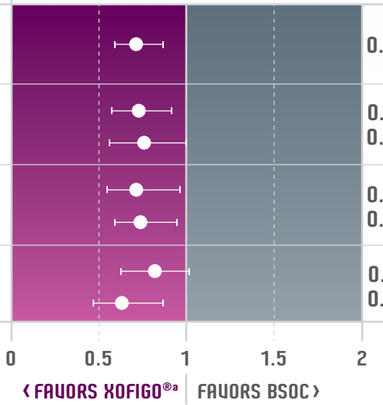
- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC 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

Xofigo® radium Ra 223 dichloride INJECTION

Overall survival (OS) analyses by prespecified subgroups[2]

PRESPECIFIED SUBGROUP SURVIVAL ANALYSIS FROM ALSYMPCA[2]

VARIABLE	SUBGROUP	n	HAZARD RATIO (HR) (95% CI)
OS		921	**0.70** (0.58-0.83)
PRIOR USE OF DOCETAXEL	yes	526	**0.71** (0.56-0.89)
	no	395	**0.74** (0.56-0.99)
CURRENT USE OF BISPHOSPHONATES	yes	374	**0.70** (0.52-0.93)
	no	547	**0.74** (0.59-0.92)
TOTAL ALKALINE PHOSPHATASE (ALP)	<220 U/L	517	**0.82** (0.64-1.07)
	≥220 U/L	404	**0.62** (0.49-0.79)



Adapted from Parker, et al.

- The primary endpoint of the ALSYMPCA study was OS[2]
- Patients were stratified into the following subgroups at randomization: prior docetaxel exposure, current bisphosphonate use, and total ALP[2]
- These subgroup analysis data are descriptive in nature—the study was not powered to detect treatment differences in OS specifically within these prestratified subgroups

CI=Confidence Interval.
[a]Plus best standard of care (BSOC).

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use 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

Please see additional Important Safety Information throughout and full Prescribing Information.

OS analyses by prespecified subgroups: prior docetaxel use

MEDIAN INCREASE IN OS WITH XOFIGO FROM ALSYMPCA[2]

DOCETAXEL NAIVE		DOCETAXEL EXPERIENCED	
4.6 MONTHS OS INCREASE		3.1 MONTHS OS INCREASE	
XOFIGO	BSOC	XOFIGO	BSOC
16.1 months n=262	vs 11.5 months n=133	14.4 months n=352	vs 11.3 months n=174
HR=0.74 (95% CI: 0.56-0.99; n=395)		HR=0.71 (95% CI: 0.56-0.89; n=526)	

BSOC=Best Standard of Care.

- The primary endpoint of the ALSYMPCA study was OS[2]
- Patients were stratified into the following subgroups at randomization: prior docetaxel exposure, current bisphosphonate use, and total ALP[2]
- These subgroup analysis data are descriptive in nature—the study was not powered to detect treatment differences in OS specifically within these prestratified subgroups

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

- **Increased Fractures and Mortality in Combination With Abiraterone Plus Prednisone/Prednisolone:** Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials. At the primary analysis of the phase 3 ERA-223 study that evaluated concurrent initiation of Xofigo in combination with abiraterone acetate plus prednisone/prednisolone in 806 asymptomatic or mildly symptomatic mCRPC patients, an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone. Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established

Xofigo® radium Ra 223 dichloride INJECTION

Xofigo® results on key biomarkers of disease progression[2,6]

Secondary endpoints: change in alkaline phosphatase (ALP) and prostate-specific antigen (PSA)[2,6]

EXPLORATORY UPDATED ANALYSIS OF SELECT SECONDARY ENDPOINTS[2,6]

	XOFIGO (n=614)	BSOC (n=307)	HAZARD RATIO (HR)	95% CONFIDENCE INTERVAL (CI)
Median time to increase in total ALP blood levels (months)	7.4	3.8	0.17	0.13-0.22
≥30% reduction in total ALP blood levels[a]	47%[b]	3%[b]	NA	NA
≥50% reduction in total ALP blood levels[a]	27%	1%	NA	NA
Median time to PSA progression (months)	3.6	3.4	0.64	0.54-0.77

BSOC=Best Standard of Care; NA=Not Applicable.
[a]Only patients who had elevated total ALP levels at baseline were included.
[b]Two hundred thirty-three of 497 patients received Xofigo and 7 of 211 patients received placebo.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

- **Embryo-Fetal Toxicity:** The safety and efficacy of Xofigo have not been established in females. Xofigo can cause fetal harm when administered to a pregnant female. Advise pregnant females and females of reproductive potential of the potential risk to a fetus. Advise male patients to use condoms and their female partners of reproductive potential to use effective contraception during and for 6 months after completing treatment with Xofigo

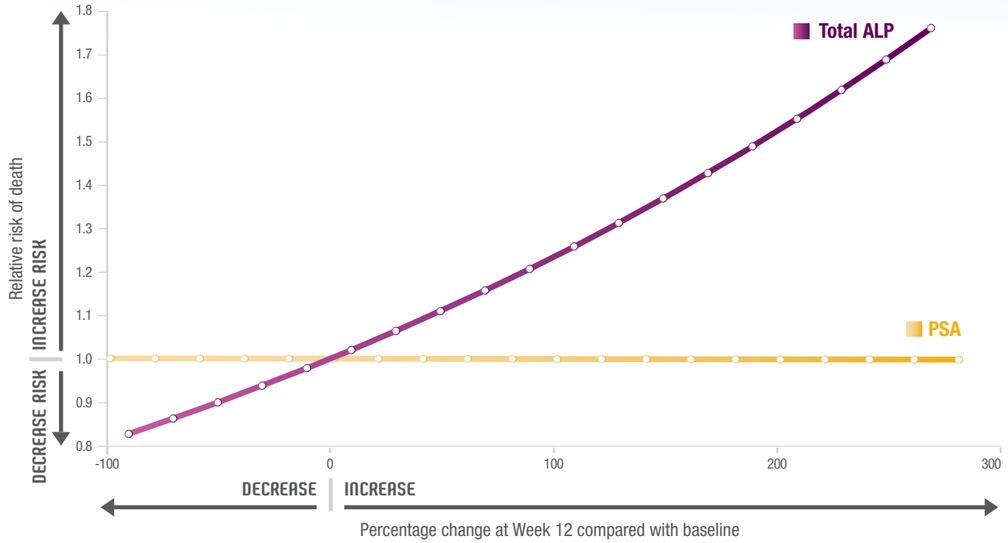
Administration and Radiation Protection: Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations

Please see additional Important Safety Information throughout and full Prescribing Information.

The association between PSA, ALP, and overall survival (OS) in ALSYMPCA

Relationship between percentage change in PSA, total ALP levels from baseline, and risk of death relative to no change in levels[7]

POST-HOC EXPLORATORY ANALYSIS[7]



A multivariate analysis evaluating the correlation between OS, PSA, and ALP at Week 12.[7]

- Only biomarker level decreases from baseline to 12 weeks were analyzed[7]
- Changes in total ALP and PSA levels after 12 weeks of treatment are not surrogates of survival[7]

Prespecified interim OS analysis

- Median OS was 14.0 months (95% CI: 12.1-15.8) for Xofigo + BSOC vs 11.2 months for BSOC (95% CI: 9.0-13.2). HR=0.695 (95% CI: 0.552-0.875) *P*=0.00185[1]
- A double-blind, randomized, placebo-controlled, phase III study of 921 patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease[1,2]

IMPORTANT SAFETY INFORMATION (cont'd)

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

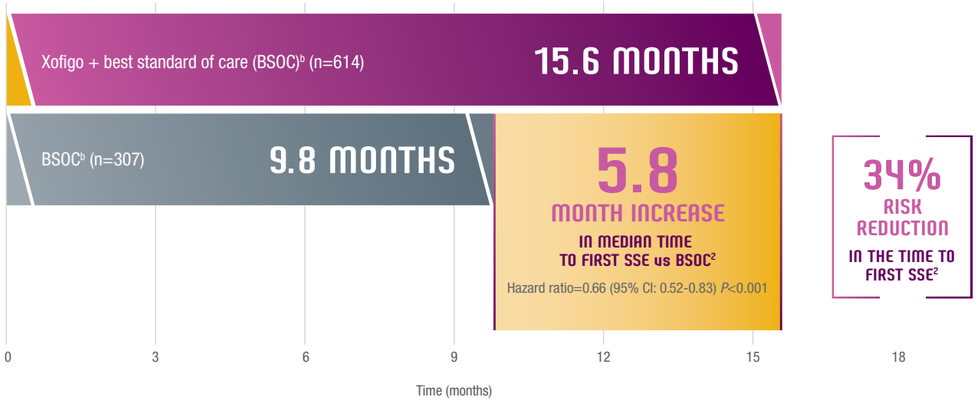
Xofigo® radium Ra 223 dichloride INJECTION

Xofigo® significantly increases time to first symptomatic skeletal event (SSE)[2]

Prespecified secondary endpoint: time to first SSE

SSE was defined as external-beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, and tumor-related orthopedic surgical intervention.[1]

MEDIAN TIME TO FIRST SSE[2a]



Adapted from Parker, et al.

- Delay in time to first SSE favored the Xofigo arm[2]
- The majority of events consisted of EBRT to bone metastases[1]

CI=Confidence Interval.
[a]Updated analysis from ALSYMPCA.
[b]BSOC was defined as antiandrogens, local EBRT, ketoconazole, estrogens, estramustine, or treatment with glucocorticoids.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

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. 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

Please see additional Important Safety Information throughout and full Prescribing Information.

Xofigo SSE component results

SSE COMPONENT IN EXPLORATORY ANALYSIS FROM ALSYMPCA[2,8]

SECONDARY EFFICACY ENDPOINTS	XOFIGO (n=614)	BSOC (n=307)	HAZARD RATIO (95% CI)
Median time to first SSE (months)	15.6	9.8	0.66 (0.52-0.83)
EBRT, n (%)	186 (30)	105 (34)	0.67 (0.53-0.85)
Spinal cord compression, n (%)	25 (4)	21 (7)	0.52 (0.29-0.93)
Pathologic bone fracture, n (%)	32 (5)	20 (7)	0.62 (0.35-1.09)
Surgical intervention, n (%)	12 (2)	7 (2)	0.72 (0.28-1.82)

Median time to first SSE was a prespecified secondary endpoint in ALSYMPCA. These SSE component analysis data are descriptive in nature, as the study was not powered to detect treatment differences in these SSE components.[2]

IMPORTANT SAFETY INFORMATION (cont'd)

Subsequent Treatment With Cytotoxic Chemotherapy: In the randomized clinical trial, 16% of patients in the Xofigo group and 18% of 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

Xofigo® radium Ra 223 dichloride INJECTION

Well-documented safety: overall Grade 3-4 adverse events (AEs) were lower than placebo[1]

Grade 3-4 AEs were reported in 57% of Xofigo®-treated patients and 63% of placebo-treated patients[1]

ADVERSE REACTIONS OCCURRING IN ≥2% OF PATIENTS[1a]

	ALL GRADES, %		GRADE 3-4, %	
	XOFIGO[b] (n=600)	PLACEBO (n=301)	XOFIGO[b] (n=600)	PLACEBO (n=301)
Pancytopenia	2	0	1	0
Nausea	36	35	2	2
Diarrhea	25	15	2	2
Vomiting	19	14	2	2
Peripheral edema	13	10	2	1
Renal failure and impairment	3	1	1	1

[a]For which the rates for Xofigo exceed the rates for placebo.[1]
[b]Plus best standard of care (BSOC).[1]

HEMATOLOGIC LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[1ab]

	ALL GRADES, %		GRADE 3-4, %	
	XOFIGO[c] (n=600)	PLACEBO (n=301)	XOFIGO[c] (n=600)	PLACEBO (n=301)
Anemia	93	88	6	6
Lymphocytopenia	72	53	20	7
Leukopenia	35	10	3	<1
Thrombocytopenia	31	22	3	<1
Neutropenia	18	5	2	<1

[a]The same patients (Xofigo, 600; placebo, 301) as in the adverse reactions patients population.[1]
[b]For which the rates for Xofigo exceed the rates for placebo.[1]
[c]Plus BSOC.[1]

IMPORTANT SAFETY INFORMATION (cont'd)

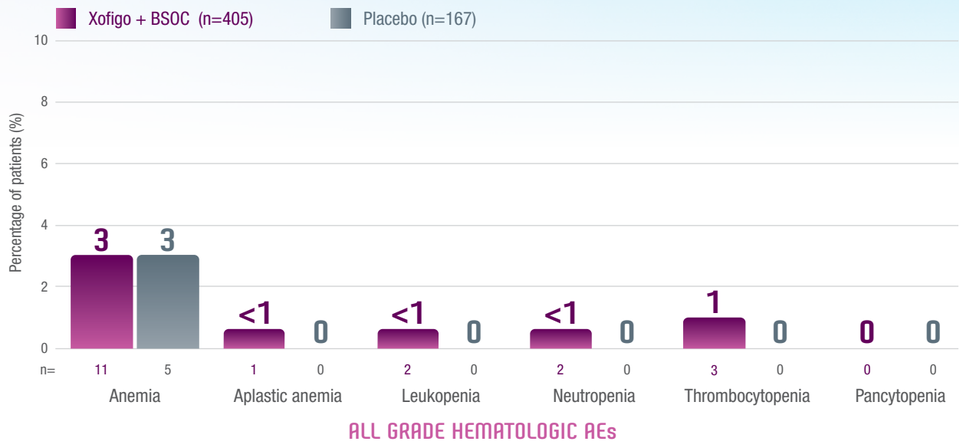
Warnings and Precautions:

- **Bone Marrow Suppression:** In the phase 3 ALSYMPCA 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.

Please see additional Important Safety Information throughout and full Prescribing Information.

3-year safety after ALSYMPCA

POST-TREATMENT, TREATMENT-RELATED HEMATOLOGIC AEs IN PATIENTS WHO ENTERED 3-YEAR, LONG-TERM SAFETY FOLLOW-UP (SAFETY POPULATION)[9]



ALL GRADE HEMATOLOGIC AEs

- Grade 3-4 hematologic AEs in the Xofigo vs placebo arm were anemia (1% vs 1%), aplastic anemia (<1% vs 0%), leukopenia (<1% vs 0%), and neutropenia (<1% vs 0%)[9]
- Across both groups, no Grade 5 hematologic AEs were reported[9]
- Grade 5 *nonhematologic* AEs included constipation, multiorgan failure, and pneumonia in the Xofigo arm (all of which were <1%)[9]

Limitations: assessment of long-term Xofigo safety may be difficult given that many participants were treated with other anticancer therapies in combination with Xofigo during the follow-up period. In addition, follow-up was limited to 3 years, which is a relatively short time to assess the number of treatment-induced cancers, including hematologic malignancies. Additional studies with longer follow-up times are necessary to more accurately assess the long-term safety of Xofigo. AEs were reported during follow-up only if considered by the investigator to be treatment related and may therefore be underreported.[9]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions (cont'd):

- **Bone Marrow Suppression** (cont'd): 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

Xofigo® radium Ra 223 dichloride INJECTION

Grade 3-4 adverse events (AEs) in patients receiving chemotherapy were similar regardless of prior Xofigo® use[10]

Study background

- **An exploratory analysis of prospectively collected data (from the ALSYMPCA patient subgroup who received chemotherapy after completing their assigned study drug treatment) was conducted to evaluate the safety of chemotherapy following Xofigo[10]**

Overall results

- **Patients in the Xofigo group had a longer time from randomization to the start of chemotherapy vs placebo (median 9.1 months vs 7.5 months, respectively)[10]**
- **Median duration of first chemotherapy was 4.6 months for Xofigo vs 4.2 months for placebo[10]**

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

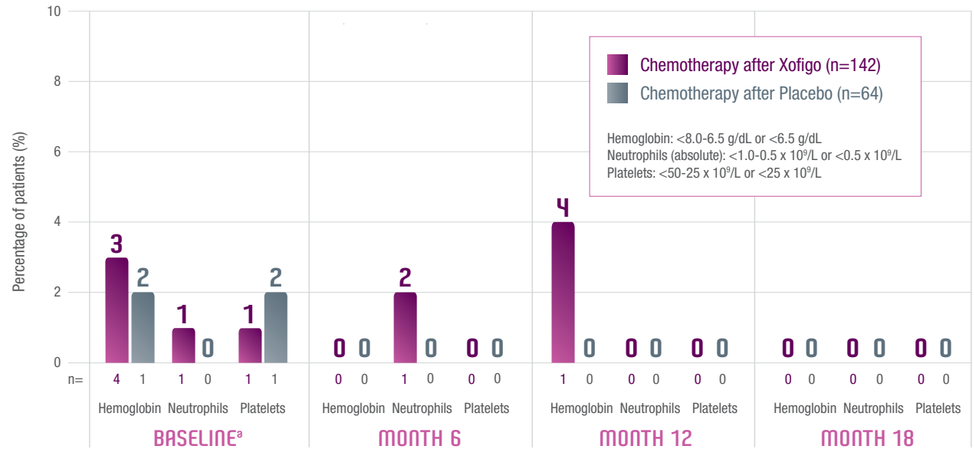
- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC 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

Please see additional Important Safety Information throughout and full Prescribing Information.

Reported frequency of Grade 3-4 hematologic AEs in patients receiving chemotherapy

Chemotherapy following Xofigo was well tolerated vs chemotherapy following placebo[10]

PERCENTAGE OF PATIENTS WITH HEMATOLOGIC LABORATORY VALUES CORRESPONDING TO GRADE 3-4 AEs IN THE CHEMOTHERAPY POST-STUDY DRUG GROUP[10]



[a]Last nonmissing measurement prior to start of first post-study drug chemotherapy. Timing of hematology laboratory values is determined according to start of chemotherapy, not by protocol-defined visits.[10]

- Incidence of Grade 3-4 hematologic AEs from baseline up to 18 months following first post-study drug chemotherapy was generally low (≤10%), **but tended to be more common among patients in the Xofigo group[10]**
- Grade 3-4 AEs for hemoglobin, neutrophils, and platelets were recorded in 8%, 10%, and 6% of Xofigo and 4%, 2%, and 2% of placebo patients, respectively[10]

IMPORTANT SAFETY INFORMATION (cont'd)

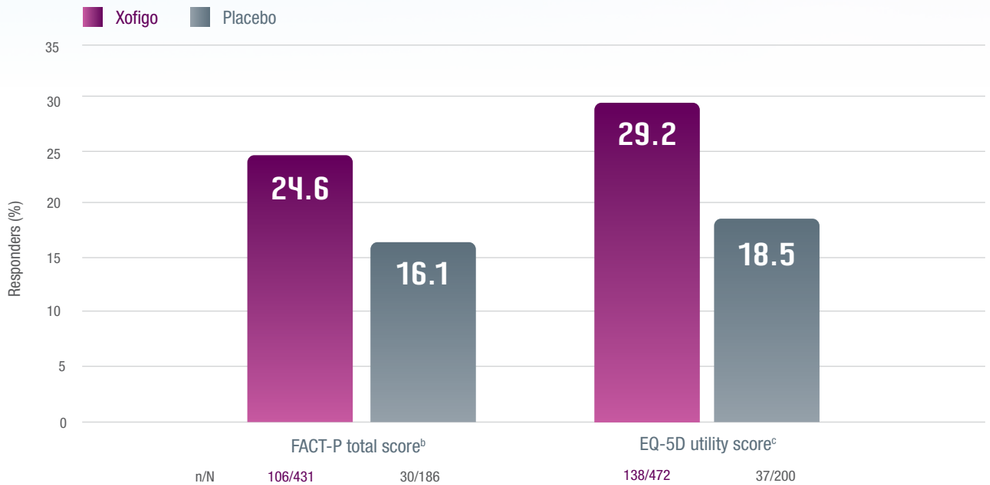
Warnings and Precautions: (cont'd)

- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use 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

Xofigo® radium Ra 223 dichloride INJECTION

Xofigo®: quality of life (QoL) measures from ALSYMPCA

CHANGES IN FUNCTIONAL ASSESSMENT OF CANCER THERAPY-PROSTATE (FACT-P) TOTAL SCORE AND EUROQoL (EQ-5D) UTILITY SCORE POST-HOC ANALYSIS[11a]



Adapted from Nilsson, et al.

- Changes in FACT-P and EQ-5D were exploratory endpoints in the ALSYMPCA trial. These endpoints were not powered to detect treatment differences in patients' QoL

[a]Post-hoc analysis from ALSYMPCA.
[b]A responder was defined as a patient having an increase in FACT-P ≥10 from baseline at Week 16 and/or Week 24.[11]
[c]A responder was defined as a patient having an increase in EQ-5D utility score of ≥0.1 from baseline at Week 16 and/or Week 24.[11]

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

- **Increased Fractures and Mortality in Combination With Abiraterone Plus Prednisone/Prednisolone:** Xofigo is not recommended for use in combination with abiraterone acetate plus prednisone/prednisolone outside of clinical trials. At the primary analysis of the phase 3 ERA-223 study that evaluated concurrent initiation of Xofigo in combination with abiraterone acetate plus prednisone/prednisolone in 806 asymptomatic or mildly symptomatic mCRPC patients, an increased incidence of fractures (28.6% vs 11.4%) and deaths (38.5% vs 35.5%) have been observed in patients who received Xofigo in combination with abiraterone acetate plus prednisone/prednisolone compared to patients who received placebo in combination with abiraterone acetate plus prednisone/prednisolone. Safety and efficacy with the combination of Xofigo and agents other than gonadotropin-releasing hormone analogues have not been established

Please see additional Important Safety Information throughout and full Prescribing Information.

Timing of Xofigo treatment is critical

START XOFIGO OR REFER TO A TREATMENT SITE WHEN YOUR PATIENT HAS THE FOLLOWING

- ☑ Rising prostate-specific antigen (PSA) on androgen deprivation therapy with testosterone ≤50 ng/dL, indicating castration-resistant prostate cancer[12a]
- ☑ Symptom(s) attributable to bone metastases[1]
- ☑ ≥2 bone metastases[1]
- ☑ No known visceral metastases[1]

Consider patients who:

- Have lymphadenopathy up to 3cm[2]
- Are referred for external-beam radiation therapy (EBRT) as part of best standard of care (BSOC)[b]

[a]Serum PSA progression defined as 2 consecutive increases in PSA over a previous reference.
[b]In the ALSYMPCA clinical trial, Xofigo was given with BSOC, which included antiandrogens, ketoconazole, local EBRT, estrogens, estramustine, or treatment with glucocorticoids.[2]

Contact Xofigo® Access Services at 1-855-6XOFIGO (1-855-696-3446)

up to 7 business days prior to each patient's scheduled treatment date to order Xofigo with Cardinal Health Nuclear Pharmacy Services

References: 1. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; December 2019. **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. **3.** Suominen MI, Fagerlund KM, Rissanen JP, et al. Radium-223 inhibits osseous prostate cancer growth by dual targeting of cancer cells and bone microenvironment in mouse models. *Clin Cancer Res*. 2017;23(15):4335-4346. **4.** Dekempeneer Y, Keyaerts M, Krasniqi A, et al. Targeted alpha therapy using short-lived alpha-particles and the promise of nanobodies as targeting vehicle. *Expert Opin Biol Ther*. 2016;16(8):1035-1047. **5.** Baidoo KE, Yong K, Brechbiel MW. Molecular pathways: targeted α-particle radiation therapy. *Clin Cancer Res*. 2013;19(3):530-537. **6.** Data on file. Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ, 2012. **7.** Reprint from *Annals of Oncology*, 28(5), Sartor O, Coleman RE, Nilsson S, Heinrich D, Helle SI, JM O'Sullivan, Vogelzang NJ, Bruland Ø, Kobina S, Wilhelm S, Xu L, Shan M, Kattan W, Parker C, An exploratory analysis of alkaline phosphatase, lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223, pages 1090-10097, Copyright 2017, with permission from Elsevir. Sartor O, Coleman RE, Nilsson S, et al. An exploratory analysis of alkaline phosphatase lactate dehydrogenase, and prostate-specific antigen dynamics in the phase 3 ALSYMPCA trial with radium-223. *Ann Oncol*. 2017;28(5):1090-1097. **8.** 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. **9.** Parker CC, Coleman RE, Sartor O, et al. Three-year safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases from phase 3 randomized alpharadin in symptomatic prostate cancer trial. *Eur Urol*. 2018;73(3):427-435. **10.** Sartor O, Hoskin P, Coleman RE, et al. Chemotherapy following radium-223 dichloride treatment in ALSYMPCA. *Prostate*. 2016;76(10):905-916. **11.** Nilsson S, Cislo P, Sartor O, et al. Patient-reported quality-of-life analysis of radium-223 dichloride from the phase III ALSYMPCA study. *Ann Oncol*. 2016;27(5):868-874. **12.** Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the prostate cancer clinical trials working group 3. *J Clin Oncol*. 2016;34(12):1402-1418. **13.** Heinrich D, Bektic J, Bergman AM, et al. The contemporary use of radium-223 in metastatic castration-resistant prostate cancer. *Clin Genitourin Cancer*. 2017;16(1):e223-e231.

IMPORTANT SAFETY INFORMATION (cont'd)

Warnings and Precautions: (cont'd)

- **Embryo-Fetal Toxicity:** The safety and efficacy of Xofigo have not been established in females. Xofigo can cause fetal harm when administered to a pregnant female. Advise pregnant females and females of reproductive potential of the potential risk to a fetus. Advise male patients to use condoms and their female partners of reproductive potential to use effective contraception during and for 6 months after completing treatment with Xofigo

Xofigo® radium Ra 223 dichloride INJECTION

When your goal is to increase survival and delay time to first symptomatic skeletal event (SSE),

Choose Xofigo® for your metastatic castration-resistant prostate cancer patients with symptomatic bone metastases and no visceral disease[1,2]

OS

XOFIGO SIGNIFICANTLY EXTENDS OVERALL SURVIVAL (OS) WITH A 30% REDUCTION IN DEATH VS BEST STANDARD OF CARE (BSOC)[2]

- Median OS was 14.0 months (95% CI: 12.1-15.8) for Xofigo + BSOC vs 11.2 months for BSOC (95% CI: 9.0-13.2). Hazard ratio (HR)=0.695 (95% CI: 0.552-0.875) *P*=0.00185[1]
- Evaluated in the ALSYMPCA trial: double-blind, randomized, placebo-controlled, phase III study of 921 patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease[1,2]

SSE

SIGNIFICANTLY IMPROVES MEDIAN TIME TO FIRST SSE BY 5.8 MONTHS[2]

- Secondary endpoint: median time to first SSE with Xofigo + BSOC was 15.6 months vs BSOC at 9.8 months (HR=0.66 [95% CI: 0.52-0.83], *P*<0.001)[2]
- The majority of events consisted of external-beam radiation therapy (EBRT) to bone metastases[1]
- SSE defined as EBRT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, and tumor-related orthopedic surgical intervention[2]

SAFETY

WELL-ESTABLISHED SAFETY PROFILE[1,2]

- Grade 3-4 adverse events were reported in 57% of the Xofigo-treated patients vs 63% of placebo-treated patients[1]
- The most common hematologic laboratory abnormalities in the Xofigo arm (≥10%) vs the placebo arm (all grades [%]), respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%)[1]
- The most common nonhematologic adverse reactions in the Xofigo arm (≥10%) vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%)[1]

CI=Confidence Interval.

Give your patients the survival benefit with 6 injections of Xofigo: a 1-minute injection every 4 weeks[1,2,13]

IMPORTANT SAFETY INFORMATION (cont'd)

Xofigo is associated with serious risks, including bone marrow suppression, increased fractures and mortality in combination with abiraterone plus prednisone/prednisolone, and embryo-fetal toxicity.[1]

Please see additional Important Safety Information throughout and full Prescribing Information.

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Xofigo®
radium Ra 223 dichloride
INJECTION