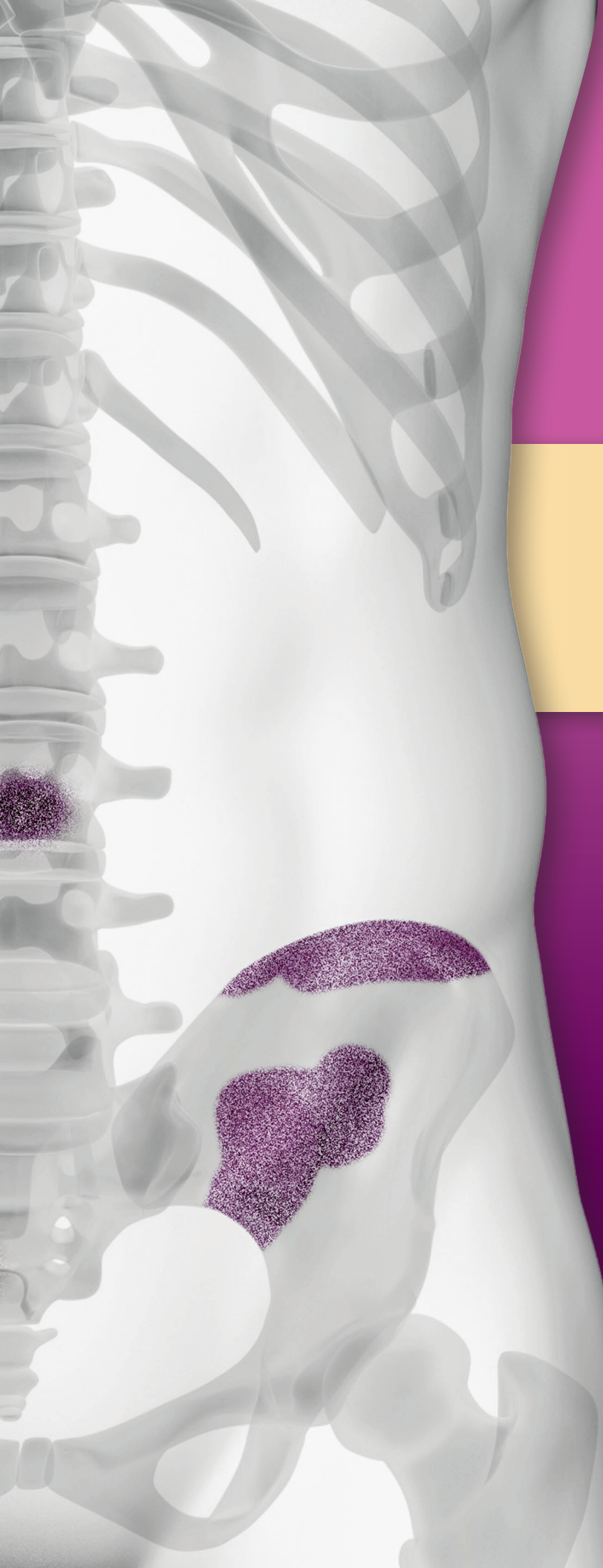


Xofigo® is the only FDA-approved targeted alpha therapy that treats bone metastases in metastatic castration-resistant prostate cancer[1]

Use Xofigo early to treat the cancer in the bone before it spreads viscerally[1,2]

Xofigo®
radium Ra 223 dichloride
INJECTION

Indication:

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:

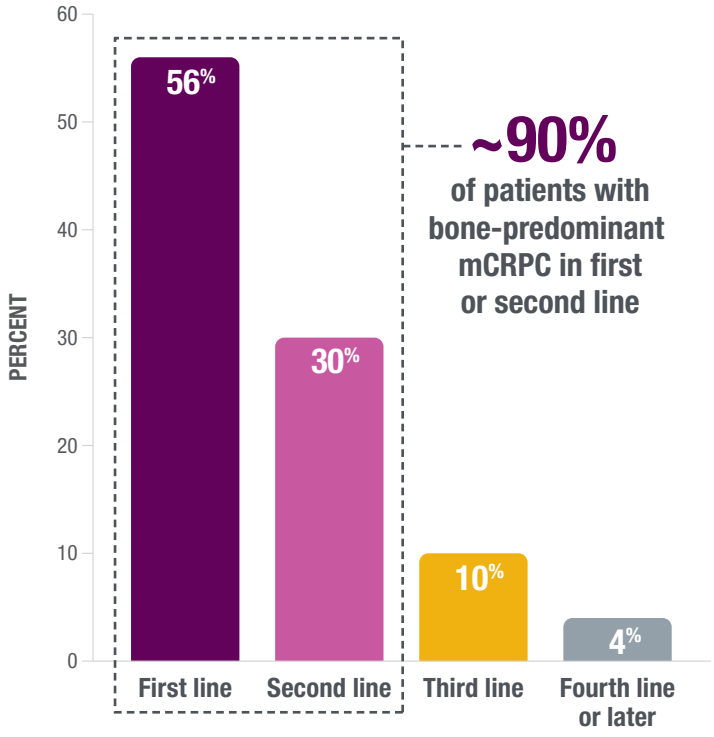
- **Bone Marrow Suppression:** In the phase 3 ALSYMPCA trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Bone metastases are highly prevalent and lead to significant mortality in metastatic castration-resistant prostate cancer (mCRPC)[3,4]

- The most common site for metastasis in mCRPC is the bone (up to 85%-90%)[5,6]
- Overall survival in patients with bone metastases decreases as the number of bone metastases increases[4]
- It is important to give your patients every opportunity to receive as many lines of therapy as possible to increase their survival[7]

BONE-ONLY METASTATIC PATIENTS BY LINE OF THERAPY[2]



Important Safety Information (cont'd)

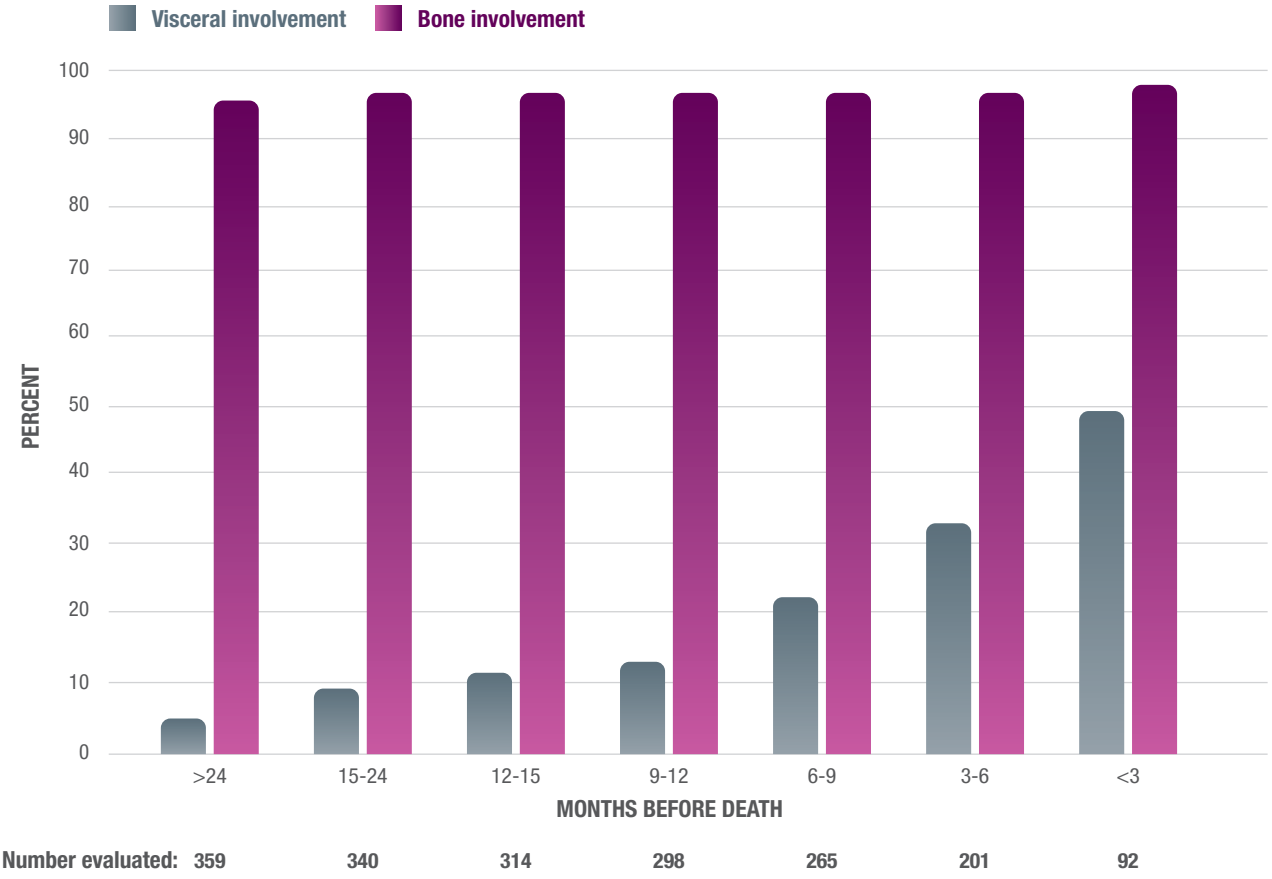
Warnings and Precautions (cont'd):

- **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

As disease progresses, so does the prevalence of visceral disease[3]

PREVALENCE OF VISCERAL AND BONE METASTASES[3]



An analysis of 442 patients with mCRPC from a database of patients enrolled in clinical trials and expanded access programs at Royal Marsden NHS Foundation Trust and Institute of Cancer Research from June 2003 to December 2011. Patients had regular computed tomography (CT) scans of the thorax, abdomen, and pelvis every 12 weeks, unless otherwise specified in the trial. Brain CT scans were performed in response to neurological symptoms. Prospectively collected scans were reviewed for evidence of visceral involvement, defined as disease involving liver, lungs, adrenal glands, peritoneum or pleura, brain, and dura. Bone metastases were assessed using standard bone scans.

EARLIER TREATMENT UPON DIAGNOSIS OF BONE-PREDOMINANT mCRPC: PATIENTS MAY HAVE LIMITED TIME BEFORE THE DISEASE MOVES BEYOND THE BONE[3,8-11]

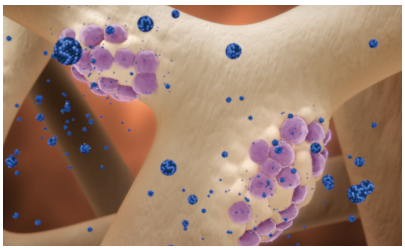
Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC), symptomatic bone metastases and no known visceral metastatic disease.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Xofigo®
radium Ra 223 dichloride
INJECTION

Treat the cancer where it lives: in the bone[1,12-14]

Xofigo® emits alpha radiation that goes to the bone[1,12]

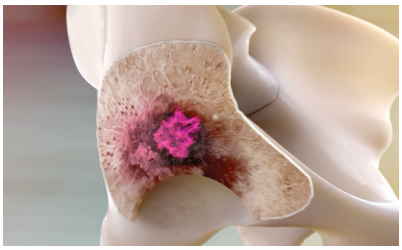


XOFIGO MIMICS CALCIUM

Like calcium, Xofigo goes to areas of increased bone turnover, such as bone metastases[1,12]

ANTI-TUMOR 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[1,12]



LIMITED DAMAGE TO NORMAL TISSUE

The short range of alpha particles emitted by Xofigo makes it a more targeted therapy. Alpha radiation powerfully targets the tumor, not surrounding tissue[1,14]

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.

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
- **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 extended overall survival (OS) by 3.6 months (14.9 months vs 11.3 months) in exploratory analysis[1,5]

Prespecified interim OS analysis

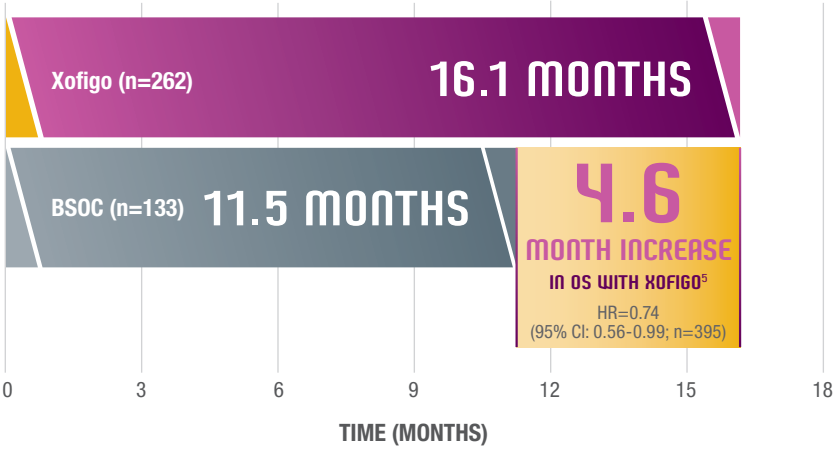
- Median OS was 14.0 months (95% CI: 12.1-15.8) for Xofigo + best standard of care (BSOC) vs 11.2 months for BSOC (95% CI: 9.0-13.2). Hazard ratio (HR)=0.695 (95% CI: 0.552-0.875) *P*=0.00185[1]
- Evaluated in the ALSYMPCA trial: double-blind, randomized, placebo-controlled, phase III study of 921 patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease[1,5]
- 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[5]

Exploratory updated OS analysis

- Median OS was 14.9 months (95% CI: 13.9-16.1) for Xofigo + BSOC vs 11.3 months for BSOC (95% CI: 10.4-12.8). HR=0.695 (95% CI: 0.581-0.832)[1,5]

ALSYMPCA SUBGROUP ANALYSIS[5a]

MEDIAN INCREASE IN OS IN CHEMOTHERAPY-NAIVE PATIENTS



- **In chemotherapy-experienced patients, median increase in OS with Xofigo (n=352) vs BSOC (n=174) was 3.1 months (14.4 months vs 11.3 months. HR=0.71 [95% CI: 0.56-0.89; n=526])[5]**
- The primary endpoint of the ALSYMPCA study was OS[5]
- Patients were stratified into the following subgroups at randomization: prior docetaxel exposure, current bisphosphonate use, and total alkaline phosphatase[5]
- 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] Chemotherapy-naive patients from ALSYMPCA were defined as docetaxel naive given study criteria.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Xofigo® radium Ra 223 dichloride INJECTION

Xofigo® significantly increases time to first symptomatic skeletal event (SSE)[5]

Sparing patients from pathologic bone fractures (5%), spinal cord compression (4%), and the need for external-beam radiation therapy (EBRT) (30%) or surgical interuention (2%)[15]

MEDIAN TIME TO FIRST SSE[5a]

Xofigo + best standard of care (BSOC)[b]
15.6 months
(n=614)

vs
P<0.001

BSOC
9.8 months
(n=307)

=

5.8 month increase
IN MEDIAN TIME TO FIRST SSE vs BSOC
Hazard ratio (HR)=0.66
(95% CI: 0.52-0.83) *P*<0.001

34% RISK REDUCTION
IN THE TIME TO FIRST SSE[5]

SSE was defined as ERBT to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, and tumor-related orthopedic surgical intervention.[1]

- Delay in time to first SSE favored the Xofigo arm[5]
- The majority of events consisted of EBRT to bone metastases[1]

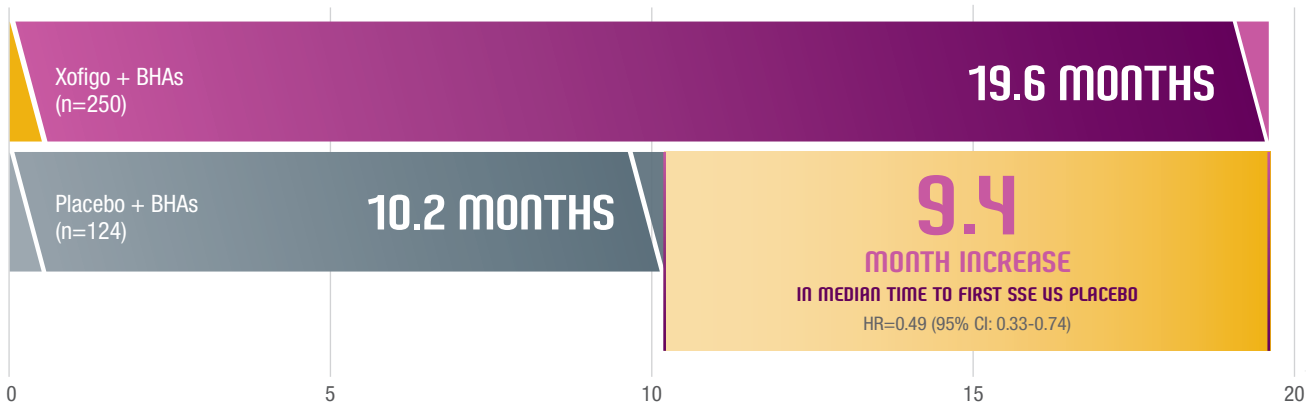
CI=Confidence Interval.
[a]Updated analysis from ALSYMPCA.
[b]BSOC was defined as antiandrogens, local EBRT, ketoconazole, estrogens, estramustine, or treatment with glucocorticoids.[5]

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

Median time to first SSE when given with bone health agents (BHAs)[15]



Study design

- Phase III, double-blind, randomized trial that enrolled patients who had symptomatic castration-resistant prostate cancer with 2 or more bone metastases and no known visceral metastases, were receiving BSOC, and had previously either received or were unsuitable for docetaxel[15]

- Without BHAs, the median time to first SSE was 11.8 months with Xofigo and 8.4 months with placebo (HR=0.77 [95% CI: 0.58-1.02])[15]

IT IS IMPORTANT TO EVALUATE A PATIENT'S NEED FOR BHAs IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Important Safety Information (cont'd)

Warnings and Precautions (cont'd):

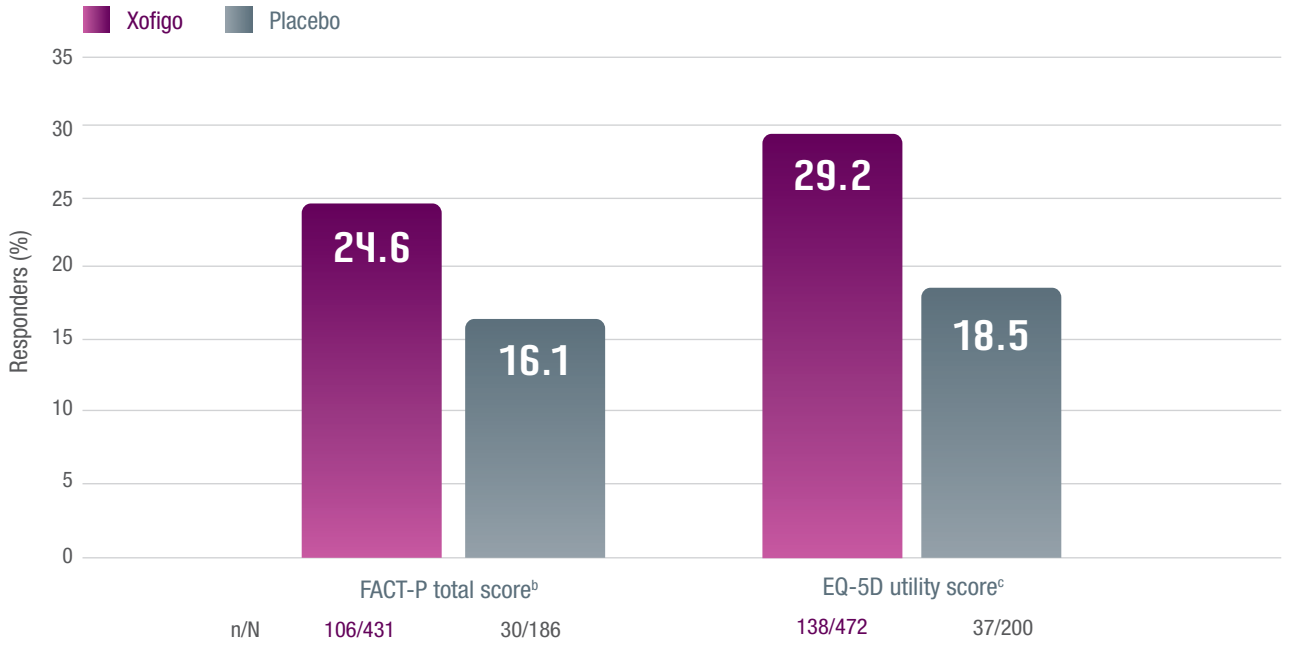
- **Embryo-Fetal Toxicity:** The safety and efficacy of Xofigo have not been established in females. Xofigo can cause fetal harm when administered to a pregnant female. Advise pregnant females and females of reproductive potential of the potential risk to a fetus. Advise male patients to use condoms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

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

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[16a]



- 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

Adapted from Nilsson, et al.

[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.[16]

[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.[16]

Important Safety Information (cont'd)

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

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

Radium Ra 223 dichloride (Xofigo) is recommended by major prostate cancer guidelines

GUIDELINE	RECOMMENDATION	NOTES
NCCN	Recommended as a **Category 1** treatment option for patients with symptomatic mCRPC with bone metastases[7]	**NCCN Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate[17]
ASCO	**"Strong" recommendation** for men with mCRPC and bone metastases[18]	**ASCO Recommendation:** strong; benefit: moderate; harm: low; evidence quality: strong[18]
ESMO	**1A recommendation** for men with bone-predominant symptomatic mCRPC without visceral metastases[19]	**ESMO 1A recommendation:** Evidence from at least one large randomized, controlled trial of good methodological quality or meta-analyses of well-conducted randomized trials without heterogeneity. Strong evidence for efficacy with a substantial clinical benefit, strongly recommended[20]
AUA	**Standard, Evidence Level Grade B** recommendation for patients with symptoms from bone metastases from mCRPC with good performance status, no prior docetaxel use, and no known visceral metastases[21]	**AUA Evidence Level Grade B:** Body of evidence is of moderate strength[21]

ASCO=American Society of Clinical Oncology; AUA=American Urological Association; ESMO=European Society for Medical Oncology; mCRPC=Metastatic Castration-Resistant Prostate Cancer; NCCN=National Comprehensive Cancer Network.

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 click here for full Prescribing Information.

Xofigo® radium Ra 223 dichloride INJECTION

Well-documented safety profile: 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 IN THE RANDOMIZED TRIAL[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

- 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]

[a]For which the rates for Xofigo exceed the rates for placebo.[1]

[b]Plus best standard of care.[1]

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

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%)

Chemotherapy following Xofigo was well tolerated us chemotherapy following placebo[22]

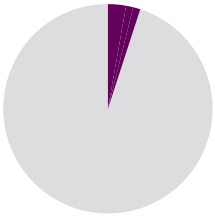
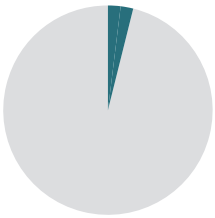
Study background

- 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[22]

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)[22]
- Median duration of first chemotherapy was 4.6 months for Xofigo vs 4.2 months for placebo[22]

PERCENTAGE OF PATIENTS WITH HEMATOLOGIC LABORATORY VALUES CORRESPONDING TO GRADE 3-4 AEs IN THE CHEMOTHERAPY POST-STUDY DRUG GROUP[22]

	VALUES AT BASELINE[a]	VALUES AT MONTH 18
Chemotherapy after Xofigo (n=142)	 **5%** (3% hemoglobin, 1% neutrophils, 1% platelets)	**0%** (0% hemoglobin, 0% neutrophils, 0% platelets)
Chemotherapy after placebo (n=64)	 **4%** (2% hemoglobin, 0% neutrophils, 2% platelets)	**0%** (0% hemoglobin, 0% neutrophils, 0% platelets)

[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.[22]

Grade 3-4 AEs in patients receiving chemotherapy were similar regardless of prior Xofigo use

- 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**[22]
- 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[22]
- At Months 6 and 12 of the trial, 1 patient presented with elevated neutropenia, and 1 patient presented with anemia[22]

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

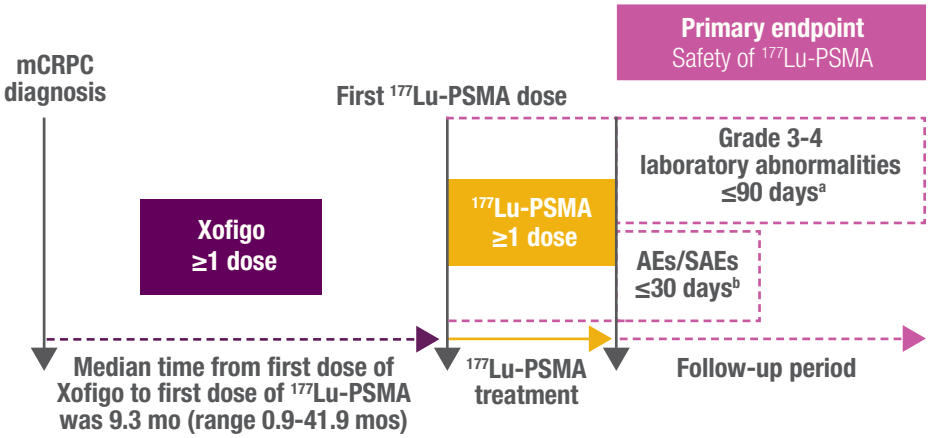
Xofigo® radium Ra 223 dichloride INJECTION

RaLu Study Evaluated the Safety and Feasibility of Using Xofigo before lutetium ^{177}Lu vipivotide tetraxetan (^{177}Lu-PSMA)

- RaLu is a retrospective medical chart review of 133 patients from German Nuclear Medical centers who received Xofigo → Taxane → ^{177}Lu-PSMA vs Taxane → Xofigo → ^{177}Lu-PSMA therapies[23]
- 13 patients who received taxane both before and after Xofigo were included in both groups
- 71% received 6 Xofigo injections
- 56% of patients received ≥4 life-prolonging therapies, including abiraterone (71%), enzalutamide (70%), docetaxel (74%) before starting ^{177}Lu-PSMA
- 73% of patients received 1–4 ^{177}Lu-PSMA cycles and 27% received ≥5 cycles

Key Inclusion Criteria

Eligible patients were males aged ≥18 years, with bone mets and a confirmed diagnosis of mCRPC, who had received ≥1 dose of Xofigo and, in any subsequent therapy line, ≥1 dose of ^{177}Lu-PSMA



Study Limitations: Chart review studies have bias related to treatment selection and unreported variables cannot be fully addressed. Outcomes are based on clinical judgment, with variability in patient and adherence that can result in different outcomes, therefore no conclusions can be drawn.

Data were retrospectively collected from Sep 2021 – Mar 2022.

[a]Measured from start of ^{177}Lu-PSMA therapy up to 90 days after last administration. [b]Measured from start of ^{177}Lu-PSMA therapy up to 30 days after last administration.

AEs, adverse events; mCRPC, metastatic castration-resistant prostate cancer; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; ^{177}Lu-PSMA.

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. 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.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Reported TEAEs and Lab Abnormalities During and Post ^{177}Lu-PSMA Treatment

REPORTED TREATMENT-EMERGENT ADVERSE EVENTS

TEAEs n (%)	All Patients (N=133)	By Treatment Sequence	
		Xofigo→Taxane→ ^{177}Lu-PSMA (n=57)	Taxane→Xofigo→ ^{177}Lu-PSMA (n=50)
Any grade	105 (79)	50 (88)	39 (78)
Grade 3-4	37 (28)	14 (25)	17 (34)
^{177}Lu-PSMA stopped, interrupted, or delayed due to TEAE	13 (10)	6 (11)	6 (12)

TEAEs ≥10% of patients	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
Dry Mouth	20 (15)	-	12 (21)	-	6 (12)	-
Nausea	12 (9)	-	7 (12)	-	3 (6)	-
Pain in Extremity	8 (6)	1 (1)	7 (12)	1 (2)	2 (4)	-
Spinal Pain	8 (6)	1 (1)	7 (12)	1 (2)	1 (2)	-

Measured from the start of ^{177}Lu-PSMA up to 30 days after last dose

REPORTED GRADE 3-4 LABORATORY ABNORMALITIES

Grade 3-4 Laboratory Abnormalities Incidence, n/N (%)	All Patients (N=133)	By Treatment Sequence	
		Xofigo→Taxane→ ^{177}Lu-PSMA (n=57)	Taxane→Xofigo→ ^{177}Lu-PSMA (n=50)
Hemoglobin	40/133 (30)	15/57 (26)	19/50 (38)
Platelet Count	17/133 (13)	7/57 (12)	9/50 (18)
Neutrophils	3/130 (2)	0/54 (0)	1/48 (2)
ASAT	2/131 (2)	1/55 (2)	1/49 (2)

ASAT, aspartate aminotransferase; N, number of patients evaluated; n, number of patients with the specified event; PSMA, prostate-specific membrane antigen; Tax, taxane-based chemotherapy; TEAE, treatment-emergent adverse event.

Measured from the start of ^{177}Lu-PSMA up to 90 days after the last dose

XOFIGO USE CHECKLIST

- With bone metastases and no known visceral disease[1]
- At least 1 symptom associated with mCRPC with bone metastases[1]
- Lymph node involvement up to 3 cm[5]

Xofigo® radium Ra 223 dichloride INJECTION

Adverse events (AEs) in Xofigo® and placebo patients in combination with external-beam radiation therapy (EBRT) us those without[24]

AEs BY CONCOMITANT EBRT USE (SAFETY POPULATION, N=901[a])[24]

	WITH CONCOMITANT EBRT				WITHOUT CONCOMITANT EBRT			
	XOFIGO (n=227)		PLACEBO (n=140)		XOFIGO (n=373)		PLACEBO (n=161)	
PATIENTS WITH AEs, %	ALL GRADES	GRADE 3-4	ALL GRADES	GRADE 3-4	ALL GRADES	GRADE 3-4	ALL GRADES	GRADE 3-4
HEMATOLOGIC AEs (ALL GRADES OCCURRING IN ≥5% OF PATIENTS IN EITHER TREATMENT SUBGROUP)								
ANEMIA	34	12	36	15	30	13	26	12
LEUKOPENIA	3	1	0	0	5	2	1	1
NEUTROPENIA	6	2	1	1	4	2	1	1
THROMBOCYTOPENIA	12	6	6	1	11	7	6	2
NONHEMATOLOGIC AEs (ALL GRADES OCCURRING IN ≥15% OF PATIENTS IN EITHER TREATMENT SUBGROUP)								
CONSTIPATION	24	2	25	1	15	1	18	2
DIARRHEA	31	0	19	2	21	2	12	1
NAUSEA	43	4	44	2	31	1	27	1
VOMITING	25	2	19	3	15	2	9	2
FATIGUE	30	4	17	2	23	4	33	9
WEIGHT DECREASED	15	1	14	1	10	1	15	2
ANOREXIA	14	1	21	0	19	2	16	1
BONE PAIN	70	35	74	34	38	12	52	18
MALIGNANT NEOPLASM PROGRESSION	14	6	12	6	12	6	17	9

Based on post-hoc analysis of the ALSYMPCA trial. These results are considered exploratory.

During the study, 30% (186/614) of Xofigo patients and 34% (105/307) of placebo patients received concomitant EBRT for bone pain[24]

- At any time prior to randomization, 50% (306/614) of Xofigo patients and 49% (149/307) of placebo patients received EBRT to bone
- Within 12 weeks prior to randomization, 16% (99/614) of Xofigo patients and 16% (48/307) of placebo patients received EBRT to bone

Patients were randomized 2:1, Xofigo:placebo[24]

[a]Safety population included all patients who received ≥1 injection of study drug. One patient in the placebo group received 1 injection of Xofigo (week 0) and is included in the Xofigo safety analysis.

Important Safety Information (cont'd)

Warnings and Precautions (cont'd):

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

Xofigo is conveniently delivered in a patient-ready dose and safely administered in a designated outpatient setting

6 ONE-MINUTE intravenous injections over 5 months

There are no post-treatment restrictions, so after treatment patients CAN[1]:

- Leave the clinic after the 1-minute infusion and go about their daily activities
- Safely be in close proximity with and hug loved ones and children, including being in a car with them
- Share a bed with a partner
- Avoid the need to quarantine

Refer to the full Prescribing Information for specific instructions for patients while receiving Xofigo.

References: 1. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; December 2019. **2.** Data on file. Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ. **3.** Pezaro CJ et al. *Eur Urol.* 2014;65(2):270-273. **4.** Moreira DM et al. *Clin Genitourin Cancer.* 2017;15(1):60-66. **5.** Parker C et al. *N Engl J Med.* 2013;369(3):213-223. **6.** Gandaglia G et al. *Prostate.* 2014;74(2):210-216. **7.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2022. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed November 30, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **8.** Gillessen S et al. *Eur Urol.* 2020;77(4):508-547. **9.** Ryan CJ et al. *N Engl J Med.* 2013;368(2):138-148. **10.** Beer TM et al. *N Engl J Med.* 2014;371(5):424-433. **11.** Loriot Y et al. *Lancet Oncol.* 2015;16(5):509-521. **12.** Suominen MI et al. *Clin Cancer Res.* 2017;23(15):4335-4346. **13.** Baidoo KE et al. *Clin Cancer Res.* 2013;19(3):530-537. **14.** Dekempeneer Y et al. *Expert Opin Biol Ther.* 2016;16(8):1035-1047. **15.** Sartor O et al. *Lancet Oncol*. 2014;15(7):738-746. **16.** Nilsson S et al. *Ann Oncol.* 2016;27(5):868-874. **17.** National Comprehensive Cancer Network website. https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines. Accessed January 11, 2022. **18.** Basch E et al. *J Clin Oncol.* 2014;32(30):3436-3448. **19.** Parker C et al. *Ann Oncol.* 2015;26(suppl 5):v69-v77. **20.** ESMO Guidelines Committee. ESMO website. https://www.esmo. org/content/download/77789/1426712/file/ESMO-Clinical-Practice-Guidelines-Standard-Operating-Procedures.pdf. 2021; version 1.0. **21.** Cookson MS et al. *J Urol.* 2013;190(2)429-438. **22.** Sartor O et al. *Prostate.* 2016;76(10):905-916. **23.** Rahbar K, et al. Presented at European Society for Medical Oncology Annual Meeting; September 9-13, 2022; Paris, France. **24.** Finkelstein SE et al. Presented at: 2015 Annual ASCO Meeting; May 29-June 2, 2015; Chicago, Illinois. Abstract 182. **25.** Mayo Clinic website. https://www.mayoclinic.org/diseases-conditions/prostate-cancer/symptoms-causes/syc-20353087. Updated June 4, 2021. Accessed July 14, 2021. **26.** American Cancer Society website. https://www. cancer.org/cancer/prostatecancer/detection-diagnosis-staging/signs-symptoms.html. Updated August 1, 2019. Accessed July 14, 2021. **27.** Ecker RD et al. *Mayo Clin Proc.* 2005;80(9):1177-1186. **28.** Lipton A et al. *J Natl Compr Canc Netw.* 2009;suppl7(suppl7):S1-S29. **29.** Farrell C. *Br J Nurs.* 2013;22(10):S4-S11. **30.** Selvaggi G, Scagliotti GV. *Crit Rev Oncol Hematol.* 2005;56(3):365-378. **31.** Parker C et al. *N Engl J Med.* 2013;369(3)(suppl):1-19.

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Xofigo®
radium Ra 223 dichloride
INJECTION

Routine monitoring requirements

Perform standard hematologic evaluations before and during treatment with Xofigo®[1]

Establishing a protocol within your practice for monitoring patients on Xofigo may be beneficial to your patient care.

BEFORE FIRST ADMINISTRATION	BEFORE SUBSEQUENT ADMINISTRATIONS
Confirm	
Absolute neutrophil count (ANC) is ≥1.5 x 10^9/L	ANC is ≥1 x 10^9/L
Platelet count is ≥100 x 10^9/L	Platelet count is ≥50 x 10^9/L
Hemoglobin count is ≥10 g/dL	

If hematologic values do not recover within 6 to 8 weeks after last administration, despite supportive care, discontinue further treatment.[1]

THERE ARE NO RESTRICTIONS REGARDING CONTACT WITH OTHER PEOPLE AFTER PATIENTS RECEIVE XOFIGO.[1]

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

Comprehensive support right when you need it

Xofigo® Access Services

Counselors are available from 9:00 AM to 7:00 PM ET, Monday through Friday

Call 1-855-6XOFIGO
(1-855-696-3446)

Fax 1-855-963-4463

XOFIGO IS AVAILABLE AT OVER 1,000 TREATMENT CENTERS NATIONWIDE[2]

VISIT

Xofigo Treatment Site Finder

TO LOCATE A TREATMENT SITE NEAR YOU

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Xofigo®
radium Ra 223 dichloride
INJECTION

It is important to discuss symptoms with your patients and caregivers when considering their next therapy

NUMEROUS SYMPTOMS ARE ASSOCIATED WITH BONE METASTASES IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC)[25-30]

- ☑ Fatigue
- ☑ General pain/discomfort in the lower back
- ☑ Difficulty moving or bending
- ☑ Difficulty doing everyday tasks
- ☑ Problems with posture
- ☑ Problems sleeping
- ☑ Neurological impairment, mild sensory loss, weakness in extremities, or numbness, due to spinal cord compression

In ALSYMPCA, inclusion criteria for symptoms was defined as regular use of analgesics or nonsteroidal anti-inflammatory drugs, as well as external-beam radiation therapy (EBRT) for bone pain.[5]

WHAT PORTION OF YOUR mCRPC PATIENTS EXHIBIT ANY OF THESE SYMPTOMS?

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

Use Xofigo® early before your mCRPC patients with symptomatic bone metastases progress to visceral metastasis

USE XOFIGO IN PATIENTS WHO HAVE:

- ☑ ≥2 bone metastases and no known visceral metastases[1]
- ☑ At least 1 symptom associated with mCRPC with bone metastases[1]

CONSIDER XOFIGO FOR NEWLY DIAGNOSED mCRPC PATIENTS WHO:

- Have been treated with 1 second-generation androgen receptor pathway inhibitor during their treatment journey
- Are chemotherapy naive
  – Nearly half (42%) of patients in the ALSYMPCA trial were chemotherapy naive[31]

ALSO CONSIDER ADDING XOFIGO WHEN REFERRING PATIENTS FOR EBRT AND IN PATIENTS WITH LYMPH NODE INVOLVEMENT OF UP TO 3 CM

EARLY TREATMENT UPON DIAGNOSIS OF BONE-PREDOMINANT mCRPC: PATIENTS MAY HAVE LIMITED TIME BEFORE THE DISEASE MOVES BEYOND THE BONE[3,8-11]

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

Please see additional Important Safety Information throughout and click here for full Prescribing Information.

Xofigo®
radium Ra 223 dichloride
INJECTION

For patients with mCRPC and symptomatic bone metastases, use Xofigo® early to treat the cancer in the bone before it spreads viscerally

Xofigo significantly extends overall survival (OS) with a 30% reduction in death vs best standard of care (BSOC)[5]

- In an interim 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). Hazard ratio (HR)=0.695 (95% CI: 0.552-0.875) *P*=0.00185[1ab]
- Evaluated in the ALSYMPCA trial: double-blind, randomized, placebo-controlled, phase III study of 809 patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease[1,5]

OS by prespecified subgroup: prior docetaxel use

MEDIAN INCREASE IN OS IN CHEMOTHERAPY-NAIVE PATIENTS[5]

- In chemotherapy-naive patients, median increase in OS with Xofigo (n=262) vs BSOC (n=133) was 4.6 months (16.1 months vs 11.5 months. HR=0.74 [95% CI: 0.56-0.99; n=395])[5]
- In chemotherapy-experienced patients, median increase in OS with Xofigo (n=352) vs BSOC (n=174) was 3.1 months (14.4 months vs 11.3 months. HR=0.71 [95% CI: 0.56-0.89; n=526])[5]
- Patients were stratified into the following subgroups at randomization: prior docetaxel exposure, current bisphosphonate use, and total alkaline phosphatase[5]
- These subgroup analysis data are descriptive in nature—the study was not powered to detect treatment differences in OS specifically within these prestratified subgroups

Overall grade 3-4 adverse events were lower than placebo[1]

- 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 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.
[a]BSOC was defined as antiandrogens, local external-beam radiation therapy, ketoconazole, estrogens, estramustine, or treatment with glucocorticoids.[5]
[b]Interim data is based on 809 patients.[1,5]

XOFIGO IS THE ONLY FDA-APPROVED TARGETED ALPHA THERAPY THAT TREATS BONE METASTASES IN mCRPC[1,12]

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

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 click here for full Prescribing Information.

PP-XOF-US-1720-2 05/2023

Xofigo®
radium Ra 223 dichloride
INJECTION