XOFIGO (Ra-223 Chloride)

INTRODUCTION:

This tutorial gives an overview of Palliation of Pain Using Ra-223 Chloride (XOFIGO).

After reviewing this tutorial, one should be able to:

- Describe XOFIGO and its physical, chemical, and biological properties as well its mode of decay.
- State the clinical indication for use of XOFIGO
- Describe the eligibility requirements for qualifying a patient for a XOFIGO study
- Describe administration procedure and frequency of injections
- List 3 contraindications for performing the procedure
- Explain the procedure for determining dose volume
- List several possible adverse reactions and side effects
- Give a brief overview of the internal radiation dosimetry associated with XOFIGO
- Explain the Kaplan-Meyer curves and overall survival based on clinical results

.

CLINICAL UTILITY OF XOFIGO (Ra-223 CHLORIDE) FOR TREATMENT OF PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER

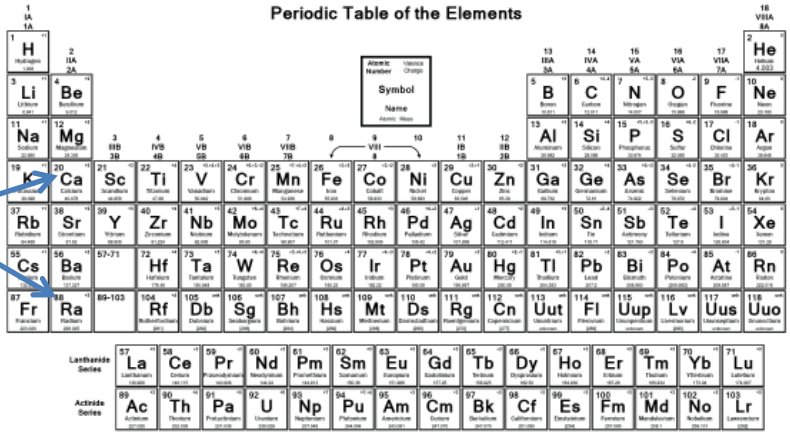
OFFICIAL NAME

XOFIGO (radium Ra 223 dichloride) Injection, for intravenous use Initial U.S. Approval: 2013

INDICATIONS AND USAGE

XOFIGO is an alpha particle-emitting radioactive therapeutic agent indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Both Ca and Ra are members of Group 2 in the Periodic Table and form divalent cations. They are therefore very similar in their chemical properties and biological uptake



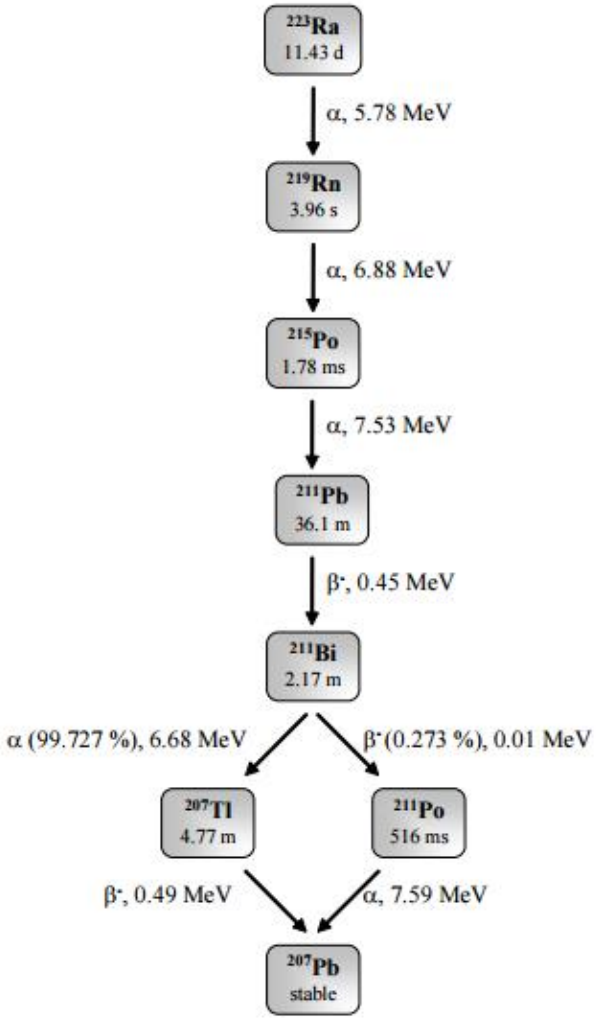
DESCRIPTION

- Radium Ra 223 dichloride, an alpha particle-emitting pharmaceutical, is a radiotherapeutic drug.
- XOFIGO is supplied as a clear, colorless, isotonic, and sterile solution to be administered intravenously with pH between 6 and 8.
- Each milliliter of solution contains 1,000 kBq radium-223 dichloride (27 microcuries), corresponding to 0.53 ng radium- 223, at the reference date. Radium is present in the solution as a free divalent cation.
- Each vial contains 6 mL of solution (6,000 kBq (162 microcurie) radium-223 dichloride at the reference date).
- The inactive ingredients are 6.3 mg/mL sodium chloride USP (tonicity agent), 7.2 mg/mL sodium

- Radium-223 has a half-life of 11.4 days.
- The fraction of energy emitted from radium-223 and its daughters as alpha-particles is 95.3% (energy range of 5 - 7.5 MeV).
- The fraction emitted as beta-particles is 3.6% (average energies are 0.445 MeV and 0.492 MeV),
- The fraction emitted as gamma-radiation is 1.1% (energy range of 0.01 - 1.27 MeV).

TYPES OF EMISSIONS FROM Ra-223

The six-stage-decay of Ra-223 to stable Pb-207 occurs via short-lived daughters, and is accompanied predominantly by alpha emissions. There are also beta and gamma emissions with different energies and emission probabilities.



Xofigo® (radium Ra 223 dichloride) Injection Emits Alpha Particles, Beta Particles, and Gamma Rays

ALGETA | BAYER

	Alpha Particles	Beta Particles	Gamma Rays
% decay energy emitted by Xofigo[1]	95.3%	3.6%	1.1%
Size[2,3]			
Description[2,3]	Consist of helium nuclei High linear energy transfer (LET)	Consist of electrons Relatively low LET	Electromagnetic wave LET not applicable
Type of DNA damage[2,4,5]	Double-strand breaks[2,4] (lethal, more difficult to repair)	Single-strand breaks[2,4] (more repairable)	Single- and double-strand breaks, oxidative base damage[5]
Particle range[2,6]	40-100 µm	0.05-12 mm	10-20 cm

1. Xofigo® (radium Ra 223 dichloride) injection [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; May 2013; 2. Kassis AI. *Semin Nucl Med*. 2008;38:358-366; 3. US Nuclear Regulatory Commission. Radiation Basics. www.nrc.gov/about-nrc/radiaton/health-effects/radiation-basics.html. Accessed August 9, 2013; 4. Barnard S, et al. *Genome Integr*. 2013;4:1-8; 5. Sudprasert W, et al. *Int J Hyg Environ Health*. 2006;209:503-511; 6. US Nuclear Regulatory Commission. Radiation Epidemiology. radepicourse2007.cancer.gov/content/presentations/handouts/INSKIP_handouts.pdf. Accessed August 20, 2013.

DOSAGE FORMS AND STRENGTHS

Single-use vial at a concentration of 1,000 kBq/mL (27 microcurie/mL) at the reference date with a total radioactivity of 6,000 kBq/vial (162 microcurie/vial) at the reference date (3)

NDC 50419-208-01 6 mL
Xofigo®
radium Ra 223 dichloride injection
1100 kBq/mL (30 microcurie/mL)
For Intravenous Administration

Sterile
Single-Dose Vial:
Discard Unused Portion
Manufactured for:
Bayer HealthCare
Whippany, NJ 07981
Manufactured in Norway

6600 kBq/vial (178 microcurie/vial) at 5 AM CST (12 noon CET) on reference date:

LOT: EXP:

84647535

CONTRAINDICATIONS

- Female patients
- Bone Marrow Suppression: Measure blood counts prior to treatment initiation and before every dose of XOFIGO. Discontinue XOFIGO if hematologic values do not recover within 6 to 8 weeks after treatment. Monitor patients with compromised bone marrow reserve closely. Discontinue XOFIGO in patients who experience life-threatening complications despite supportive care measures.

SIDE EFFECTS AND ADVERSE REACTIONS: MAIN ISSUE IS BONE MARROW SUPPRESSION

It is necessary to measure blood counts prior to treatment initiation and before every dose of XOFIGO.

- It is necessary to discontinue XOFIGO treatment if hematologic values do not recover within 6 to 8 weeks after treatment. One must monitor patients with compromised bone marrow reserve closely.
- It is also necessary to discontinue XOFIGO in patients who experience life-threatening complications despite supportive care measures
- The most common adverse drug reactions (≥ 10%) in patients receiving XOFIGO were nausea, diarrhea, vomiting, and peripheral edema.
- The most common hematologic laboratory abnormalities (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia

DOSAGE AND ADMINISTRATION

The Recommended dose regimen of XOFIGO is 50 kBq (1.35 microcurie) per kg body weight, given at 4-week intervals for 6 injections. Safety and efficacy beyond 6 injections with XOFIGO have not been studied. The volume to be administered to a given patient should be calculated using:

- Patient's body weight (kg)
- Dosage level 50 kBq/kg body weight or 1.35 microcurie/kg body weight
- Radioactivity concentration of the product (1,000 kBq/mL; 27 microcurie/mL) at the reference date
- Decay correction factor to correct for physical decay of radium-223.

The total volume to be administered to a patient is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 50\ \text{kBq/kg body weight}}{\text{Decay factor} \times 1{,}000\ \text{kBq/mL}}$$

or

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight in kg} \times 1.35\ \text{microcurie/kg body weight}}{\text{Decay factor} \times 27\ \text{microcurie/mL}}$$

Table 1: Decay Correction Factor Table

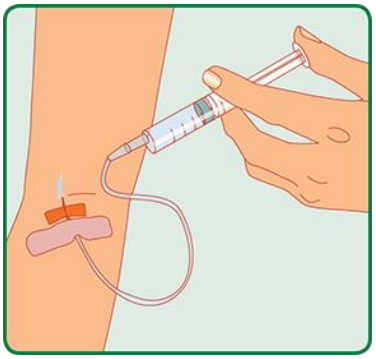
Days from Reference Date	Decay Factor	Days from Reference Date	Decay Factor
-14	2.296	0	0.982
-13	2.161	1	0.925
-12	2.034	2	0.870
-11	1.914	3	0.819
-10	1.802	4	0.771
-9	1.696	5	0.725
-8	1.596	6	0.683
-7	1.502	7	0.643
-6	1.414	8	0.605
-5	1.330	9	0.569
-4	1.252	10	0.536
-3	1.178	11	0.504
-2	1.109	12	0.475
-1	1.044	13	0.447
		14	0.420

The Decay Correction Factor Table is corrected to 12 noon Central Standard Time (CST). To determine the decay correction factor, count the number of days before or after the reference date. The Decay Correction Factor Table includes a correction to account for the 7 hour time difference between 12 noon Central European Time (CET) at the site of manufacture and 12 noon US CST, which is 7 hours earlier than CET.

DOSE CALIBRATION

Immediately before and after administration, the net patient dose of administered XOFIGO should be determined by measurement in an appropriate radioisotope dose calibrator that has been calibrated with a National Institute of Standards and Technology (NIST) traceable radium-223 standard (available upon request from Bayer) and corrected for decay using the date and time of calibration. The dose calibrator must be calibrated with nationally recognized standards, carried out at the time of commissioning, after any maintenance procedure that could affect the dosimetry and at intervals not to exceed one year.

DOSE ADMINISTRATION
Administer XOFIGO by slow intravenous injection over 1 minute. Flush the intravenous access line or cannula with isotonic saline before and after injection of XOFIGO.



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.

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 EDTA) solution is recommended to remove contamination.

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 As Low As Reasonably Achievable (ALARA) principle for minimization of radiation exposure, one should minimize the time spent in radiation areas, maximize the distance to radiation sources, and 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.

INTERNAL RADIATION DOSIMETRY

- Calculations of absorbed radiation doses were performed using a software program based on the Medical Internal Radiation Dose (MIRD) algorithm
- For radium-223, which is primarily an alpha particle-emitter, assumptions were made for intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations for XOFIGO, considering its observed biodistribution and specific characteristics.
- The calculated absorbed radiation doses to different organs are listed in Table 2. The organs with highest absorbed radiation doses were bone (osteogenic cells), red marrow, upper large intestine wall, and lower large intestine wall. The calculated absorbed doses to other organs are lower.

Table 2: Calculated Absorbed Radiation Doses to Organs

Target Organ	Mean (Gy/MBq)	Mean (rad/mCi)	Coefficient of Variation (%)
Adrenals	0.00012	0.44	56
Brain	0.00010	0.37	80
Breasts	0.00005	0.18	120
Gallbladder wall	0.00023	0.85	14
LLI[1] Wall	0.04645	171.88	83
Small intestine wall	0.00726	26.87	45
Stomach wall	0.00014	0.51	22
ULI[2] wall	0.03232	119.58	50
Heart wall	0.00173	6.40	42
Kidneys	0.00320	11.86	36
Liver	0.00298	11.01	36
Lungs	0.00007	0.27	90
Muscle	0.00012	0.44	41
Ovaries	0.00049	1.80	40
Pancreas	0.00011	0.41	43
Red marrow	0.13879	513.51	41
Osteogenic cells	1.15206	4262.60	41
Skin	0.00007	0.27	79
Spleen	0.00009	0.33	54
Testes	0.00008	0.31	59
Thymus	0.00006	0.21	109
Thyroid	0.00007	0.26	96
Urinary bladder wall	0.00403	14.90	63
Uterus	0.00026	0.94	28
Whole body	0.02311	85.50	16

[1]LLI: lower large intestine
[2]ULI: upper large intestine

RISK OF 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 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 & 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.

WARNINGS AND PRECAUTIONS

- 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.

ELIGIBILITY CRITERIA

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 should be $\geq 100 \times 10^9$ /L
- hemoglobin should be ≥ 10 g/dL.

BEFORE SUBSEQUENT ADMINISTRATIONS OF XOFIGO,

- the ANC should be $\geq 1 \times 10^9$ /L
- 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.

ADVERSE REACTIONS

- The most common adverse reactions (≥ 10%) in patients receiving XOFIGO were nausea, diarrhea, vomiting, and peripheral edema
- 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
- 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%).

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.

PREGNANCY

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

MALES OF REPRODUCTIVE POTENTIAL: CONTRACEPTION

Because of potential effects on spermatogenesis associated with radiation, men should use condoms and their female partners of reproductive potential to should use a highly effective contraceptive method during and for 6 months after completing treatment with XOFIGO

OVERDOSAGE

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

CLINICAL PHARMACOLOGY: MECHANISM OF ACTION

- The active moiety of XOFIGO is the alpha particle-emitting isotope radium-223 (as radium Ra 223 dichloride), which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases.
- The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases.
- The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

PHARMACODYNAMICS

- The pharmacokinetics of radium-223 dichloride in blood was linear in terms of dose proportionality and time independence in the dose range investigated (46 to 250 kBq [1.24 to 6.76 microcurie] per kg body weight).
- Distribution After intravenous injection, radium-223 is rapidly cleared from the blood and is distributed primarily into bone or is excreted into intestine.
- Fifteen min post-injection, about 20% of injected radioactivity remained in blood.
- At 4 hours, about 4% of the injected radioactivity remained in blood, decreasing to less than 1% at 24 hours after the injection.
- At 10 minutes post-injection, radioactivity was observed in bone and in intestine.
- at 4 hours post-injection, the percentage of the radioactive dose present in bone and intestine was approximately 61% and 49%, respectively.
- No significant uptake was seen in other organs such as heart, liver, kidneys, urinary bladder, and spleen at 4 hours post-injection [see Dosage and Administration

Injection Site Reactions

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

Secondary Malignancies

- 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, 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.

ANIMAL TOXICITY STUDIES

1. 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 0.541 - 2.16 μCi per kg body weight.

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

METABOLISM

Radium-223 Chloride decays but is not metabolized.

ELIMINATION

- The whole-body measurements indicated that approximately 63% of the administered radioactivity was excreted from the body within 7 days after injection (after correcting for decay). Fecal excretion is the major route of elimination from the body.
- At 48 hours after injection, the cumulative fecal excretion was 13% (range 0 - 34%), and the cumulative urine excretion was 2% (range 1 - 5%). There was no evidence of hepatobiliary excretion based on imaging data.
- Patients with a slower intestinal transit rate could potentially receive a higher intestinal radiation exposure.

PEDIATRIC PATIENTS

Safety and effectiveness of XOFIGO have not been established in children and adolescents below 18 years of age.

PATIENTS WITH HEPATIC IMPAIRMENT

Since radium-223 is not metabolized and there is no evidence of hepatobiliary excretion based on imaging data, hepatic impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

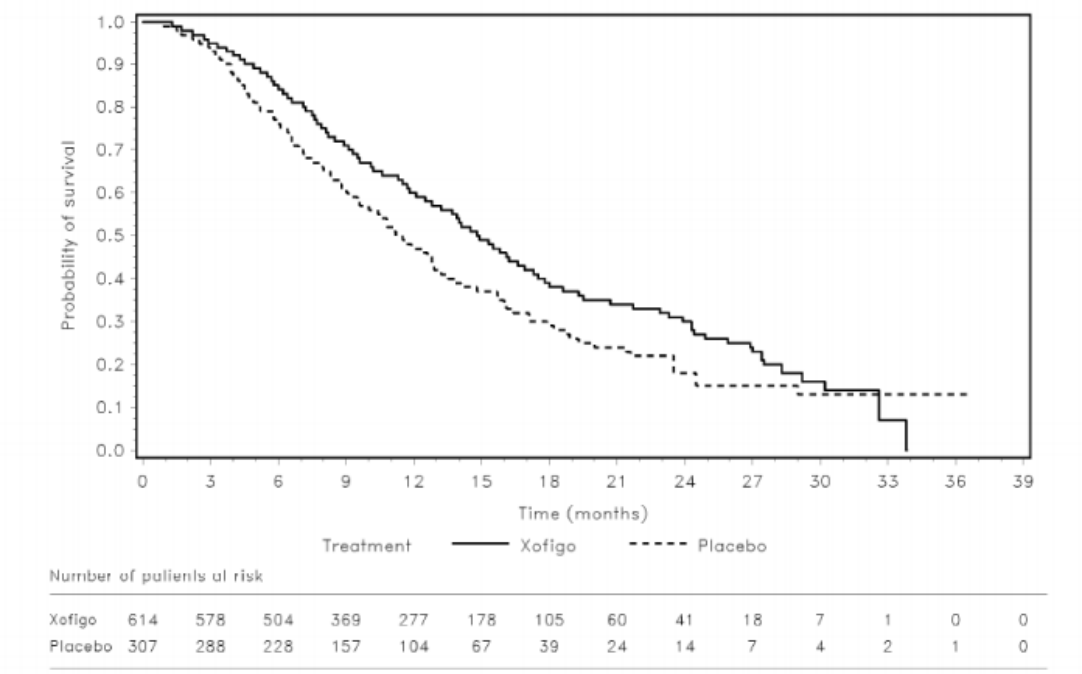
PATIENTS WITH RENAL IMPAIRMENT

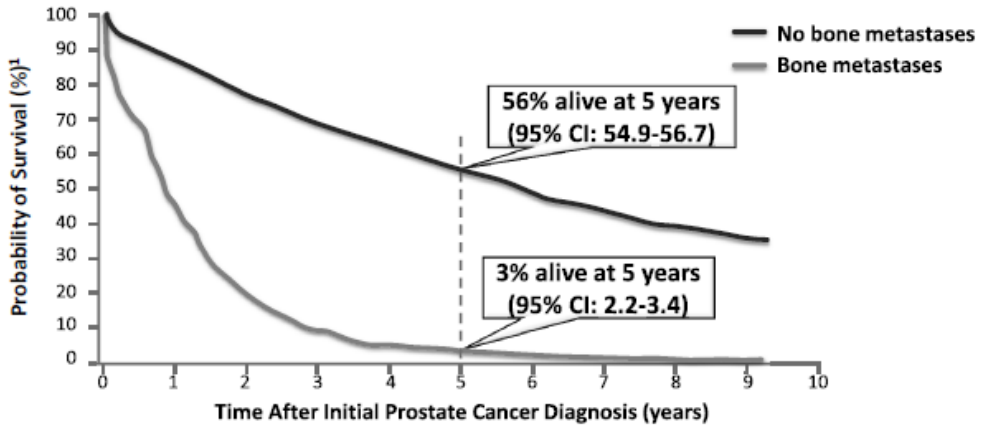
Since excretion in urine is minimal and the major route of elimination is via the feces, renal impairment is not expected to affect the pharmacokinetics of radium-223 dichloride.

KAPLAN-MEIER CURVES

The Kaplan-Meier curves for overall survival based on the updated survival results are shown below

Figure 1: Kaplan-Meier Overall Survival Curves from the Phase 3 Clinical Trial





*Of the 23,087 patients with initial diagnosis of prostate cancer, 22,404 had no bone metastases and 569 presented with bone metastases.

- Skeletal tumor burden is an independent predictor of death in patients with advanced prostate cancer[2]

1. Nørgaard M, et al. *J Urol*. 2010;184:162-167; 2. Noguchi M, et al. *Br J Cancer*. 2003;88:195-201.