BrUOG L301

IND EXEMPT 124745

BrUOG L301: Xofigo Following Frontline-Line Chemotherapy For Patients With Non-Small Cell Lung Cancer and Bone Metastases

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The values in this protocol have been revised as per the United States (US) National Institute of Standards and Technology (NIST) standardization update (agreed on 17 MAR 2015)

Original protocol 5/21/14
Amendment #1 5/19/15
Amendment # 2, 2/19/16
Amendment # 3 3/3/16
Amendment #4 11/30/16

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1.0 OBJECTIVES

1.1 PRIMARY OBJECTIVE:

1.1.1 To evaluate if Xofigo can reduce symptomatic skeletal events (SSE) in patients with NSCLC and bone metastases who have had stable or responding disease following initial systemic chemotherapy.

1.2 SECONDARY OBJECTIVES:

1.2.1 To evaluate toxicity of Xofigo in patients with NSCLC and bone metastases following front-line chemotherapy.

1.2.2 To evaluate time to symptomatic skeletal events.

1.2.3 To evaluate changes in health-related quality of life, using the EORTC QLQ-C30 and QOL-BM22 questionnaires, in patients with NSCLC and bone metastases treated with Xofigo.

1.2.4 To evaluate the impact of treatment with Xofigo on alkaline phosphatase levels in patients with NSCLC and bone metastases.

1.2.5 To measure progression-free survival and overall survival of patients with NSCLC and bone metastases and stable or responding disease after front-line chemotherapy treated with Xofigo.

2.0 BACKGROUND

Non-Small Cell Lung Cancer (NSCLC): Lung cancer is the most common cause of cancer death worldwide, with an estimated 1,600,000 new cases and 1,380,000 deaths per year.[1] In the United States, there are an estimated 228,000 new cases of lung cancer and 159,500 deaths, yearly.[2]

Bone Metastases from NSCLC: Approximately 50% of patients with advanced lung cancer will develop progressive bone metastases during the course of their illness.[3] Bone metastases from NSCLC are frequently symptomatic leading to significant morbidity due to pain, pathologic fracture and neural compression. Primary treatment has relied upon radiation therapy.[3-6] Local external-beam radiation can be effective in patients with a small number of metastases, but its clinical utility in patients with disseminated metastatic bone disease is limited by the number of sites that can be treated. The potential for toxicity to neighboring tissues at an effective radiation dose can also limit retreatment to certain sites. Chemotherapy can be helpful until the disease becomes refractory.[3]

Bisphosphonates and Denosumab in NSCLC and Bone Metastases: Bisphosphonates have a modest impact in reduction of skeletal related events in NSCLC and other solid tumors.[7-9] In the phase III study of zoledronic acid for patients with bone metastases from solid tumors, the time to a skeletal related event was increased from 163 days to 230 days with zoledronic acid versus

placebo. In this study, approximately 40% of patients with bone metastases from NSCLC had a new skeletal related event within 4 months.[7,8]

The monoclonal antibody denosumab also demonstrates a modest benefit in reduction of skeletal events in NSCLC.[9,10] Denosumab binds to RANKL inhibiting osteoclast formation. Bisphosphonates and denosumab act primarily on osteoclasts and do not treat metastases directly. Furthermore, they each are associated with osteonecrosis of the jaw.[7-10]

Radium-223 (Xofigo): Xofigo is an alpha-particle emitting radiotherapeutic drug (radium-223 dichloride) which mimics calcium and forms complexes with hydroxyapatite at areas of increased bone turnover, such as bone metastases.[11] Xofigo targets bone metastases by delivering high-energy, short-range (<100 um) alpha-particles. These alpha particles can potentially provide greater dose to the exact site of bone metastases while also reducing marrow toxicity due to their shorter path length. [12] The phase III, double blind ALSYMPCA study randomized patients 2:1 to receive Xofigo, 6 injections every 4 weeks or placebo. Xofigo significantly improved overall survival in patients with castrate resistant prostate cancer (median overall survival 14.9 versus 11.3 months; $P < 0.001$).[11] Xofigo significantly delayed time to first symptomatic skeletal events including reducing pathologic bone fracture, spinal cord compression, need for surgical intervention for a bone metastasis, and time to external beam radiotherapy. Xofigo also reduced pain and opioid use.

Standard Front-line Treatment of NSCLC and Optimal Role for Xofigo: The initial treatment for patients with metastatic NSCLC who do not have a driver mutation (EGFR or ALK mutation) involves combination chemotherapy for 4-6 cycles with agents such as cisplatin, carboplatin, paclitaxel, pemetrexed. [13,14] For patients with stable or responding disease, maintenance chemotherapy with pemetrexed or docetaxel may be utilized. [15] After initial front-line chemotherapy, patients with stable or responding disease are often given a treatment break from chemotherapy and followed symptomatically and radiographically. In patients with bone metastases, denosumab or zoledronic acid are commonly administered to reduce symptomatic skeletal events but their effects are on osteoclasts and do not directly treat metastases. Their effectiveness is very limited with approximately half of all patients expected to have new symptomatic skeletal events within the next 4 months.[7,8] It is within this period following completion of front-line chemotherapy that this protocol will investigate Xofigo.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for Patient Eligibility

3.1.1 Age ≥ 18 years.

3.1.2 Advanced non-small cell lung cancer with bone metastases.

3.1.3 Stable or responding disease after completion of initial systemic chemotherapy as defined by RECIST criteria. “Initial systemic treatment,” is to include all treatment and therapy given before a patient progresses. Therefore, a patient may receive different agents, including radiation, as part of their initial treatment as long as they have not and do not progress at any point prior to BrUOG 301 enrollment. However, patient must have received chemotherapy. Site to submit pre-treatment scan with post treatment scan for RECIST and confirmation to BrUOG. Document

blastic or lytic lesions (and for lytic soft tissue or no soft tissue component. Soft tissue component requires measurements for RECIST).

3.1.4 At least 3 weeks must have elapsed since completion of last chemotherapy and 4 weeks since last radiation, prior to first dose of Xofigo. Patients are not permitted to receive any form of 'maintenance' chemotherapy or biologic/targeted anticancer therapy while being treated on this study

3.1.5 Life expectancy of at least 12 weeks (3 months).

3.1.6 Patients with treated brain metastases are allowed, but must have brain imaging showing evidence of stability since most recent treatment for brain mets, prior to first dose of Xofigo. For patients with brain metastases only, brain imaging is required as per section 6 and scan must be sent to BrUOG with registration information before patient is registered on study. Patients who do not have brain metastases or symptoms of potential brain metastases are not required to have baseline brain imaging, but this must be confirmed in writing to BrUOG at time of registration.

3.1.7 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 – 1.

3.1.8 Required entry laboratory parameters within 14 days of study entry: White Blood Cell Count (WBC) ≥ 3,000/mm3; Absolute Neutrophil Count (ANC) ≥ 1,500/mm3; Platelet (PLT) count ≥ 100,000/mm3; Hemoglobin (Hgb) ≥ 9g/dl, Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN); Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN ; Creatinine ≤ 1.5 x ULN; Albumin > 2.5 g/dL.

3.1.9 Concurrent treatment with bisphosphonates and denosumab is allowed. Information on start and stop date and drug with dose to be sent to BrUOG if patient to be treated concurrently.

3.1.10 Prior skeletal related events (pathologic fracture, radiation or surgery to bone, or spinal cord compression) are allowed if they have been managed and now patient is stable for 4 weeks prior to study entry. Must submit how events managed to BrUOG for documentation to confirm eligibility criterion. (For example, if a patient experienced a SSE and had radiation for 2 weeks they must then be stable for 4 weeks after the completion of radiation prior to study entry)

3.1.11 Subjects must be able to understand and be willing to sign the written informed consent form.

3.1.12 All acute toxic effects related to prior treatment(s) must have resolved to NCI-CTCAE v4 Grade 1 or less at the time of registration except for alopecia. Please note blood transfusion is allowed at baseline to bring HGB within study requirements, see section 5.2

3.1.13 Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.

3.1.14 Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 30 days after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the treating physician.

3.1.15 Willing and able to comply with the protocol, including follow-up visits and examinations

3.2 Conditions for Patient Ineligibility

3.2.1 Received systemic therapy with radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188, or Radium Ra 223 dichloride) for the treatment of bony metastases

3.2.2 No prior invasive malignancy within the prior two years. However, patients with an early stage malignancy that is not expected to require treatment in the next 2 years (such as early stage, resected breast cancer or asymptomatic prostate cancer) are eligible

3.2.3 Untreated brain metastases.

3.2.4 Any other serious illness or medical condition that in the investigator's opinion would interfere with protocol treatment, such as but not limited to: Any active infection ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 Grade 2 or Cardiac failure New York Heart Association (NYHA) III or IV

3.2.5 Women who are pregnant or breast-feeding.

3.2.6 Inability to comply with the protocol and/or not willing or who will not be available for follow-up assessments.

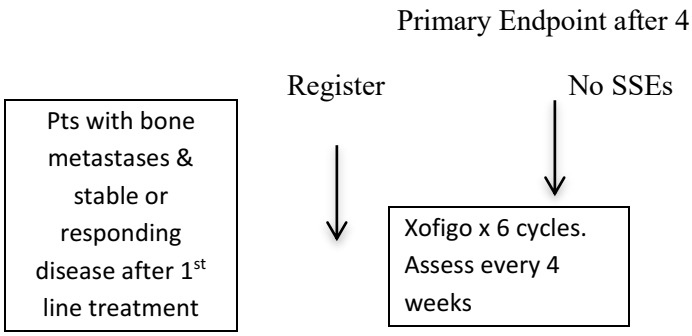
3.2.7 Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.

3.2.8 Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than Ra 223 dichloride.

3.2.9 Major surgery within 28 days of starting study drug. Central venous catheter placement is not considered major surgery.

4.0 TREATMENT

Schema:



Xofigo, 50 kBq/kg body weight (55kBq/kg body weight after NIST implementation), will be administered in the nuclear medicine department as a bolus intravenous (IV) injection (up to 1 minute) at intervals of every 4 weeks for up to 6 cycles. (Treatment should be administered

within +/- 3 days of cycle due date). Treatment delays of up to 14 days due to patient, physician or facility scheduling issues should be reported but will not constitute a deviation. Weight used for drug order is to be from pre-cycle assessment (done within 7 days prior to cycle start). Patients are to be dosed based on drug order weight and weight collected the day of dosing, prior to dosing, is to only be used to confirm patient's weight has not changed by more than 10% (see section 5.1). Patient's dose is not to be adjusted based on day of weight.

For dosing please refer to appendices F and G

Filling of the syringe should take place in a safety bench or similar in the radiopharmacy/Nuclear Medicine department. Personnel should wear medical gloves and eye protection during syringe filling to prevent contamination of the radioactive solution to skin and eyes. The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe.

The syringe should be handed over to the nuclear medicine personnel who will perform the injection. There is no need for shielding from alpha particle radiation during preparation and administration of the patient doses. (Alpha particles from radioactive decay of radium-223 and progeny are easily stopped by the thickness of a sheet of a paper or the walls of a glass vial.)

Aseptic technique should be used in the administration of Xofigo. The agent is administered as a slow bolus intravenous injection. After administration, the equipment used in connection with the preparation and administration of drug, are to be treated as radioactive waste and should be disposed in accordance with hospital procedure for the handling of radioactive material.

In general, the administration of radioactive drugs involves a potential risk for third parties, due to radiation from the patient and due to possible contamination by spilling urine or feces. When Xofigo has been injected intravenously into a patient, the risk for external radiation exposure to third parties is extremely low, due to the short range of the alpha particles (<100 μm) and the very low portion of beta and gamma radiation. For these reasons the product can be administered on an outpatient basis.

Patients are informed to practice good hygiene for at least 1 week after study administration including washing hands, flushing the toilet several times after each use and washing clothes that are soiled with stool or urine promptly and separately from other clothes.

4.1 Duration of Treatment

Xofigo will be administered every 4 weeks for a maximum of 6 treatments. See 5.2 for reasons for study discontinuation. (Treatment should be administered within +/- 3 days). Treatment delays of up to 14 days due to patient, physician or facility scheduling issues should be reported but will not constitute a deviation.

5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

5.1

If labs are re-drawn post enrollment and prior to cycle 1 day 1 dosing, the following criteria are required to be met before dosing cycle 1:

- ANC must be $\geq$ 1.5 prior to day 1 dose of treatment (cycle 1)
- (PLT) count must be $\geq$ 100,000/mm3 prior to day 1 dose of treatment (cycle 1)
- Hemoglobin (Hgb) must be $\geq$ 9g/dl prior to day 1 dose of treatment (cycle 1)

A new course (cycle 2-6) of treatment should not begin until the following criteria are met:

- Platelets $\geq$ 50,000x10^9/L
- Granulocytes $\geq$1000x10^9/L (1000/mm^3)
- Recovery from other treatment related, non-hematologic toxicities to $\leq$ Grade 2
- Diarrhea $\leq$ grade 2
- Nausea or vomiting $\leq$ grade 2 or to baseline levels

If the patient does not meet these criteria delay day 1 until these requirements are met. Patients who require a treatment delay of more than 4 weeks from the scheduled treatment day due to toxicity will be removed from protocol treatment.

Weight prior to cycles 2-6 can be taken up to7 days prior to dosing each cycle. Weight within 7 days of each cycle to be used for drug order and drug dosing for that cycle. Weight must again be assessed the day of drug administration, but this weight is only to be used to confirm patient's weight has not changed by > 10% since the prior assessment pre-dosing (for example 7 days prior). If weight has not changed by >10% then, the patient is considered okay to treat. See section 6 subscript K for more details

5.2 Dose Modification/Study Discontinuation

Toxicity: NCI common toxicity version 4 will be utilized to assess toxicity.

Every effort should be made to administer the full dosing regimen of Radium Ra 223 dichloride. Adjustment of dose level is not permitted.

- Blood transfusion at baseline is acceptable to obtain baseline value of $\geq$9 and between study drug administrations, but not on the same day as Xofigo administration. Use of biologic myeloid growth factors such as G-CSF, is allowed in the management of acute toxicity.

Gastrointestinal events:

Diarrhea should be treated as per local institutional practices. The next cycle should not begin before diarrhea is recovered to CTCAE v4 Grade 2 or less.

Nausea or vomiting should be treated as per local practice. A further dose of study medication should not be given before nausea or vomiting is recovered to CTCAE v.4 Grade 2 or baseline levels.

Xofigo will be permanently discontinued for the following:

- Symptomatic Skeletal Event:
  - Pathologic fracture: Pathologic fractures are to be treated in a manner that attempts to maintain the best functional status and quality of life. Study treatment should be discontinued if the pathologic fractures are due to disease.
  - Spinal cord compression: If the patient experiences spinal cord compression during the treatment period, the patient should be treated for the event, and may not receive further study drug administration.
  - Radiation therapy to bone
  - Surgery to bone

- Patients with lung cancer progression requiring treatment with chemotherapy, radiation or surgery.
- Unacceptable toxicity (see section 5)
- **Surgical Intervention:** If surgery is required, and not due to disease progression, the patient may continue with study treatment, following a period of at least 4 weeks, if this is considered safe in the treating Investigator's opinion.
- **Non-pathological fractures:** For traumatic fractures in weight-bearing bones during treatment phase, the study drug administration should be discontinued.
- Incidental, asymptomatic new or worsening bone metastases will not require discontinuation of Xofigo.

6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR

Parameter	Pre-study (to be sent to BrUOG prior to registration)	Prior to each Day 1 of Each Cycle (within 7 days) (Every 4 weeks) [CK]	At study completion for all patients(30 days- 5 weeks post last dose of Xofigo)	FU[H]
Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X			
History , Demographics (baseline only)	X			
Physical examination	X	X	X	
Weight	X	X[K]	X	
Vital signs	X	X[K]	X	
Toxicity Assessment	X	X[E]	X[EF]	
QOL questionnaires[A]	X	X	X	
Performance Status	X	X	X	
CBC, diff, platelet count[C]	X (within 14 days)	X	X	
Alk phos [C]	X (within 14 days)	X	X	
T. bili, AST, ALT, Cr, albumin [C]	X (within 14 days)			
Serum Pregnancy[B,C]	X (within 7 days of drug)			
CT scan of Chest/abd/pelvis[DG]	X[D](within 28 days)	Per treating physician	Per treating physician	Per treating physician
Bone Scan	X[J]			
Brain imaging (CT or MRI)- contrast to be used unless documented allergy or inadequate renal function	X[I]			
Survival and Disease status			X	X[H]

[A] See Appendix F for EORTC QLQ-C30 and QOL-BM22 questionnaires. Quality of life to be at baseline, after completion of cycles 2, 4, and 6, and end of treatment. If patients complete 6 cycles, end of cycle 6 questionnaire to count for end of treatment questionnaire as well.

[B] Post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, document status.

[C] It is appropriate to use labs from screening for cycle 1 day 1, if labs are within 14 days (pregnancy must be within 7 days as noted above for applicable patients). It is required that if labs are re-drawn prior to day 1 cycle 1 that ANC must be ≥ 1.5, PLT ≥100k, HGB ≥9 prior to cycle 1 dosing or dosing must be delayed

until criteria are met. It is appropriate to use physical, weight, vitals, toxicity assessment and PS from screening for cycle 1 day 1 if within 14 day screening window.
[D] CT Scan for disease assessment should be performed within 28 days of study entry. A PET scan may substitute for a CT scan. Report required.
[E] All patients removed from the study for any reason, including completion will have toxicity assessments performed at time of removal from study.
[F] Adverse event evaluation, inclusive of SAE evaluation, and Performance status assessment will be done 30 days (+1 week) post last dose of drug. SAEs occurring outside this 30 day window must be reported if the event is considered to be possibly related to the drug. If a patient begins a new treatment, AE evaluation will be stopped unless the patient experiences an event that is thought to be possibly related to the study treatment. SAEs will continue to be captured even if patient begins a new treatment within the 30 day window if event thought to be possibly related to Xofigo..
[G]Although it is not a study requirement, it is suggested that CT scans be completed approximately every 2 months (approximately every 2 cycles) or per treating physician.
[H] The time to first progression and the time to first SSE is to be reported to BrUOG on a 2-3 month basis. Overall survival is to be reported every 2-3 months. Follow-up will be for 1 year.
[I]For patients with treated brain metastases must have brain imaging showing evidence of stability prior to first dose of Xofigo. Scan must be sent to BrUOG with registration information before patient is registered on study.
J: A bone scan is required to have been done or to be done on each patient prior to registration. Bone scan results required to be sent to BrUOG for registration. However, the bone scan is not required to be positive as long as other imaging or pathology/cytology is positive for bone metastases. Documentation to be sent to BrUOG.
K: It is required that weight and vitals be captured the day of infusion, prior to drug administration and these values be reported to BrUOG even if patient already had weight and vitals done pre-cycle within 7 day window. If patient has weight done 7 days before dosing and then again pre-drug administration (day of), unless patient's weight changed by > 10% (since the +7 day assessment) then drug can be administered. Pre-cycle weight to be used for drug ordering and drug dosing. Day of weight is only to be used to confirm % of weight change if applicable.
**Any radiographic scans or tests, such as MRIs, PETs, CTs, Bone Scans (etc) that are performed before, during or after study treatment (up to 1 year) , to be submitted to BrUOG

6.1 Patient Assessments:

Patients will undergo a baseline radiographic assessment with either a CT scan or PET scan after completion of 1st-line treatment as per institutional standard of care. Patients meeting study eligibility may be entered on the study. Patients will have a physical monthly prior to each Xofigo treatment. Patients with new signs or symptoms suggesting bone metastases, or other sites of disease progression, will have additional radiographic assessment for evaluation as per institutional standards. The primary endpoint will be the assessment of how many patients develop an SSE during the study treatment and in particular during the first 4 cycles (approximately 4 months) on study. Following completion of all 6 treatments, patients will undergo restaging radiographic studies as per institutional standard of care.

6.2 Alkaline Phosphatase Assessment:

Alkaline phosphatase was found to be an important biomarker in the ALSYMPCA trial.[16] Alkaline phosphatase levels will be assessed at study entry and prior to each dose of Xofigo. We will secondarily assess the following: 1. Time to an increase in alkaline phosphatase by ≥ 25% from baseline, 2. Alkaline phosphatase response (reduction of ≥ 30% from baseline value), and 3. Normalization of the alkaline phosphatase level (defined as a return to normal range in patients with an elevated level at baseline).

6.3 Quality of Life Assessments:

The EORTC QLQ-C30 and BM22 questionnaires will be performed monthly prior to each administration of Xofigo, and at study completion. The EORTC QLQ-30 assesses quality of life in patients with cancer, and the BM22 assesses quality of life in patients with bone metastases.[17]

7.0 DEFINITION OF PROGRESSION:

Progression

- 7.1 Progression of bone metastases Symptomatic Skeletal Event:
  - Pathologic fracture: Pathologic fractures are to be treated in a manner that attempts to maintain the best functional status and quality of life. Study treatment should be discontinued if the pathologic fractures are due to disease.
  - Spinal cord compression: If the patient experiences spinal cord compression during the treatment period, the patient should be treated for the event, and may not receive further study drug administration.
  - Radiation therapy to bone
  - Surgery to bone
- Incidental, asymptomatic new or worsening bone metastases **will not require** discontinuation of Xofigo.

7.2 Progression of lung cancer will be evaluated in this study using the international criteria proposed in the Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis).

- Patients with lung cancer progression requiring treatment with chemotherapy, radiation or surgery will be removed from the study. Patients not requiring treatment with chemotherapy, radiation, or surgery may continue on study at physician discretion.

Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

8.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

Kayla Rosati
Director, BrUOG
Brown University Oncology Research Group,
Brown University
Box G-R 001
Providence, RI 02912
Fax: 401-863-3820
Phone: 401-863-3000

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form.

9.0 PHARMACEUTICAL INFORMATION

9.1 (Xofigo) Radium Ra 223 dichloride

9.1.1 Description

Radium Ra 223 dichloride is an alpha particle emitter with a physical half-life of 11.4 days. The product is isotonic and has a pH of 6.0-8.0.

The radioactive concentration at the reference date is 1,000 kBq/mL (1,100 kBq/mL after implementation of NIST update).The product has a pre-calibration of 14 days. When administered on a day other than the reference day, the volume should be corrected according to the physical decay table accompanying each shipment.

Radium Ra 223 dichloride, is manufactured by Bayer Healthcare LLC contract manufacturer Algeta's Institute for Energy Technology, Isotope laboratories, Kjeller, Norway. The product is produced according to Good Manufacturing Practice (GMP). The product will be delivered in a glass vial, ready-to-use with a certified activity. Radium Ra 223 dichloride is shipped in a lead container and Type A radioactive package according to international transportation guidelines for radioactive materials.

The volume per vial is 6 mL, corresponding to 6 MBq (6.6 MBq after implementation of NIST update) at the reference day. Radium Ra 223 dichloride has a shelf life of 28 days from production day, when stored at ambient temperature. The shelf life has been demonstrated for temperatures from cold storage (2-8°C) up to 40°C. In addition, it has been shown that the product quality is not jeopardized upon freezing.

All study drugs will be labeled according to the requirements of local law and legislation. For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulkware of the ingredients

9.1.2 Mechanism of Action

The active moiety of Radium Ra 223 dichloride 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.

9.1.3 Instructions for use/handling

9.1.3.1 General warning

Radium 223 dichloride should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Radium 223 dichloride are subject to the regulations and/or appropriate licenses of the competent official organization. Radium 223 dichloride should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

9.1.3.2 Radiation protection

The administration of Radium Ra 223 dichloride is associated with potential risks for other persons (e.g. medical staff, care givers and members of the patient's family) from radiation or contamination from spills of body fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

<u>For drug handling</u>

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 Radium Ra

223 dichloride, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diaminetetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care

Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Radium Ra 223 dichloride 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 considerably lower in comparison to other radiopharmaceuticals for therapeutic purposes as the administered radioactivity will usually be below 8 MBq (0.216 mCi) 8.8MBq(0.238mCi after implementation of NIST. In keeping with the **A**s **L**ow **A**s **R**easonably **A**chievable (ALARA) principle, for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance to radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations. The gamma radiation associated with the decay of radium-223 and its daughters allows for the radioactivity measurement of Radium Ra 223 dichloride and the detection of contamination with standard instruments.

9.1.4 Dose calibration

A table with decay correction factors will be provided with each vial of Xofigo.

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.

Immediately before and after administration, the net patient dose of administered radium-223 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 (a new reference vial will be sent to each center corresponding to the updated NIST reference material) 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.

As of December 2015, Bayer visited the Nuclear Medicine department located at the Miriam Hospital to provide to them the new 2015 NIST standard reference material for establishing the revised dial setting on the dose calibrator. The Nuclear medicine department was informed that the new dial setting is not to be used until Bayer has obtained approval from the FDA of an activation date in the 2nd quarter of 2016. Additionally Bayer has agreed to send notification via memo to BrUOG of the implementation date and the memo has been approved at the hospital's IRB. Radium Ra 223 dichloride can be measured in a normal dose calibrator instrument. Different clinical study centers possess dose calibrators from various suppliers; thus, the isotope calibration factor may differ from center to center. Consequently, each center must perform the Radium Ra 223 dichloride dial setting on their relevant dose calibrator(s). For dial setting, the clinical study center will receive a sealed vial containing a Radium Ra 223 dichloride solution for calibration only. The vial is identical to the vials used for study treatment. The amount of Radium Ra 223 dichloride in the vial will be stated on the label. Instructions for the dial setting, including the calibration log form, will be enclosed with the dispatch of the calibration sample.

9.1.5 NIST Standardization Update

The quantification of radium-223 radioactivity in Xofigo (radium-223 dichloride; BAY 88-8223) is based on the primary standardization performed by the US NIST. National Institute of Standards and Technology prepares the standard reference material (SRM) using an official dial setting (primary standardization) as published (17).The NIST SRM is used to calibrate the instruments in production and quality control for both the drug substance and drug product. Additionally, the NIST SRM is used to prepare the NIST traceable Ra-223 reference materials which are then sent to the end-users (e.g., nuclear medicine laboratory physicians or technicians) for dial-setting of their dose calibrators, to allow verification of the patient dose.
In 2014, NIST performed a re-assessment of the primary standardization based on preliminary information suggesting a potential discrepancy of approximately 8-10% between the published NIST primary standardization (17) and results obtained by other national metrology institutes (United Kingdom, Germany, Japan). After completion of there-assessment, NIST reported their findings (18) and had issued a revised NIST SRM in 2015.The discrepancy in the NIST standardization was determined to be −9.5% between activity values obtained using the old reference standard relative to the new primary standardization. Consequently the current numerical values need to be corrected by approx. + 10.5%.

The current (NIST(NIST 2010) standard for radium-223 dichloride will remain in effect until the FDA has fully approved the regulatory variation submitted for Xofigo and is anticipated in the 2nd quarter of 2016. Sites are not able to implement the new NIST standards and are not to use the new dial settings until the site IRB has received and approved the Bayer activation memo documenting the implementation date for the change.
The change in the numerical description of the patient's dose, product strength and labeled vial activity does not impact the safety or efficacy of Xofigo. The change in the NIST radium-223 standard has no impact on subjects; dose subjects are receiving, and will continue to receive. Subjects will receive the same actual dose and volume that was studied in Study 15245 (BC1-06 dosimetry study) and is associated with the proven safety and efficacy of radium-223 dichloride, though the stated nominal radiation dose received is being updated to reflect the new standard. The formula for the calculation of the volume to be administered has to be changed respectively. (see dosing section 9.1.8)

9.1.6 Dosimetry

The absorbed radiation dose calculation was performed based on clinical biodistribution data. Calculations of absorbed doses were performed using OLINDA/EXM (Organ Level INternal Dose Assessment/EXponential Modeling), a software based on the Medical Internal Radiation Dose (MIRD) algorithm, which is widely used for established beta and gamma emitting radionuclides. For radium-223, which is primarily an alpha emitter, additional assumptions were made for the intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed dose calculations for Radium Ra 223 dichloride, considering its observed biodistribution and specific characteristics.

For an administered activity of 3.65 MBq (0.0987 mCi) (50 kBq (0.00135 mCi) (55kBq (.0015 after NIST update) per kg body weight to a 73-kg adult), the calculated absorbed doses to the bone (osteogenic cells) is 4.2050 Gy (420.5 rad) and to the red marrow is 0.5066 Gy (50.66 rad).

The calculated absorbed doses to the main excretory organs are 0.0265 Gy (2.65 rad) for the small intestine wall, 0.1180 Gy (11.8 rad) for the upper large intestine wall and 0.1696 Gy (16.96 rad) for the lower large intestine wall.
The calculated absorbed doses to other organs are low, e.g. heart wall (0.0063 Gy, 0.63 rad), lung (0.0003 Gy, 0.03 rad), liver (0.0109 Gy, 1.09 rad), kidneys (0.0117 Gy, 1.17 rad), urinary bladder wall (0.0147 Gy, 1.47 rad), testes (0.0003 Gy, 0.03 rad), and spleen (0.0003 Gy, 0.03 rad).

The hematological adverse drug reactions observed in the clinical studies with Ra-223 are much lower in frequency and severity than what could be expected from the calculated absorbed doses to the red marrow. This may be related to spatial distribution of alpha particle radiation resulting in non-uniform radiation dose to the red marrow.

9.1.7 Dose handling

Radium-223 has an 11.4-day half-life allowing sufficient time for its distribution, preparation, and administration

The Radium Ra 223 dichloride vials must be stored inside their lead container in a secure facility. The study drug should be used within 28 days of production. The shelf life of the drug in the patient ready dose syringe that is drawn by Cardinal is 4 days. When delivered, the syringe will be labeled with the expiration date on the prescription reflecting this 4-day shelf-life.
Radium Ra 223 dichloride is an alpha-pharmaceutical and should be handled by individuals who are qualified by training and experience in the safe handling of radionuclides. One dedicated person and a back-up designee will have responsibility as assigned from the Primary Investigator for handling and storage of Radium Ra 223 dichloride. All administrations of Radium Ra 223 dichloride are based on the certified activity of Radium Ra 223 dichloride at the calibration date.

9.1.8 Dose calculation

Please see appendix F regarding pre- new NIST changes and Appendix G post new NIST change implementation which is contingent upon IRB approval of the Bayer activation memo and which cannot be implemented prior to Bayer activation date as indicated in the Bayer activation memo.

9.1.9 Dose preparation

Personnel should use appropriate protective clothing and equipment during syringe filling and application to prevent contamination with the radioactive solution (medical gloves / protective glasses). The individual responsible for study drug preparation will draw the correct volume of study drug into a syringe. The size of the syringe should be chosen according to the applied volume to reach the required dosing accuracy. Radium Ra 223 dichloride should not be diluted or mixed with any solutions. Do not store above 40°C (104°F). If the vials have been stored in a refrigerator, they should be left at room temperature for 1 hour prior to use, since cold material should not be injected in a patient. Store Radium Ra 223 dichloride in the original container or equivalent radiation shielding. This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

9.1.10 Dose administration

Before administration of study drug, the patient must be well hydrated; the patient should be instructed to drink ad libitum. Aseptic technique should be used in the administration of Radium Ra 223 dichloride. The syringe should be handed over to the individual who will perform the

injection. The study medication will be administered as a bolus intravenous (IV) injection (up to 1 minute). After administration, the equipment used in connection with the preparation and administration of drug is to be treated as radioactive waste and should be disposed in accordance with local procedure for the handling of radioactive material. The short penetration of the alpha particles allows for the use of standard radiation protection measures during shipping and administration. Standard dose calibrators and regular contamination monitors are used during drug handling Radium-223 becomes non-active after ten half-lives (approximately 4 months), thus waste can be stored for 4 months, then discarded as normal clinical waste, or as according to standard operating procedures of the institutions nuclear medicine department.
Patients will receive radium-223 as outpatients and there is no restriction to public or family contact afterwards.

9.1.11 Toxicities

The most common adverse reactions (≥ 10%) in patients receiving Radium Ra 223 dichloride were nausea, diarrhea, vomiting, and peripheral edema. Grade 3 and 4 adverse events were reported among 57% of Radium Ra 223 dichloride-treated patients and 63% of placebo treated patients. The most common hematologic laboratory abnormalities in Radium Ra 223 dichloride-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Treatment discontinuations due to adverse events occurred in 17% of patients who received Radium Ra 223 dichloride and 21% of patients who received placebo.

The most common hematologic laboratory abnormalities leading to discontinuation for Radium Ra 223 dichloride were anemia (2%) and thrombocytopenia (2%).

Table 1 below shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Radium Ra 223 dichloride exceeds the incidence for placebo.

Table 1 Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Radium Ra 223 dichloride (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 2 shows hematologic laboratory abnormalities occurring in > 10% of patients and for which the incidence for Radium Ra 223 dichloride exceeds the incidence for placebo.

Table 2: Hematologic Laboratory Abnormalities

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

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Radium Ra 223 dichloride and in 2% of patients on placebo. Among patients who received Radium Ra 223 dichloride, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status
Dehydration occurred in 3% of patients on Radium Ra 223 dichloride and 1% of patients on placebo. Radium Ra 223 dichloride 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 Radium Ra 223 dichloride.

Secondary malignant neoplasms
No cases of radiation-induced cancer have been reported in reported in clinical trials with radium-223 dichloride in follow-up of up to three years. However, the radiation dose resulting from therapeutic exposure may result in higher incidence of cancer (e.g. sarcomas of the bone, or leukemia), mutations and a potential for development of hereditary defects.

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

Bone Marrow Suppression
In the randomized trial, 2% of patients on the Radium Ra 223 dichloride 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 Radium Ra 223 dichloride, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Radium Ra 223 dichloride 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 Radium Ra 223 dichloride-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 Radium Ra 223 dichloride and placebo.

Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Radium Ra 223 dichloride. 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 Radium Ra 223 dichloride, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Radium Ra 223 dichloride 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

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Radium Ra 223 dichloride. Before the first administration of Radium Ra 223 dichloride, the absolute neutrophil count (ANC) should be ≥ 1.5 x 109/L, the platelet count ≥ 100 x 109/L and hemoglobin ≥ 9 g/dL. Before subsequent administrations of Radium Ra 223 dichloride, the ANC should be ≥ 1 x 109/L and the platelet count ≥ 50 x 109/L. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when
clinically indicated. Discontinue Radium Ra 223 dichloride in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Radium Ra 223 dichloride 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, Radium Ra 223 dichloride should be discontinued.

10.0 AGENT ACCOUNTABILITY

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from manufacturer using a Drug Accountability Record Form. The nuclear medicine department will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.
It is required that each drug order form and drug destruction form be sent to the BrUOG office for tracking and record keeping.

Destruction and Return

At the end of the study, unused supplies of Ra 223 dichloride and other investigational agents should be destroyed appropriately and according to institutional policies, but only after BrUOG is sent the accountability logs outlining all drug shipments, receipts, each time patients are dosed and only after BrUOG obtains approval from Bayer, to have site destroy drug.

Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction for Ra 223 dichloride should be sent to BrUOG each time.

10.1 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The nuclear medicine department will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

11.0 ADVERSE DRUG REACTION (ADR) REPORTING

BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Xofigo ® whether or not considered related to Xofigo ®. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

11.1 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Unexpected adverse event
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.2 Monitoring of Adverse Events and Period of Observation
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS
Investigators are required by Federal Regulation to report adverse drug reactions. Question regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4. A copy of the CTCAE Version 4can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

11.3.1 Pregnancies

Pregnancies occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. If the subject is on study drug, the study drug is to be discontinued immediately. The pregnancy must be reported to the Brown University Oncology Research Group with 24 hours and BrUOG will in turn report to Bayer within 24 hours (1 working day) of the Investigator's knowledge of the pregnancy by email and/or facsimile using the SAE Form. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 4 weeks (30 days) of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Bayer Drug Safety immediately by facsimile, or other appropriate method (to be done by BrUOG), using the Medwatch3500A form (MedWatch 3500A-to be completed by site).

The Investigator will follow the subject until completion of the pregnancy, and must notify Bayer (by informing BrUOG) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial report .If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG who will then report to Bayer by facsimile within 24 hours (1 working day) of being made aware of the event).

Any suspected fetal exposure to Xofigo ® must be reported to BrUOG within 24 hours who will then report to Bayer within 1 working day of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in utero exposure to the study drug should also be reported. In the case of a live "normal" birth, Bayer should be advised as soon as the information is available.

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

11.3.2 Serious Adverse Event Reporting Procedures

All pregnancies or suspected pregnancies, including suspected fetal exposure or neonatal deaths must be reported to the Brown University Oncology Research Group within 24 hours. BrUOG will report all pregnancies to Bayer within 1 working day of being made aware of the event.

All other SAEs are to be documented via email to BrUOG within 24 hours. Sites will have 5 business days to send the written report (Medwatch 3500A) to BrUOG (from date of being notified of event), who will then report the SAE to Bayer product safety within 1 working day when possible of discovery or notification of the event Initial SAE information and all amendments or additions must be recorded on an SAE Form and faxed to Bayer.

Bayer Drug Safety Contact Information: (to be reported to by BrUOG)

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address: **Mail only:**	Global Pharmacovigilance - USA Bayer HealthCare P.O. Box 915 Whippany, NJ 07981-0915
Address: **FDX or UPS only**	100 Bayer BLVD., Whippany, NJ 07981 67 Whippany Road, Whippany, NJ 07981

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone: 1-888-842-2937

The principal investigator has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, Bayer, and all sites participating in the trial. All SAE reports will be forwarded to Bayer Product Safety by BrUOG. All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form). Sites must alert BrUOG to SAEs within 24 hours via email, and will then have 5 business days to submit formal notification via the 3500A (5 days from date of being notified of event). BrUOG will then alert Bayer within 1 business day when possible. BrUOG will submit the SAE memo, and Medwatch 3500A to the FDA within 7 days.

Expedited Reporting by Investigator to Bayer

Serious adverse events (SAE) are defined above. All events must be reported, by FAX or email, to the Brown University Oncology Research Group who must inform Bayer in writing using a MEDWATCH 3500A form of any SAE within 1 business day (when possible) of being aware of the event. The written report must be completed and it will then be supplied by BrUOG to Bayer by facsimile within 24 hours/1 business day (when possible) of BrUOG being made aware of the event. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory

values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE (such as discharge from hospital) is required. The Bayer tracking number (ONC-2014-099) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Bayer. A copy of the fax transmission confirmation of the SAE report to Bayer should be attached to the SAE and retained with the study records at BrUOG. (Bayer does NOT send a confirmation so BrUOG will have to use documentation from their fax that it was sent)

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of Xofigo, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported to BrUOG within 5 business days or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks (30 days +1 week) after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). If a patient begins a new therapy AE evaluation is to stop but SAEs are to continue if SAE is thought to be possibly related to Xofigo.

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Bayer study drug (or therapy) is suspected.
For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

11.4 Reporting requirements and procedures depend upon:

1. Whether investigational agents are suspected of causing toxicity;
2. Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity); and
3. The severity of grade of the toxicity.

11.5 Assessing Causality:
Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used:

Yes: if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No:if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.6 Types of Report: For sites:
Telephone report: For SAE's initial or follow-up, contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours).

Written report: Send the copy of the Medwatch 3500A form within 5 business days of being made aware of the event to the BrUOG Central Office by email, scan or Fax:

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: Kayla_rosati@brown.edu and Kristen_Mitchell@brown.edu

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported to BrUOG within 5 business days or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

MedWatch 3500A Reporting Guidelines: The following information is a requirement to be included in the initial SAE report, sites please be aware:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Name and contract information of reporter
- Patient identification such as initials, study number, age, sex, weight
- Treatment regimen (name of study drug, dosing frequency, combination therapy)
- Date and time of administration of study drug
- Concomitant medications
- Protocol description (and number, if assigned)
- **Description of event, severity (grade) , treatment, and outcome, if known**
- Supportive laboratory results and diagnostics- medical treatment provided
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication
- ****It is required that you put the following numbers on the Medwatch form for tracking:**
    - **BrUOG 301 and ONC-2014-099**

Sites should also be sure to include the following when possible at initial if known:

- date of onset
- time from administration to start of event
- any possibly etiology for event
- final diagnosis or syndrome
- action taken

A final report to document resolution of the SAE (such as discharge from hospital) is required.

The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" as defined above are present. The Brown University Oncology Research Group is responsible for reporting serious adverse events to Bayer as described above.

Follow-up information:
Additional Info may be added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report).

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

11.7 BrUOG Responsibility Regarding Reporting:
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 7 calendar days after initial receipt of the information. BrUOG will alert Bayer to a SAE within 1 business day (when possible) of being made aware of the event via documentation. SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. They will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA(which will be sent to the Medwatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND)

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All SAEs that are serious and reasonably or probably related to the use of Xofigo ® will be faxed to: Bayer

11.8 Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

a. Expedited IND Safety Reports:
BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA – 0178, unless per the IND status BrUOG is to submit the SAEs to the Division Fax instead.

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to Bayer as well as any pregnancy occurring in association with use of a Bayer product to:

BrUOG will send to: Bayer via Email: DrugSafety.GPV.US@bayer.com

b. IND Annual Reports, for IND study only
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Bayer Corporation as a supporter of this study as follows.

11.9 Adverse event updates/IND safety reports
Bayer shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. **Disease Progression: Any patient with disease progression should be removed from study as per section 7.1 and 7.2. Details and tumor measurements should be documented on flow sheets.**
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
3. The physician feels it is in the best interest of the patient to stop the treatment.
4. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment

5. Non protocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol or treatment—major violation
7. Pregnancies or Suspected Pregnancies(including positive pregnancy test)
8. Patient is lost to follow-up
9. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
10. Death

In this event notify:

Brown University Oncology Research Group (BrUOG) Central Office,
Phone: (401) 863-3000
Fax: (401) 860-3820

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason as well as patients who complete therapy will be followed for time to disease progression at any site, time to SSE, and overall survival (up to 1 year). Information will be sent to BrUOG central office every 2-3 months. At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days post the last dose of study drug (+1 week). If a patient begins a new treatment AEs do not need to be captured but SAEs must continue to be captured for the 30 day period and post 30 days if the event is thought to be potentially related to Xofigo. In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Angela Taber, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is supported by Bayer (the makers of Xofigo ®).

14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided to Brown University Oncology Research Group, and Bayer. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Bayer of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and Bayer. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.3 Protocol amendments or changes in study conduct:
Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved by Brown University Oncology Research Group, Bayer and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and Bayer.

- Examples of amendments requiring such approval
- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and Bayer in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group and Bayer must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

- Changes in the staff used to monitor trials (Bayer considers a change in Principal Investigator or the addition of sub-site(s) to be substantial and requires Bayer approval prior to implementation)
- Minor changes in the packaging or labeling of study drug.

15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

15.1 Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Patient Confidentiality: In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Bayer or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.3 Protocol Compliance: The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Bayer and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Bayer and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

15.4 On-site Audits: Regulatory authorities, the IEC/IRB and/or Bayer clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

15.5 Drug Accountability: Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Bayer for disposal of the drug (if applicable and if approved by Bayer) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing Xofigo ® will be treated and disposed of as hazardous waste in accordance with governing regulations.

15.6 Premature Closure of the Study: This study may be prematurely terminated, if in the opinion of the investigator or Bayer, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Bayer by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to Bayer.

15.7 Record Retention:

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Angela Taber, M.D.) and Brown University Oncology Research Group Manager of Operations (Kayla Rosati) will monitor this study. The case report forms will be monitored against the submitted documents every 3 months for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Bayer will notify the Principle Investigator if an application is filed.

16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

17.0 STATISTICS

This protocol will evaluate the effect of Ra 223 on patients with NSCLC who had stable to responding disease after completion of first line chemotherapy. The primary end point is the proportion of patients who experience their first symptomatic skeletal event (including pathologic bone fracture, spinal cord compression, need for surgical intervention for a bone metastasis, and time to external beam radiotherapy) during study treatment. A second primary endpoint is to evaluate the reduction of SSEs after 4 cycles of treatment (approximately 4 months) following the first Ra 223. The control is a historic experimental arm consisting of 257 patients (the majority having advanced NSCLC) from a study by Rosen *et al* [7,8] who received zoledronic acid 4mg q 3 weeks with concomitant antineoplastic therapy. Approximately 40% patients experienced their first symptomatic skeletal event by 4 months in that study.

We hypothesize that the addition of Ra 233 to standard chemotherapy would reduce the proportion of patients with first symptomatic skeletal event at 4 months by half, i.e., to 20% compared to historic controls who received zoledronic acid. Using Fisher's exact test, we calculated a sample size of 36 patients to detect this 20% difference in the proportion of patients

having their first symptomatic skeletal event at 4 months with power of 75% and two sided α error probability of 0.1.

Progression-free survival (PFS) and overall survival (OS): PFS and OS will be determined from the time of study entry.

Time to symptomatic skeletal events: Will be determined from the time of study entry.

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APPENDIX A

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

BrUOG L301: Xofigo Following Frontline-Line Chemotherapy For Patients With Non-Small Cell Lung Cancer and Bone Metastases

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> hospital follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Angela Taber, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

You are being asked to take part in this study because you have been diagnosed with advanced lung cancer which has spread to your bones. You have already received standard chemotherapy for your lung cancer.

In this study you will receive the medicine Xofigo which is a radioactive drug that is FDA approved to treat prostate cancer that has spread to the bones. Cancer that has spread to the bones can cause pain and increase the risk of a broken bone (fracture) by weakening the bone. If the cancer has spread to the bones of your spine there is a risk that a damaged bone could put pressure on your spinal cord, causing paralysis. In patients with prostate cancer that had spread to the bones, treatment with Xofigo reduced the risks of bone pain and fractures and prolonged survival. Xofigo has not previously been tested to treat lung cancer that has spread to the bones. Your doctors are studying the effects, good and bad, of Xofigo when used to treat lung cancer that has spread to the bones.

This study is supported by Bayer, the makers of Xofigo.

How Many People will take part in the Study?

We expect to enroll approximately 36 subjects into this study. The study is sponsored by the Principal Investigator Angela Taber, MD.

Explanation of Procedures

<u>What will happen if I take part in this research study?</u>

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures, while on the study. They are part of regular cancer care.

Baseline

- CT scan of your chest, abdomen, and pelvis or PET scan prior to starting treatment. You may also need to have a bone scan if you have not had one since your diagnosis.
- History and Physical examination prior to starting treatment inclusive of vital signs, weight, toxicity assessment, performance assessment.
- Blood tests prior to starting treatment (about 3 tablespoons)
- Pregnancy test if you are a female of childbearing potential
- Quality of life questionnaires

On study

- Physical examination prior to treatment every 4 weeks inclusive of vital signs, weight, toxicity assessment, performance assessment.
- Blood tests prior to treatments every 4 weeks (about 3 tablespoons)
- Quality of life questionnaires every 8 weeks

Xofigo is administered IV over 1 minute in the nuclear medicine department approximately every 4 weeks for up to 6 treatments (about 6 months.)

You should drink plenty of fluids (at least 2 liters/day) the day that you receive Xofigo.

How long will I be in the study?

You will receive Xofigo for up to six months (6 treatments) or as long as your cancer does not grow or spread or cause worsening bone pain or a fracture for which you require surgery or radiation and you do not have severe side effects from Xofigo. After completion of Xofigo, you will be followed for up to 1 year for survival.

Off study and follow-up:

- Your physician may decide to order CT scans of your chest, abdomen, and pelvis or PET scans in follow-up as necessary
- Physical examination inclusive of vital signs, weight, toxicity assessment, performance assessment.
- Toxicity assessment again approximately 30 days after the last dose of Xofigo
- Blood tests (about 3 tablespoons)
- Quality of life questionnaires
- Follow-up for disease status and survival information every 2-3 months for 1 year

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include: the investigational drug:

Xofigo. The drug will be paid for by the study and will be provides by Bayer, the maker of the drug at no charge; the cost will not be billed to you or your health insurance company.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are all study doctor visits, blood tests, drugs used to reduce side effects and CT scans.

These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact the Principal Investigator, <INSERT SITE PI NAME AND CONTACT>

Discomforts and Risks

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away. Taking part in this study may lead to time away from work.

Xofigo

The following side effects are expected to occur in less than 20% of patients

- Nausea
- Diarrhea
- Vomiting
- Swelling in the hands and legs
- Low red blood cells (which can cause fatigue)
- Low white blood cells (which can increase the risk of infection).
- Low platelets (which can increase the risk of bleeding).
- Inflammation and pain at the injection site.
- Kidney damage
- Dehydration.

Risk of Secondary Cancers or Leukemia: Xofigo may increase the risk of other cancers or leukemia (a blood cancer).

In general, when a person is given a radioactive drug, there is a potential risk for the people around you, due to radiation from your body and due to possible contamination by spilling urine or feces. When Xofigo has been injected into a patient, the risk for external radiation exposure to other people is extremely low, due to the short range of the radiation particles in Xofigo (less than 1mm, which is less than one-twenty-fifth of an inch). For these reasons the product can be administered on an outpatient basis. However, you should practice good hygiene including washing hands, flushing the toilet several times after each use and washing clothes that are soiled with stool or urine promptly and separately from other clothes, for _7__ days after each Xofigo treatment.

Reproductive Risks

Xofigo may decrease sperm count. This is usually temporary but is infrequently permanent, which would result in sterility. Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study Ask your study doctor for more information regarding preventing pregnancy during the study treatments. You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

By signing this document you are acknowledging that you understand and agree to the information presented in this Reproductive Risks section.

Antiemetics (anti-nausea medications): Various medications used to prevent and treat nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive Xofigo by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment.

Risk of CT imaging: CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits

Taking part in this study may or may not make your health better. While doctors hope that Xofigo will be active against the lung cancer that has spread to your bones and that the side effects are not too severe, this is not yet known. We do know that the information from this study will help doctors learn more about Xofigo as a treatment for lung cancer that has spread to the bones. This information could help future cancer patients.

Alternative Therapies

What other choices do I have if I do not take part in this study?

You have just finished receiving standard chemotherapy for lung cancer. You may already be taking another medicine to reduce the risk of bone pain or fracture. Other options may include

- Additional chemotherapy
- Radiation
- Observation
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative or supportive care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

Follow-up after Withdrawal of Consent

If you leave the study, it would still be useful for us to know how you do over the next year. *We would appreciate if you would permit us to get follow-up information about your health from your doctor or your medical record.*

____ If I withdraw from the study, you have my permission to collect information about my health from my doctor or medical record.

_____ I do not give my permission for you to continue to collect information about me if I stop participating in the study.

Signature of study volunteer Date

You have the right to change your mind at any time regarding follow-up after withdrawal. If you decide to quit the study please tell the head researcher <INSERT NAME AND CONTACT>

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Angela Taber, the sponsor of the study, nor BrUOG, the coordinating center, nor Bayer, the maker of the drug Xofigo, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <INSERT IRB CONTACT AND NUMBER>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of

conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor, BrUOG, The Brown University Oncology Research Group and Bayer (maker of the drug being used on this study and financial supporter of this study);
- Doctors, nurses, laboratories and others who provide services to you in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

For more detail about your privacy rights see the<INSERT HOSPITAL NAME> Joint Privacy Notice which has or will be given to you.

Research authorization for use and disclosure of information.

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.

We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.

Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to Angela Taber, MD c/o the Medical Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONTACT WITH PHONE NUMBER>

Uses and releases covered by this authorization (permission)

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

☒ Every research site for this study, including this hospital, and including each site's research staff and medical staff

☒ Health care providers who provide services to you in connection with this study

☒ Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol

☒ The following research sponsors or supporters and the people and companies that they use to oversee, administer, or conduct the research: BrUOG, the group coordinating the study, and Bayer (maker of the drug being used on this study and financial supporter of this study)

☒ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights

☒ The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study

☒ Principal Investigator and other Investigators

☒ Study Coordinator

☒ Additional members of the Research Team

☐ The Patient Advocate or Research Volunteer Protector: _____

☒ Members of the hospital's administrative staff responsible for administering clinical trials and other research activities

☐ Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)

☒ Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee

☐ The members and staff of the hospitals affiliated Privacy Board (if such a board is used)

☐ Others: _____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

☒ The entire research record and any medical records held by the hospital may be used and released.

☐ The following information: _____

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the*<INSERT HOSPITAL NAME> *Privacy Notice*

This informed consent document expires on _____.

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____

Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____

Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____

Signature of Translator Date

_____ _____ _____

Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

_____

_____

APPENDIX B: Checklist

BrUOG L301: Xofigo Following Frontline-Line Chemotherapy For Patients With Non-Small Cell Lung Cancer and Bone Metastases

Inclusion Criteria

_____(y/n) Advanced non-small cell lung cancer with bone metastases

_____(y/n) Stable or responding disease after completion of initial systemic chemotherapy as defined by RECIST criteria. Site to submit pre-treatment scan with post treatment scan for RECIST and confirmation to BrUOG. Document blastic or lytic lesions (and for lytic soft tissue or no soft tissue component. Soft tissue component requires measurements for RECIST).
_____(y/n) At least 3 weeks have elapsed since prior chemotherapy and 4 weeks since radiation prior to first dose of Xofigo. Patients are not permitted to receive any form of 'maintenance' chemotherapy or biologic/targeted anticancer therapy while being treated on this study

_____(y/n) Voluntary, signed written informed consent, Date signed_____

_____(y/n) Age ≥18

_____(y/n) Must be willing to consent to use effective contraception while on treatment and for at least 30 days afterwards.

_____(y/n) CT scan of chest/abdomen prior to registration (PET scan can substitute), report to be submitted to BrUOG

_____(y/n) Labs within 14 days of study registration: Date:_____

_____(y/n) serum pregnancy test negative within 7 days of beginning study drug for women of childbearing potential: Date if applicable: if not applicable because patient is male document with N/A. If post-menopausal female (defined as no menses for at least 1 year) then document here with N/A and write in note to submit to BrUOG

_____(y/n) Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 30 days after the last dose of study

drug. The definition of adequate contraception will be based on the judgment of the treating physician.

_____(y/n) Absolute neutrophil count ≥ 1,500/ul, Date_____

_____(y/n) WBC ≥ 3,000/mm3; date:_____

_____(y/n) Platelet ≥ 100,000/uL, Date_____

_____(y/n) HGB ≥ 9g/dl: Date:_____

_____(y/n) Total bilirubin ≤ 1.5 x ULN, Date_____

_____(y/n) AST≤ 2.5x ULN, ALT ≤ 2.5x ULN, albumin > 2.5g/dl Institution Date_____

_____(y/n) creatinine ≤ 1.5xULN Date:_____

_____(y/n) All acute toxic effects related to prior treatment(s) must have recovered to ≤ grade 1 except for alopecia at time of registration.

_____(y/n) ECOG 0-1

_____(y/n) Life expectancy of at least 12 weeks: treating investigator to document and confirm in note

_____(y/n)Is patient going to be treated with concurrent bisphosphonates or denosumab? if yes, please send BrUOG the information on drug, start date and dose

_____(y/n) Prior skelteal events (pathologic fracture, radiation or surgery to bone, or spinal cord compression)?? allowed if stable and managed prior and now patient is stable for 4 weeks prior to study entry. Must submit how events managed to BrUOG for documentation to confirm eligibility criterion. (For example, if a patient experienced a SSE and had radiation for 2 weeks they must then be stable for 4 weeks after the completion of radiation prior to study entry)

_____(y/n) Willing and able to comply with the protocol, including follow-up visits and examinations

_____(y/n) Bone scan baseline

Exclusion Criteria:

_____(y/n) No prior invasive malignancy within the prior two years. However, patients with an early stage malignancy that is not expected to require treatment in the next 2 years (such as early stage, resected breast cancer or asymptomatic prostate cancer) are eligible.

_____ (y/n) Patients with untreated brain metastases ** if patient has treated bone mets, must have brain imaging showing evidence of stability prior to first dose of Xofigo.

_____(y/n) Received systemic therapy with radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188, or Radium Ra 223 dichloride) for the treatment of bony metastases

_____(y/n) Patients on concurrent anticancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than Ra 223 dichloride.

_____(y/n) major surgery within 28 days of study treatment start date. Central venous catheter placement is not considered major surgery.See eligibility for more details

_____(y/n) Any other serious illness or medical condition that would interfere with protocol treatment, such as but not limited to: Any active infection ≥ National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4 Grade 2 or Cardiac failure New York Heart Association (NYHA) III or IV;

_____(y/n): Inability to comply with the protocol and/or not willing or not available for follow-up assessments.

_____(y/n): Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.

_____(y/n) Pregnant or breastfeeding. Women of child bearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to beginning of treatment. Post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, please document status in note.

Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form Enclosed __Not Enclosed _____ Not Applicable __

2) Heme/Onc initial note Enclosed __Not Enclosed _____ Not Applicable __

3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __

4) MRI/CT Report(s) Enclosed __Not Enclosed _____ Not Applicable __

5) Lab Source Document Enclosed __Not Enclosed _____ Not Applicable __

6) ICF signature page

7) Other documents, please list_____

IRB approval date of protocol: _____

Hospital where patient will be treated with Oncologist: _____

Date patient will begin treatment: _____ Primary Physician: _____

Nuclear Medicine physician:_____

Your signature: _____

APPENDIX C

1.1 NCI CTC Version 4

Toxicity will be scored using NCI CTC Version 4 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4

APPENDIX D

ECOG PATIENT PERFORMANCE STATUS

STATUS	KARNOFSKY	ZUBROD-ECOG-WHO	Description
No complaints	100	0	Normal activity
Able to carry on normal activities	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		

Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

APPENDIX E

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms

APPENDIX F:

Treatment for use pre-Bayer activation memo for NIST standards:

The current dose calibration is referenced to the 2010 NIST standard and corresponds to 50KBq/kg.

The volume to be administered to a given patient should be calculated using the:

– 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 amount (volume to be drawn into the syringe) to be administered to a patient should be calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (50 kBq/kg b.w)}}{\text{DK factor} \times \text{1,000 kBq (0.027 mCi)/mL}}$$

A table with decay correction factors will be provided with each vial of Xofigo.

Weight used for drug order is to be from pre-cycle assessment (done within 7 days prior to cycle start). Patients are to be dosed each cycle based on drug order weight and weight collected the day of dosing (prior to dosing), is to only be used to confirm patient's weight has not changed by more than 10% (see section 5.1). Patient's dose is not to be adjusted based on day of weight.

APPENDIX G:

Treatment:
The revised dose 55kBq/kg corresponds to the new NIST standard reference material (NIST 2015), which is to be used upon IRB approval of Bayer activation memo but cannot be used prior to the date indicated in Bayer activation memo expected in 2Qof 2016.

The volume to be administered to a given patient should be calculated using the:

– Patient's body weight (kg)
– Dosage level 55 kBq/kg body weight or 1.49 microcurie /kg body weight– Radioactivity concentration of the product 1,100 kBq/mL;29.7 microcurie/mL at the reference date
– Decay correction factor to correct for physical decay of radium-223.

The total amount (volume to be drawn into the syringe) to be administered to a patient should be calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (55 kBq/kg b.w)}}{\text{DK factor} \times \text{1,100 kBq (29.7 microcurie)/mL}}$$

A table with decay correction factors will be provided with each vial of Xofigo.

Weight used for drug order is to be from pre-cycle assessment (done within 7 days prior to cycle start). Patients are to be dosed each cycle based on drug order weight and weight collected the day of dosing (prior to dosing), is to only be used to confirm patient's weight has not changed by more than 10% (see section 5.1). Patient's dose is not to be adjusted based on day of weight.