DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

REQUEST FOR PROJECT TEAM MEMBER APPLICATIONS TO CONDUCT CLINICAL TRIALS USING RADIUM-223 DICHLORIDE (NSC# 793433)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) will now accept Project Team Member Applications (PTMAs) for clinical and non-clinical projects using Radium-223 dichloride (BAY 88-8223, Alpharadin, Xofigo, NSC# 793433) solution for injection as an alpha particle-emitting radiopharmaceutical being developed by CTEP as an anticancer agent in collaboration with Bayer AG (Leverkusen, Germany). Radium-223 ($t_{½}$ = 11.4 days) acts as a divalent cation ($^{223}Ra^{2+}$) like calcium to localize in areas of increased bone turnover by forming complexes with bone hydroxyapatite. Alpha particle emission, which comprises 95% of the emitted energy, produces sublethal and lethal nuclear double-strand DNA breaks. In 2013, the Food & Drug Administration (FDA) granted radium-223 dichloride approval for the treatment of patients with castration-resistant prostate cancer with symptomatic bone metastases and no known visceral metastatic disease. Radium-223 in combination with paclitaxel/docetaxel, inhibitors of ataxia telangiectasia and Rad3-related (ATR) protein, or immunotherapy checkpoint modifiers are of highest clinical interest for CTEP and Bayer AG.

Available clinical and non-clinical pharmacokinetic (PK) data support the use of radium-223 dichloride as a solution for injection by vein. A single administration dose of 55 kBq/kg body weight is the recommended phase 2 dose as monotherapy (achieves >1.15 Gray/megabecquerel [Gy/MBq] [4260 rad/millicurie {mCi}] absorbed dose to bone surface or red marrow in humans). Pharmacological safety studies revealed an insignificant absorbed dose in mammalian cardiovascular, respiratory, gastrointestinal, or central nervous system tissues after prolonged exposure (<0.047 Gy/MBq; greatest absorbed dose to lower colon as it is the dominant organ for agent elimination). Studies involving radium-223 monotherapy in patients with castration-resistant prostate cancer have shown the radiopharmaceutical to be very well tolerated with limited grade 2 gastrointestinal or marrow toxicities (Parker *et al*., 2013). Phase 3 clinical efficacy data from the Alpharadin in Symptomatic Prostate Cancer (ALSYMPCA) trial found a 3.6-month gain in overall survival after radium-223 therapy (14.9 months) versus placebo (11.3 months) (Parker *et al*., 2013).

The current Bayer AG drug development plan for radium-223 includes final analyses of a completed phase 1 study of radium-223 plus paclitaxel in solid tumors (Study 17110, NCT2442063), initiation of a phase 1 study of radium-223 in patients with early relapsed multiple myeloma (Study 18987, NCT2928029), and a randomized phase 2 study in metastatic breast cancer with bone metastases in two or more lesions (Study 17096, NCT02258451).

Currently, CTEP plans to sponsor up to three randomized phase 2 combination trials of radium-223 for the treatment of patients with relapsed refractory cancers and symptomatic bone metastases. The role of the project team is to evaluate all available evidence to modify and to refine this initial plan. The project team will include:

1. **Clinician scientists in radiation oncology, medical oncology, or nuclear medicine** with expertise in radiopharmaceutical therapies and an interest in randomized phase 2 trials for solid tumors, especially hormone refractory prostate cancer or lung cancer (fill out **Part A** of the attached Application; Clinician Scientists must belong to a qualifying NCI grant funded institution as defined at the end of this letter);
2. **Translational scientists** with expertise in biomarker development for radiotherapy effect upon tumor cells in bone, especially as it relates to taxane biology or DNA damage response modifiers like ATR inhibitors (fill out **Part B** of the attached Application and see the submission instructions at the end of this letter);
3. **Radiation medicine physicists or radiopharmacologists** with expertise in clinical trials and an interest in radionuclide dosimetry (fill out **Part B** of the attached Application and follow the submission instructions for translational scientists); and

4. **Basic scientists** with expertise in DNA double-strand break repair (fill out **Part C** of the attached Application and see the submission instructions at the end of this letter).

Prospective project team members may apply for multiple roles using a single application form by completing all the appropriate parts (Part A, B, or C). The project team will be recruited nationally, and the team will be responsible for prioritizing the research questions regarding radium-223 in combination trials, including prioritization of relevant biomarker studies. It is anticipated that clinicians on the project team will be tasked with writing the Letters of Intent (LOIs) describing study design for CTEP approval. It is anticipated that these clinicians will ultimately lead the proposed project team's clinical studies. It is also anticipated that other extramural members of the project team will stay involved in the subsequent design and the execution of the proposed trials. The project team should aim to complete its work in three months or less.

Background / Biomarker Rationale

Radium-223 dichloride is a therapeutic alpha particle-emitting radiopharmaceutical with targeted anti-tumor effect on bone metastases (Investigator's Brochure, 2017; Henriksen *et al*., 2002). The isotope radium-223 (as radium-223 dichloride) mimics calcium and selectively targets bone, pronouncedly in areas of bone metastases, by forming complexes with the bone mineral hydroxyapatite (Henriksen *et al*., 2003). The high linear energy transfer (LET) of alpha emitters (80 kiloelectron volt/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in a potent and localized anti-tumor effect that spares normal tissue cells. The alpha particle range for radium-223 is less than 100 micrometers (less than 10 cell diameters) which minimizes damage to the surrounding normal tissue.

RADIUM-223

Chemical Name:	Radium-223 dichloride
USAN (United States Adopted Name):	Radium-223 dichloride
BAY number:	BAY 88-8223
Chemical formula:	$^{223}RaCl_2$
Molecular weight for $^{223}RaCl_2$:	293.9 g/mol
Atomic weight for ^{223}Ra	223.02

Mechanism of Action

Radium-223 dichloride solution is an alpha particle-emitting radiopharmaceutical that represents a new generation of natural bone-seeking radionuclides. Radium-223 is a sterile aqueous solution of radium-223 dichloride for injection by vein. The vehicle is citrate in saline solution. The active moiety in radium-223 dichloride solution for injection is the divalent cation ($^{223}Ra^{2+}$) of the alpha particle-emitting nuclide, radium-223. The divalent cation $^{223}Ra^{2+}$ and daughter nuclides (Figure 1) have a number of properties which contribute to the mechanism of action:

- Radium-223 selectively targets areas of increased bone turnover in bone metastases. It is thought that there are direct DNA damaging effects in cancer cells overlying bone turnover. There is also evidence that lethal DNA damage accumulates in osteoblasts/osteoclasts, mitigating the effects of malignant destruction of normal bone.
- The high-energy alpha particle radiation emitted from radium-223 and its daughter nuclides induces double-strand DNA breaks resulting in a potent effect only in the areas containing metastatic cancer cells.
- The short path length of alpha particle radiation ensures that toxicity to adjacent healthy tissue, and particularly the bone marrow, is kept at a minimum.
- Distribution of radium-223 and its short-lived daughter nuclides to soft tissue is limited, potentially minimizing risk of systemic organ side effects.

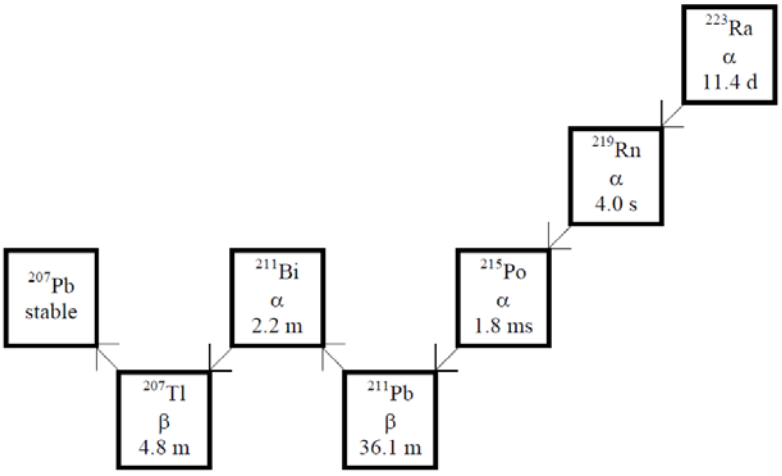

Figure 1: Radioactive decay of radium-223

Nonclinical Studies of Radium-223

Non-clinical studies have been performed to characterize the biopharmaceutical and pharmacodynamic properties of radium-223 dichloride. The pharmacology data include *in vitro* and *in vivo* activities in pharmacological models. Batteries of pharmacological safety studies were conducted to assess potential effects on vital organ functions (central nervous system, respiratory, and cardiovascular). Moreover, non-clinical studies were performed to explore the PK, biodistribution, and excretion characteristics of radium-223 dichloride. Metabolism studies were not conducted and are not appropriate because there are no known pathways metabolizing radium-223. The toxicological program included studies to investigate the systemic and late radiation toxicity of radium-223 dichloride after single and repeated administration. Local tolerance after administration by vein was high. Supplemental studies were conducted in rats to investigate the toxicity of combined treatment with radium-223 dichloride and docetaxel (Taxotere). The combination was tolerated, with no significant overlapping toxicities.

Radium-223 is rapidly eliminated from blood, distributed to bone or excreted into the gastrointestinal tract. Fecal excretion is the main route of elimination from the body. Urinary excretion is minimal. No specific uptake was visible on scintillation camera images in normal organs such as the heart, liver, gallbladder, kidneys, urinary bladder, stomach, and spleen. The calculated absorbed doses to these organs were low, and well below dose levels associated with toxicity. The methodology to estimate dosimetry for alpha emitters is still at a very early stage and the available software developed for beta and gamma emitters does not apply. In reviewing these dosimetry results, it is essential to understand that they only represent the best possible approximation of average absorbed organ doses given the current state of knowledge. The calculated absorbed doses in the bone (osteogenic cells) and red marrow were 1.15 Gy/MBq (4260 rad/mCi {1 Ci = 3.7×10^{10} Bq}]) and 0.14 Gy/MBq (514 rad/mCi), respectively. The calculated absorbed doses to the intestines, which is the dominating excretory organ, were low (small intestine wall 0.00726 Gy/MBq, upper large intestine wall 0.0323 Gy/MBq, and lower large intestine wall 0.0465 Gy/MBq, corresponding to 26.9, 120, and 172 rad/mCi, respectively). The highest absorbed doses were seen in bone (osteogenic cells) and red marrow. However, the safety data from clinical phase 1 and 2 trials with radium-223 dichloride are not consistent with such high absorbed doses to these organs.

The patient dose is calculated based on date of injection, a decay correction (DK) factor specific to number of days from reference date applied to correct for physical decay of radium-223, and patient weight. A table of DK factors is provided to the clinical sites with every shipment. The volume to be administered for the current dose is calculated as follows:

$$\text{Volume to be administered (mL)} = \frac{\text{Body weight (kg)} \times \text{dose (55 kBq/kg body weight)}}{\text{DK factor} \times \text{1,100 kBq (0.0297 mCi)/mL}}$$

Preclinical and Clinical Pharmacology of Radium-223

No metabolic pathways exist for the element isotope radium-223. Therefore, studies of the metabolism of radium-223 are neither considered appropriate nor relevant to the safety evaluation of radium-223 dichloride. Because radium-223 is administered by vein, it is 100% bioavailable. In both mice and dogs, excretion of radium-223 occurred by gastrointestinal and renal route. Maximum urinary and fecal excretion in mice was seen until 6 hours and in dogs at 2 and 12 hours, the first sampling times for these parameters, respectively. Small detectable amounts of radium-223 were excreted in the urine and feces in mice throughout a period of 56 days after a single dose radium-223 administration. The cumulative urine to feces ratios in mice were found to be 1:1 and 1:3 five days after administration, respectively. A low recovery rate of 16% was observed and can be explained by the retention of radium-223 in the bone tissue. The biodistribution studies in mice, rats, and dogs confirmed that radium-223 is primarily distributed to bone tissue with much higher affinity relative to soft tissues. Recalculations of organ concentration data from these studies reveal that in total about 70% of the administered dose was bound to bone tissue (<1% in soft tissue) already 12 hours after administration. The results of a 56-day study in mice suggested that once bound to bone (femur, sternum, and skull) radium-223 remained within the bone at least up to approximately 5 half-lives and probably for the entire decay period. Little radioactivity was detected in soft tissue, with the exception of the spleen in mice. The PK or biodistribution of radium-223 was not affected by administration of a bisphosphonate (zoledronic acid) 2 hours earlier.

Clinical Studies of Radium-223

Radium-223 has been under investigation as a monotherapy and in combination with other therapies in several clinical studies for the treatment of advanced oncologic malignancies. A brief outline for its study in metastatic prostate cancer is provided below (Table 1).

Table 1: Radium-223 clinical trial listing on ClinicalTrials.gov

NCT	Phase	Agent(s)	Disease/Indication	Study Start - End	Status / Sponsor	Accrual	Publication
NCT00748046	I	radium-223 monotherapy	Hormone-refractory prostate cancer, study 15303	Aug 2008 – Oct 2009	completed / Bayer	N=10	Carrasquillo *et al*., 2013
NCT00459654	II	radium-223 monotherapy	Hormone-refractory prostate cancer, study 15280	Feb 2004 – May 2006	completed / Bayer	N=64	Nilsson *et al*., 2007
NCT00699751	III	radium-223 monotherapy	Hormone-refractory prostate cancer, study 15245	Jun 2008 – Jul 2011	completed / Bayer	N=901	Parker *et al*., 2013

CTEP Plans for Radium-223 Clinical Development through the Project Team:

CTEP would like to utilize a radium-223 project team to develop up to three clinical trials with radium-223 as well as to devise appropriate PK or pharmacodynamic biomarker studies for those trials. The role of the project team is to evaluate all available evidence to modify and refine this initial clinical development plan. CTEP is willing to discuss different or additional radium-223-agent combination trials, and the radium-223 project team applicants can suggest such studies either in the response to this PTMA or during the project team process, if the applicant is accepted to the team. In a similar fashion, applicants for a basic science or translational position on the project team may suggest alternative trials, combinations, or biomarker strategies based on their experience in the field.

Another goal of this PTMA is to develop the infrastructure necessary for handling radionucleide therapeutics throughout the Experimental Therapeutics Clinical Trials Network (ETCTN). This includes the storage and distribution of radionucleides outside of the Pharmaceutical Management Branch, as well as the handling of biospecimens. This PTMA also aims to introduce radiation oncologists, who deliver radionucleide therapeutics, into the ETCTN program.

CTEP is interested in radium-223 due to its induction of double-strand breaks in cells from a broad number of malignancies. Radium-223 has favorable *in vivo* PK ($t_{½}$ = 11.4 days) and pharmacodynamic cancer cytotoxic and bone remodeling profiles. Tumor growth delay or regression effects in human tumor-bearing xenograft mammals have been demonstrated. The localization of radium-223 to bone might also contribute to better tolerability of cytotoxic agent combinations without undue injury to vital organs. Radium-223 associates with minimal adverse events when given as an injection by vein monthly, which favors multiple cycles (*e.g.*, up to six) of on-therapy time.

Radium-223 demonstrates cell lethal additivity with paclitaxel. Paclitaxel is a cytoskeletal drug that targets tubulin. Paclitaxel-treated cells have defects in mitotic spindle assembly, chromosome segregation, and cell division through stabilization of the microtubule polymer and protects it from disassembly. This blocks the progression of mitosis and prolonged activation of the mitotic checkpoint triggers apoptosis. Cells blocked at the mitotic checkpoint are sensitive to the cell lethal effects of radiation. CTEP and Bayer AG are interested in a randomized phase 2 trial of radium-223 + paclitaxel *vs*. paclitaxel in patients with two or more bony lesions whose cancer has an indication for paclitaxel treatment.

Radium-223 demonstrates cell lethal synergy with ATR kinase inhibitors in preclinical work. ATR kinase inhibitors prevent ATR-mediated signaling in the ATR-checkpoint kinase 1 (Chk1) signaling pathway. This prevents DNA damage checkpoint activation, disrupts DNA damage repair, and induces tumor cell apoptosis. CTEP and Bayer AG are interested in a safety lead-in followed by a randomized phase 2 trial of radium-223 + BAY 1895344 (Bayer AG's ATR inhibitor) *vs*. radium-223 in patients with metastatic castration-resistant prostate cancer after prior abiraterone (where radium already has an indication).

Radiation exposure induces the expression of neoantigens on the surface of irradiated cells (reviewed in Corso *et al*., 2011). Because of this phenomenon, CTEP and Bayer AG are interested in a randomized phase 2 trial of radium-223 + immunotherapy (TBD) *vs*. immunotherapy in patients with two or more bony lesions from metastatic non-small cell lung cancer on or after platinum-based chemotherapy.

Biomarker Studies of Interest to CTEP:

CTEP is interested in the development of biomarker studies examining the effects of radium-223 or other parameters of DNA damage response in tumor biopsies and other patient-derived materials obtained from patients receiving the agent. It is important to note, however, that radium-223 quickly localizes to bone and bone biopsies are difficult to procure. Prior trials with radium-223 have found that a confirmed decline in blood total alkaline phosphatase levels might indicate effective treatment. CTEP and Bayer AG are interested in collecting this biomarker across all of its studies. Biomarker technology and assays measuring other effects of radium-223 agent combinations *in vivo* are of interest for clinical

development. Limited funding for these biomarker studies may be available through a cooperative research and development agreement (CRADA) agreement for radium-223 between NCI CTEP and Bayer AG, and/or through a UM1 grant supplement mechanism. PTMAs should specifically indicate whether biomarker funding is already available or being requested from NCI, if this is pertinent to the application.

A CTEP project team could make recommendations for limited preclinical studies for radium-223 alone or in combination to examine biomarkers or to justify proposed clinical studies, as well as to plan biomarker studies to occur within the study period. If the project team requests such studies, a proposal with a budget will be requested from the appropriate project team translational researcher involved, and the studies may be funded through a UM1 grant supplement.

Radium-223 Project Team Selection, Composition, and Tasks:

The radium-223 project team will meet regularly by WebEx to review available evidence, determine promising strategies, examine clinical trial designs to test those strategies, and to identify biomarkers to evaluate those strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician scientists with experience in phase 2 trials in prostate, lung, and other refractory solid tumor patients; translational scientists with expertise in DNA damage biomarker development; radiation medicine physicists or clinical radiopharmacologists with experience in radiopharmaceuticals; and basic scientists with expertise in DNA double-strand break repair. Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of success in accruing to and/or leading early phase clinical studies in the relevant indications, as represented in the NIH Biosketch.

Questions regarding this request for applications may be addressed to Charles Kunos, M.D., Ph.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: charles.kunos@nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical oncology research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors to participate as Project Team members to develop Career Development Letters of Intent (CrDLs) after conclusion of Project Team activities.

https://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the Radium-223 Project Team (clinician scientist, translational scientist, radiation medicine physicists or radiopharmacologist, or basic scientist). An NIH Biosketch containing a personal statement customized to this project should also accompany the PTMA. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), March 29, 2018.** The most recent version of the PTMA form, which has been distributed with this communication, must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI
E-mail: CTEPPTMASubmissions@mail.nih.gov .

Please note that Clinician Scientists may only participate through association with the ETCTN, an NCTN Group, or a consortium (see below), and will need to submit the PTMA through their ETCTN Lead Academic Organization's (LAO's) Coordinating Center or the Group/Consortium Operations office, as applicable. That

organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. Please allow sufficient time for your organization's review. Qualifying clinical institutions include:

- ETCTN Participating Institution (under UM1 grant)
- NCTN Group member institution (under U10 grant; Alliance, COG, ECOG-ACRIN, NRG Oncology, or SWOG)
- Institutional affiliation with the Pediatric Brain Tumor Consortium (PBTC), Adult Brain Tumor Consortium (ABTC), or Cancer Immunotherapy Trials Network (CITN)

Basic and **Translational Scientists** who belong to a participating ETCTN institution (LAO or Affiliated Organization [AO]) **must** submit applications through your LAO's Coordinating Center. Please allow sufficient time for your organization's review. Basic and Translational Scientists from non-ETCTN-affiliated institutions may directly submit their applications to PIO.

Bibliography

Investigator's Brochure: Radium-223 dichloride (also referred to as BAY 88-8223). Version 6.0. Release Date: 31 March 2017, Bayer AG.

Carrasquillo JA, O'Donoghue JA, Pandit-Taskar N, *et al*. Phase I pharmacokinetic and biodistribution study with escalating doses of ^{223}Ra-dichloride in men with castration-resistant metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*. 2013 Sep; 40(9):1384-93. doi: 10.1007/s00259-013-2427-6.

Corso CD, Ali AN, and Diaz R. Radiation-induced tumor neoantigens: imaging and therapeutic implications. *Am J Cancer Res*. 2011; 1(3):390-412.

Henriksen G, Breistøl K, Bruland ØS, Fodstad Ø, Larsen RH. Significant antitumor effect from bone-seeking, alpha-particle-emitting (223)Ra demonstrated in an experimental skeletal metastases model. *Cancer Res*. 2002; 62(11):3120-5.

Henriksen G, Fisher DR, Roeske JC, Bruland OS, Larsen RH. Targeting of osseous sites with alpha-emitting 223Ra: comparison with the beta-emitter ^{89}Sr in mice. *J Nucl Med*. 2003; 44(2):252-9.

Nilsson S, Franzén L, Parker C, Tyrrell C, Blom R, Tennvall J, *et al.* Bone-targeted radium-223 in symptomatic, hormone-refractory prostate cancer: a randomized, multicentre, placebo-controlled Phase II study. *Lancet Oncol*. 2007; 8(7):587-94.

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