



Medical Use of Radium-223 Chloride



Science For A Better Life

Advisory Committee on the
Medical Uses of Isotopes

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Section 1: Purpose, Introduction and Clinical Overview

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Purpose

- Present the clinical and radiation safety aspects of radium-223 chloride
- Discuss licensing options for radium-223 chloride
 - Option 1: Licensing under § 35.300
 - Option 2: Licensing under § 35.1000
- Obtain ACMUI perspective regarding licensing of radium-223 chloride



Introduction

- **Product name** Radium-223 chloride solution for injection
- **Interim Tradename** Alpharadin
- **Chemical name** Radium-223 chloride ($^{223}\text{RaCl}_2$)
- **Proposed Indication** Treatment of castration resistant (hormone refractory) prostate cancer patients with bone metastases



Introduction (cont'd)

- **Dosage Form** Sterile, isotonic aqueous solution of radium-223 chloride
- **Route of Admin.** Intravenous injection
- **Dosing Regimen** 50 kBq per kg body weight (95 mCi for a 70 kg patient) given at 4 week intervals for 6 cycles
- **Manufacturer**
Norway
Institute for Energy Technology (IFE),
Algeta ASA, Norway (for release)



Current Development Status

- Currently under investigation for the treatment of castration resistant (hormone refractory) prostate cancer patients with bone metastasis
- ALSYMPCA (Phase III pivotal trial) interim analysis results were positive in June 2011
- FDA Fast Track designation granted on August 18, 2011
- Expanded access program in the US will start enrolling in 2Q12
- NDA submission planned in 2Q12



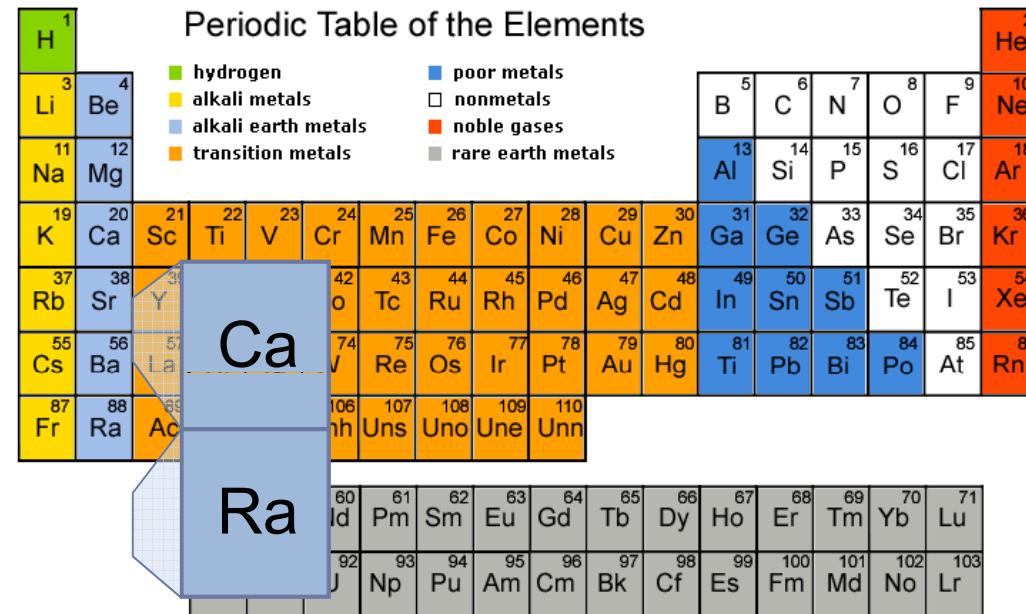
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Clinical Overview



Radium-223 Targets Bone Metastases

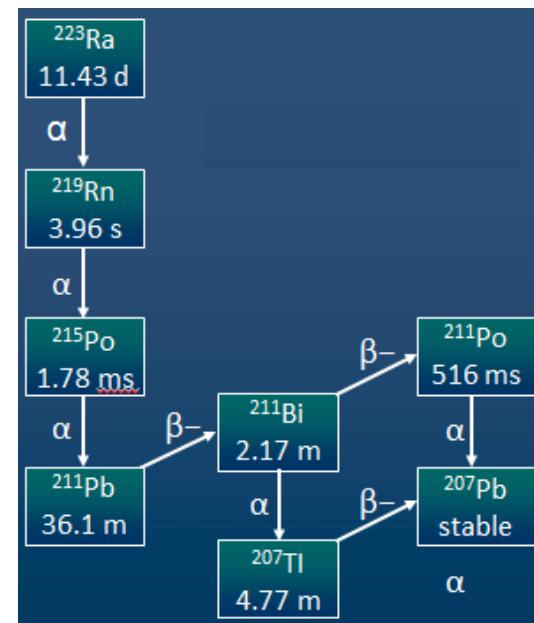
- Radium-223 acts as a calcium mimetic
- Naturally targets new bone growth in and around bone metastases



Radium-223 Properties

- Radium-223 chloride is an investigational alpha-emitting radiopharmaceutical
- $t_{1/2} = 11.43$ days
- It decays via a series of α , β and γ emitting daughters

Radium-223 decay chain
(predominant type of decay)



Henriksen G, et al. Cancer Res. 2002;62:3120–3125



Radium-223 Properties (cont'd)

- Of the total decay energy¹
 - 95.3% emitted as α particles
 - 3.6% emitted as β particles
 - 1.1% emitted as photons (γ or X-rays)
- Easily measured on standard equipment

Photon emissions associated²

Nuclide	Energy (keV)	Intensity % per decay
^{223}Ra	11.7	22.90
^{223}Ra	45.8	12.70
^{223}Ra	55.8	18.50
^{223}Ra	81.1	15.20
^{223}Ra	83.8	25.10
^{223}Ra	94.9	11.50
^{223}Ra	269.5	13.90
^{219}Rn	271.2	10.80
^{211}Bi	351.1	13.00

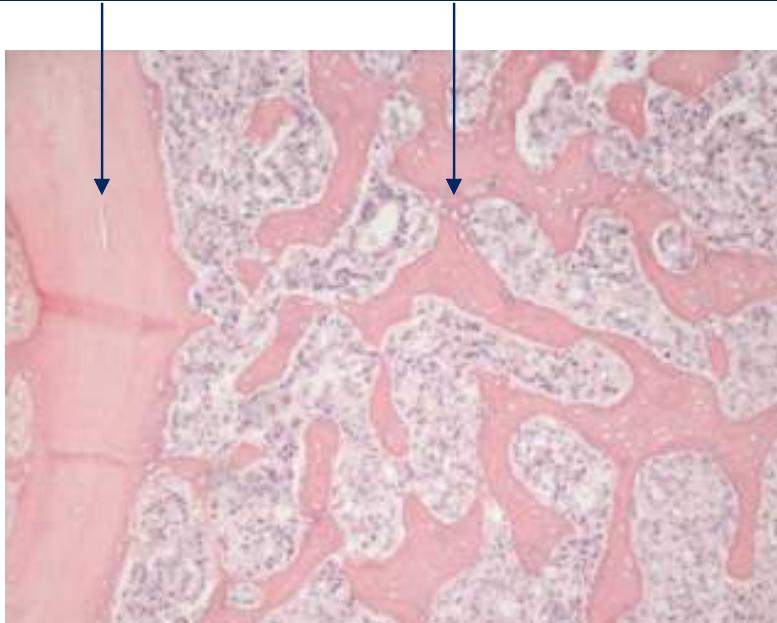
¹ Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s–57s

² ENSDF Decay Data in the MIRD (Medical Internal Radiation Dose) Format. Only emissions with an intensity of 10 % or more have been included.



Radium-223 Chloride is a Bone-Seeking Radionuclide

The target is: Hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$



Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s-57s

Histologic section of an osteoblastic bone metastasis in a patient with prostate cancer. Note the presence of abundant woven bone distributed as a mesh in between cords of tumor cells



Radium-223 Chloride is a Bone-Seeking Radionuclide

Radium-223 has preferential uptake in areas of new bone formation

Normal spongyous bone



Bone marrow

Osteoblastic zone



Microautoradiography from a dog injected with radium-223
Distribution of α -particle tracks in normal spongyous bone and
an osteoblastic zone

Bruland OS, et al. Clin Cancer Res. 2006;12(20):6250s–57s

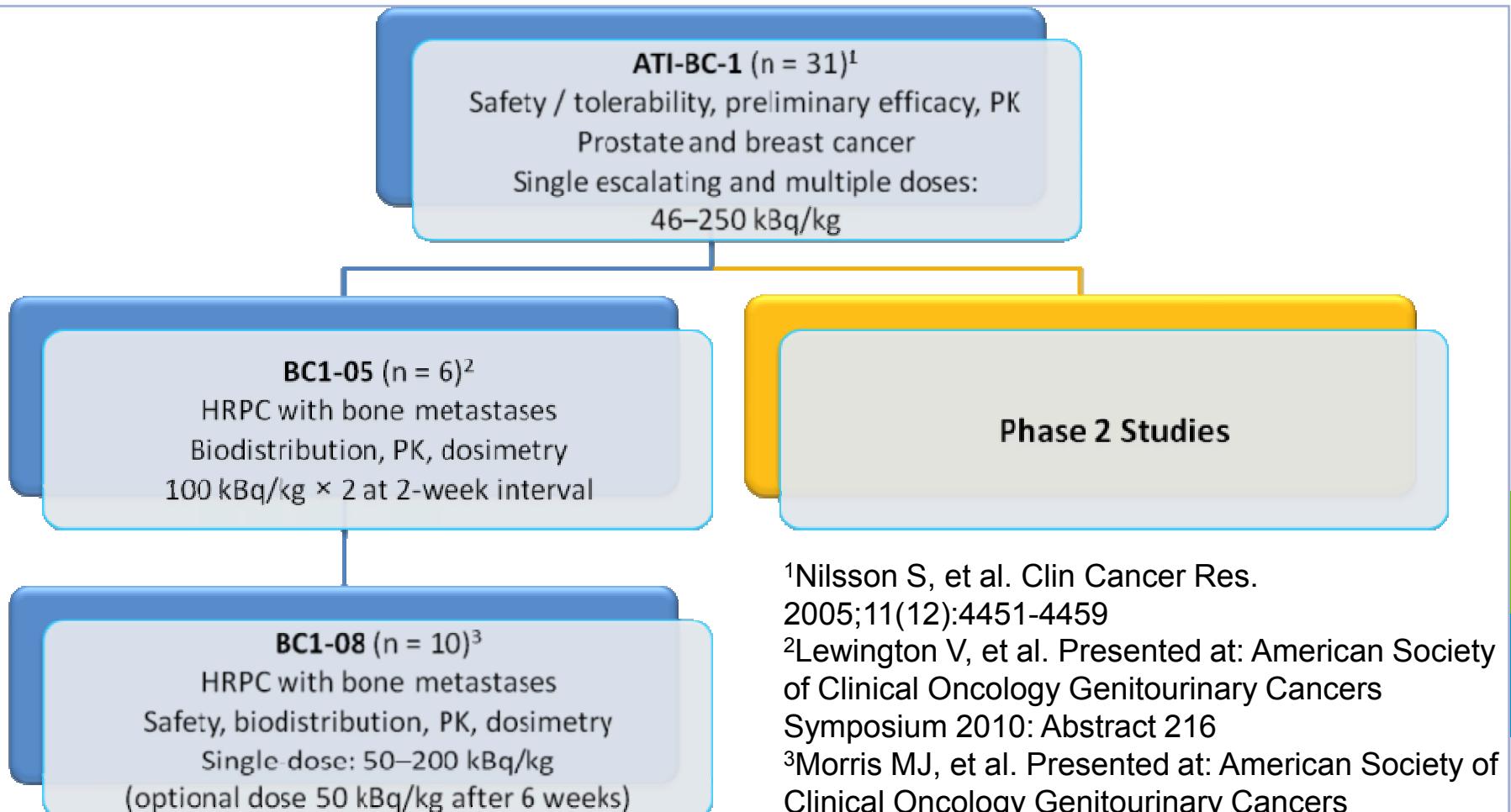


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Radium-223 Chloride Clinical Data Overview



Clinical Development Overview of Phase I Studies



¹Nilsson S, et al. Clin Cancer Res. 2005;11(12):4451-4459

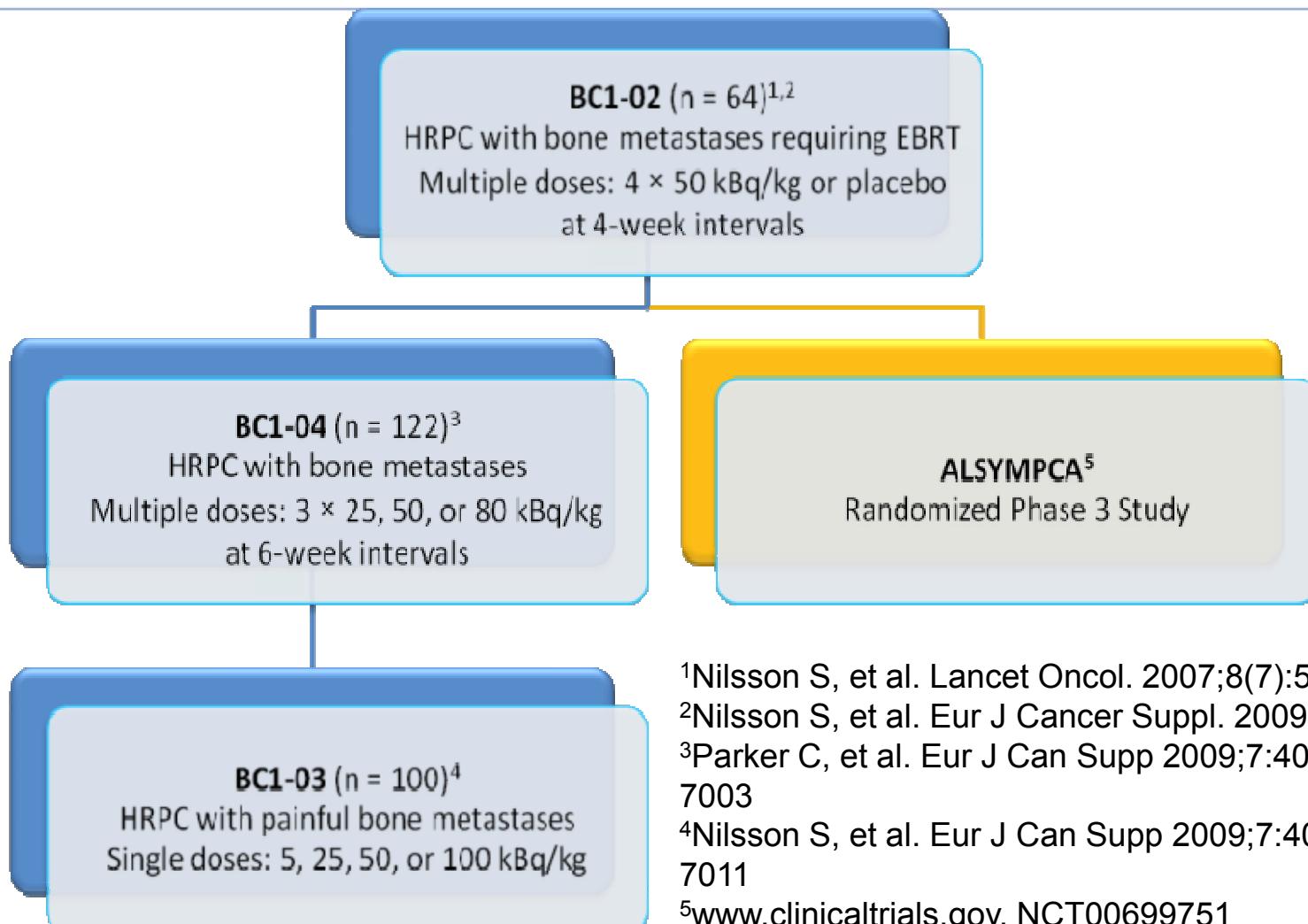
²Lewington V, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium 2010: Abstract 216

³Morris MJ, et al. Presented at: American Society of Clinical Oncology Genitourinary Cancers Symposium 2010: Abstract 211



Clinical Development

Overview of Phase II and III Studies



¹Nilsson S, et al. Lancet Oncol. 2007;8(7):587-594

²Nilsson S, et al. Eur J Cancer Suppl. 2009;7:412 P-7018

³Parker C, et al. Eur J Can Supp 2009;7:406 Abstract 7003

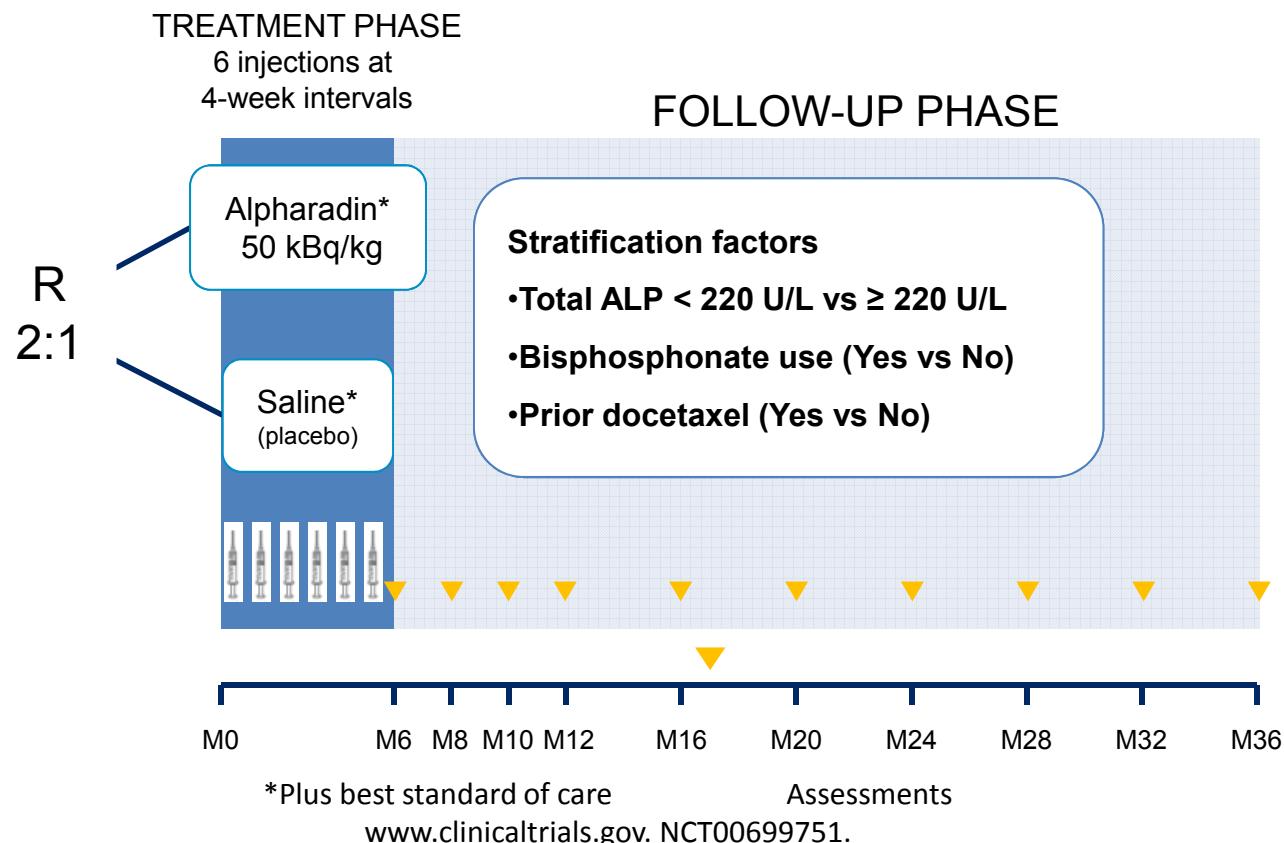
⁴Nilsson S, et al. Eur J Can Supp 2009;7:409 Abstract 7011

⁵www.clinicaltrials.gov. NCT00699751



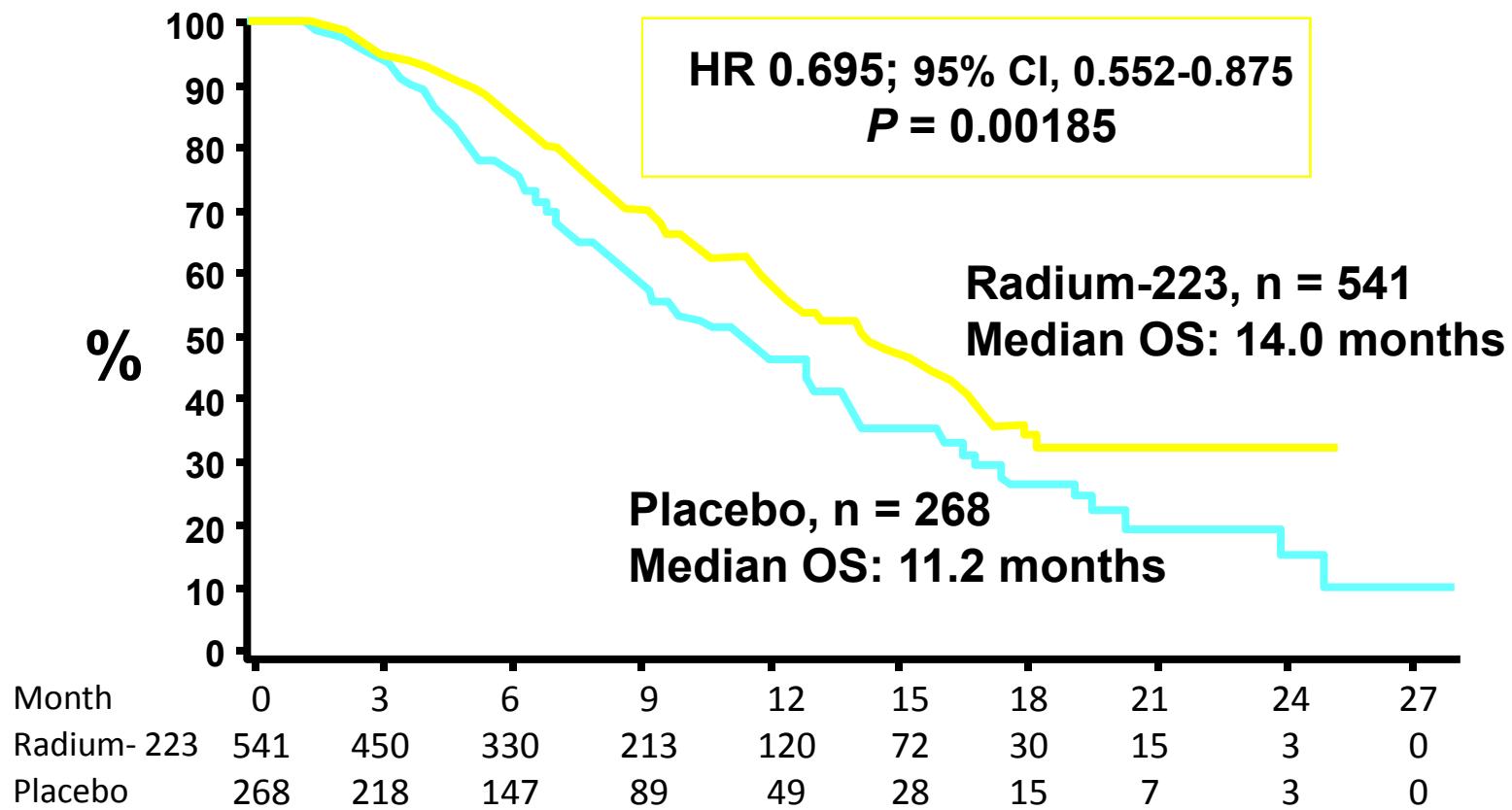
ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) Phase 3 Study Design

**Enrollment: 921 patients with symptomatic CRPC and skeletal metastases
136 centers in 19 countries (7 centers in the US) enrolled patients**





ALSYMPCA Overall Survival





ALSYMPCA Adverse Events of Interest Hematologic

	All Grades		Grades 3 or 4	
	Radium- 223 (n = 509)	Placebo (n = 253) n (%)	Radium- 223 (n = 509)	Placebo (n = 253) n (%)
Hematologic				
Anemia	136 (27)	69 (27)	54 (11)	29 (12)
Neutropenia	20 (4)	2 (1)	9 (2)	2 (1)
Thrombocytopenia	42 (8)	14 (6)	22 (4)	4 (2)



ALSYMPCA Adverse Events of Interest

Non-Hematologic

	All Grades		Grades 3 or 4	
	Radium- 223 (n = 509)	Placebo (n = 253)	Radium- 223 (n = 509)	Placebo (n = 253)
	n (%)	n (%)	n (%)	n (%)
Bone pain	217 (43)	147 (58)	89 (18)	59 (23)
Diarrhea	112 (22)	34 (13)	6 (1)	3 (1)
Nausea	174 (34)	80 (32)	8 (2)	4 (2)
Vomiting	88 (17)	32 (13)	10 (2)	6 (2)
Constipation	89 (18)	46 (18)	6 (1)	2 (1)



Conclusion

In the ALSYMPCA Phase III study evaluating castration resistant (hormone refractory) prostate cancer patients with bone metastases:

- Radium-223 significantly prolonged OS compared to placebo
- Radium-223 was well tolerated compared with placebo
- To date more than 1000 patients have been treated with radium-223 chloride within the clinical development program
 - During the ongoing 3 year follow-up period for ALSYMPCA, there have been no reports of secondary malignancies associated with exposure to radium-223 chloride to date



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Section 2: Handling and Safety of Radium-223 Chloride

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General Aspects of Handling & Safety

Although radionuclide therapy with Radium-223 Chloride uses α particles in contrast to established standard treatments, standard radiation safety practices already employed by sites are adequate for safe handling

The Drug Product: A Ready-to-Use Radium-223 Chloride Solution for Intravenous Injection



Vialed product - standardized, stable and ready to use

- 10 mL vial containing ~6 mL solution
- Direct i.v. injection via syringe (no generators, elutions, chelating involved)
- 6 MBq (162 µCi) Radium-223 per vial at calibration date
- Predominant alpha decay
- Shelf-life = 28 days
- Decay-in-storage to non-radioactive daughter product

If a licensee requests a unit dosage in a syringe, a radiopharmacy can provide unit doses to the site.



External Radiation Exposure Associated with Radium-223 Chloride Handling is Low

Dose rates as calculated values¹
(All data presented are unshielded values)

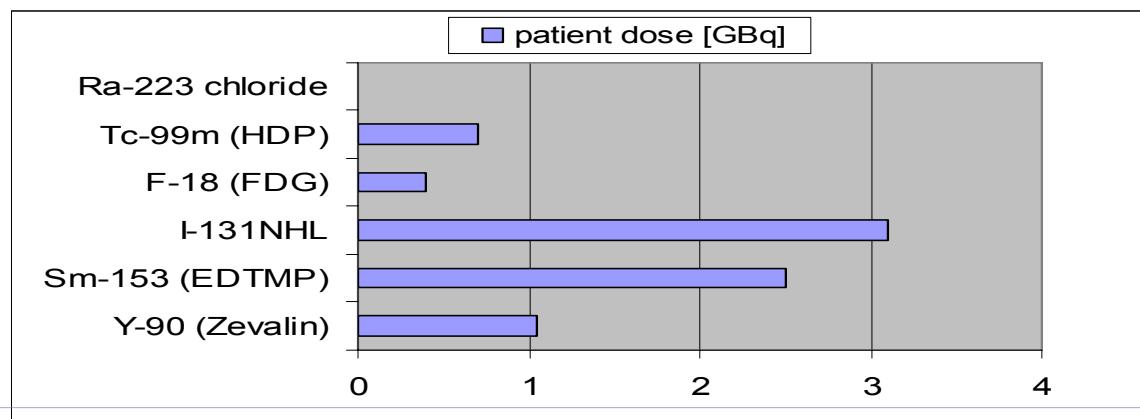
Distance from vial	$\mu\text{Sv/h}$ per MBq		$\mu\text{Sv/h}$ per patient dose	
	Ra-223	Tc-99m	Ra-223 3.5 MBq (95 μCi)	Tc-99m 740 MBq (20000 μCi)
one meter	0.02	0.02	0.07	14.8
one centimeter	~ 200	~200	~12*	2460*

* Estimated finger dose per minute,
assuming handling of unshielded source

¹ reference: Exposure rate constants published by David S. Smith & Michael G. Stabin
(Health Physics 2012; 102:271-291)



Generally, Patient Doses Being Handled are Considerably Lower Compared to Common Radiopharmaceuticals



Ra-223 Chloride	Bone Mets	3.5 MBq*	(95 µCi)
F-18 FDG	PET Imaging	300 MBq	(8100 µCi)
Tc-99m HDP	Scintigraphy	740 MBq	(12700 µCi)
Y-90 Ibritumomab Tiuxetan	NHL	1184 MBq	(32000 µCi)
Sm-153 EDTMP	Bone pain	2590 MBq	(70000 µCi)
I-131 Tositumomab	NHL	3108 MBq	(84000 µCi)

* 70 kg body weight

Straightforward Application Procedure Supports Safe Handling, Especially Avoidance of Contamination of Surfaces or Accidental Intake



Delivery:

TYPE A certified package containing:

- Vial
- Shielding container
- Shipment documents
- Certificate of analysis
- Table for decay correction



Dosing and Administration:

1. Calculate the patient dose volume (50 kBq/kg body weight)
2. Draw up the desired volume into a syringe
3. Inject the product into the patient (slow i.v. injection)

Note: If a licensee requests a unit dosage in a syringe, the radiopharmacy will perform steps 1 and 2; the licensee will perform step 3.



Dosing and Administration

Dose Calibrator is Not Required for

Radium-223 Chloride

10 CFR 35.63 (Determination of administered dosages pre-administration)

- Direct measurement (i.e. use of a dose calibrator) is not required to determine administered dosage
- If licensee receives vial: Measurement can be made using a combination of volumetric measurements and mathematical calculations, based on the measurement made by an appropriately licensed preparer
- If licensee receives patient-ready dosage in syringe: Measurement can be made by a decay correction, based on the activity determined by an appropriately licensed preparer



Dosing and Administration

Dose Calibrator is Not Required for Radium-223 Chloride (cont'd)

10 CFR 35.41(Procedures for administrations requiring a written directive)

- Need to verify that the administration is in accordance with the WD
- Data from clinical trial indicated that, on average, 0.7% of the administered activity remained in syringe after injection (no residual activity >3%). For a typical 3.5 MBq administration, this corresponds to a residual activity of 0.66 μ Ci, an activity that cannot be accurately measured in a dose calibrator



Dosing and Administration

Dose Calibrator is Not Required for Radium-223 Chloride (cont'd)

- Given these data (and further that the administered activity can be +/-10%), a thorough flushing procedure followed by a visual assessment of the syringe is recommended as the standard procedure for verifying that the administration is in accordance with the written directive in the commercial setting
- In the event of an issue encountered during administration that precludes complete administration of the patient-specific dosage, a direct measurement of the residual activity should be made (instruments other than a dose calibrator, such as a calibrated survey meter, can be used for this purpose)



Waste Disposal

No Specific Precautions Needed for Radium-223 Chloride After Decay-in-Storage

- Due to the short physical half life of radium-223 (11.4 days), it can be disposed of in a suitable clinical waste stream after an appropriate amount of time (decay-in-storage) pursuant to 10 CFR 35.92
 - Photon emissions allow for contamination monitoring and control measures against background by standard survey meters
- ➡ No instruments dedicated to α -emission detection needed



After Being Treated with Radium-223 Chloride, Patient is Immediately Releasable Pursuant to 10 CFR 35.75



Administered activity approx. 3.5 MBq (95 µCi) for a 70 kg patient

External radiation exposure to others

- Dose rate at 1 m from patient:
 $= 0.0002 \text{ mrem/hr MBq} \times 3.5 \text{ MBq} = 0.007 \text{ mrem/hr}$
- **1000 hours constant exposure = 7 mrem (<< 500 mrem limit)**

After Being Treated with Radium-223 Chloride, Patient is Immediately Releasable Pursuant to 10 CFR 35.75 (cont'd)



Internal radiation exposure to others

- ~ 75 % is excreted from the body within 1 week, mainly via feces
- Little (about 5 %) excretion through urine
- **Contamination and intake of activity highly unlikely**

Although regulations do not require patient instructions to be provided since the risk of radiation exposure to others is below the regulatory limit, some instructions will be provided, e.g. hygiene measures



Sites Provided With Relevant Information Material and Instructions Needed for Safe Handling of Radium-223 Chloride

- Staggered approach
 - Mandatory: Thorough review of information materials
 - As needed: Q&A sessions via T-Con with Bayer experts
 - On request: Site visits*
- Information materials consist of video, slide deck and SOP's
- Specific instructions are related to dose preparation, e.g.
 - Dose volume calculation
 - Dose drawing
- Receipt and review of material is confirmed by site
 - Confirmation is tracked
 - New employees: responsibility of site to inform and instruct
- Helpdesk (Bayer technical staff) available for support

* Case by case decision



In Summary, Standard Radiation Safety Practices are Adequate for Safe Handling of Radium-223 Chloride

- Radium-223 chloride is a ready-to-use radiopharmaceutical solution for injection which can be used as an out-patient treatment
- Compared to other radiopharmaceuticals, administered activity and associated dose rates are considerably lower
- The presence of some photon (α and γ) emissions allows for measurement of the product with standard instrumentation
- The risk of radiation exposure is minimal when using established standard radiation safety practices and hygiene measures
- Some drug specific information, e.g. dose preparation, will be provided to safely administer Ra-223 chloride
- Over 1000 patients have been treated in clinical studies without any radiation safety incidents



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Section 3: Licensing Issues and Recommendations for NRC Consideration

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Bayer Consultant



^{223}Ra : Licensing Under § 35.300

- Pursuant to § 35.300, licensee may use *any* unsealed byproduct material prepared for medical use and for which written directive required that is either obtained from or prepared by those specified in the rule
- Logistics of administering and providing radiation safety support for the radiopharmaceutical, ^{223}Ra , are similar to any other radiopharmaceutical already regulated under § 35.300
- ^{223}Ra emits betas, photons, and treatment involves low administered activities (microcuries) and dose rates
- Only additional training needed is product-specific and will be provided by manufacturer (i.e., training for prescribing and information about radiation safety practices specific for medical use of ^{223}Ra)



AUs

Gray Areas for Licensing of ^{223}Ra Under § 35.300

- Which dosage category for ^{223}Ra pursuant to § 35.390(b)(1)(ii)(G):
 - (3) Parenteral admin of any beta emitter, or a photon-emitting radionuclide with a photon energy less than 150 keV, for which a WD is required
 - ^{223}Ra emits betas (~ 4% of E emitted as β s) ; or
 - (4) Parenteral admin of any other radionuclide, for which a WD is required
 - **§ 35.57** Do AUs identified on licenses prior to 4/29/05 have “deemed” status for medical use of ^{223}Ra ? If so, no further cases/training required and they can serve as preceptors for, and supervisors of, AU applicants
- FRN for Final Rule (Vol. 67, No. 79, 4/24/02): These AUs have “deemed” status, i.e., they will continue to be recognized as AUs for type(s) of use(s) of byproduct material for which they already have AU status → authorized for therapeutic use of unsealed byproduct material pursuant to § 35.930



Expanded Part 35 Rulemaking

FRN (Vol. 76, No. 98, 5/20/11, p 29174)

Preliminary draft rule language (5/6/2011) in pre-rulemaking stage

- § 35.390(b)(1)(ii)(G). The issue is work experience for α emitters. “Contrary to what has been intended, the current language in category 4 does not allow the category to encompass *any* byproduct material, since the NRC staff has determined that no pure alpha emitter exists.”
- Expand from 4 → 6 dosage categories: New Dosage Category 5: Parenteral administration of any radionuclide that is primarily used for its alpha radiation characteristics, for which a written directive is required
 - Forecasts NRC’s intention to license alpha emitters under § 35.300



§ 35.1000

New Medical Use/Emerging Technology

NRC to determine if medical use of ^{223}Ra requires licensing under § 35.1000 (e.g., if specific risks associated with medical use of ^{223}Ra warrant additional regulatory requirements) or if this “new” technology is type of use already regulated under § 35.300

- ^{90}Y microspheres regulated under § 35.1000
- AU to meet T&E pursuant to § 35.390 plus additional training required: operation of delivery system, safety procedures and clinical use (to include minimum of 3 supervised hands-on cases by AU or manufacturer representative)
- ^{90}Y microspheres are brachytherapy devices, unlike ^{223}Ra , which is a radiopharmaceutical (unsealed source)



Licensing Proposals for Medical Use of ^{223}Ra Chloride

1. License under § 35.300 based on existing dosage category (3) pursuant to § 35.390(b)(1)(ii)(G)(3)
2. License under § 35.300 based on existing dosage category (4) pursuant to § 35.390(b)(1)(ii)(G)(4)
 - AUs identified on a license prior to April 29, 2005 will have deemed status for the medical use of ^{223}Ra
3. License under § 35.300, but temporarily place under § 35.1000 until Expanded Part 35 rulemaking finalized, and then move to § 35.300
 - AUs identified on a license prior to April 29, 2005 will have deemed status for the medical use of ^{223}Ra