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# Medical Use of Radium-223 Chloride

## Advisory Committee on the Medical Uses of Isotopes

April 17, 2012



# Content Overview

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  - Clinical Overview
- Section 2
  - Handling and Safety of Radium-223 Chloride
- Section 3
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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** Institute for Energy Technology (IFE),  
Norway  
  
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

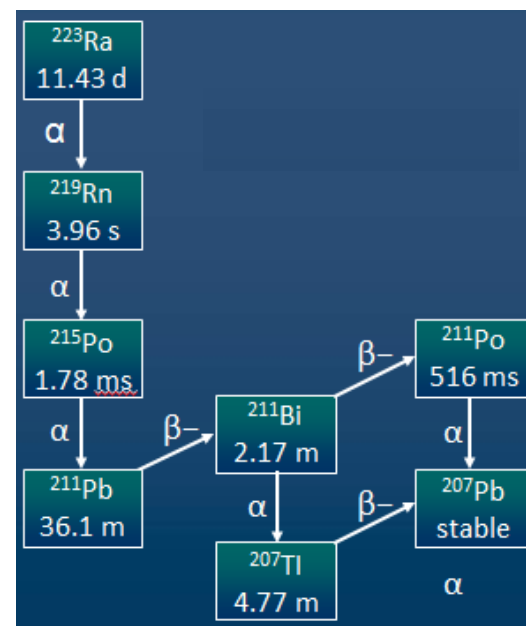




# Radium-223 Properties

- Radium-223 chloride is an investigational alpha-emitting radiopharmaceutical
- $t_{1/2} = 11.43$  days
- It decays via a series of  $\alpha$ ,  $\beta$  and  $\gamma$  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 energy<sup>1</sup>
  - 95.3% emitted as  $\alpha$  particles
  - 3.6% emitted as  $\beta$  particles
  - 1.1% emitted as photons ( $\gamma$  or X-rays)
- Easily measured on standard equipment

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

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

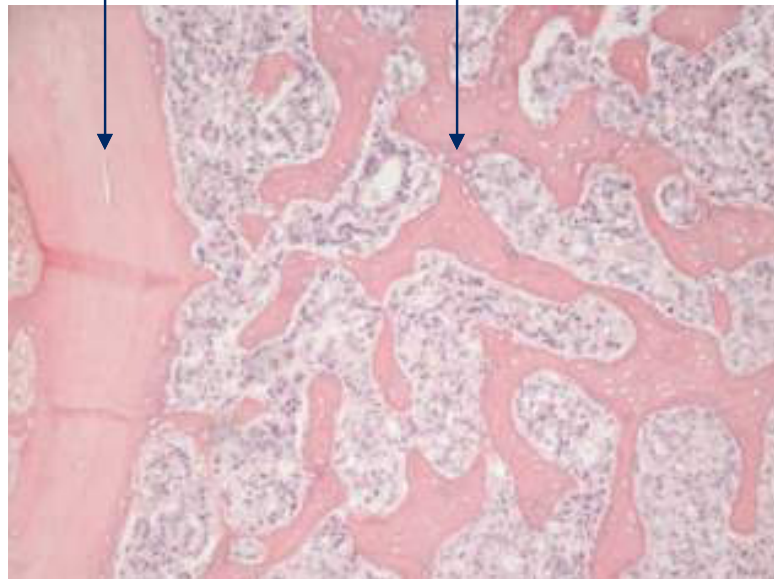
### Photon emissions associated<sup>2</sup>

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

# 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

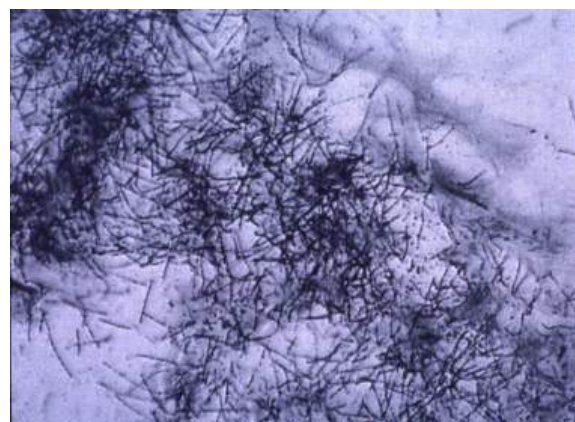
**Radium-223 has preferential uptake in areas of new bone formation**

Normal spongy bone



Bone marrow

Osteoblastic zone



Microautoradiography from a dog injected with radium-223  
Distribution of  $\alpha$ -particle tracks in normal spongy bone and an osteoblastic zone

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



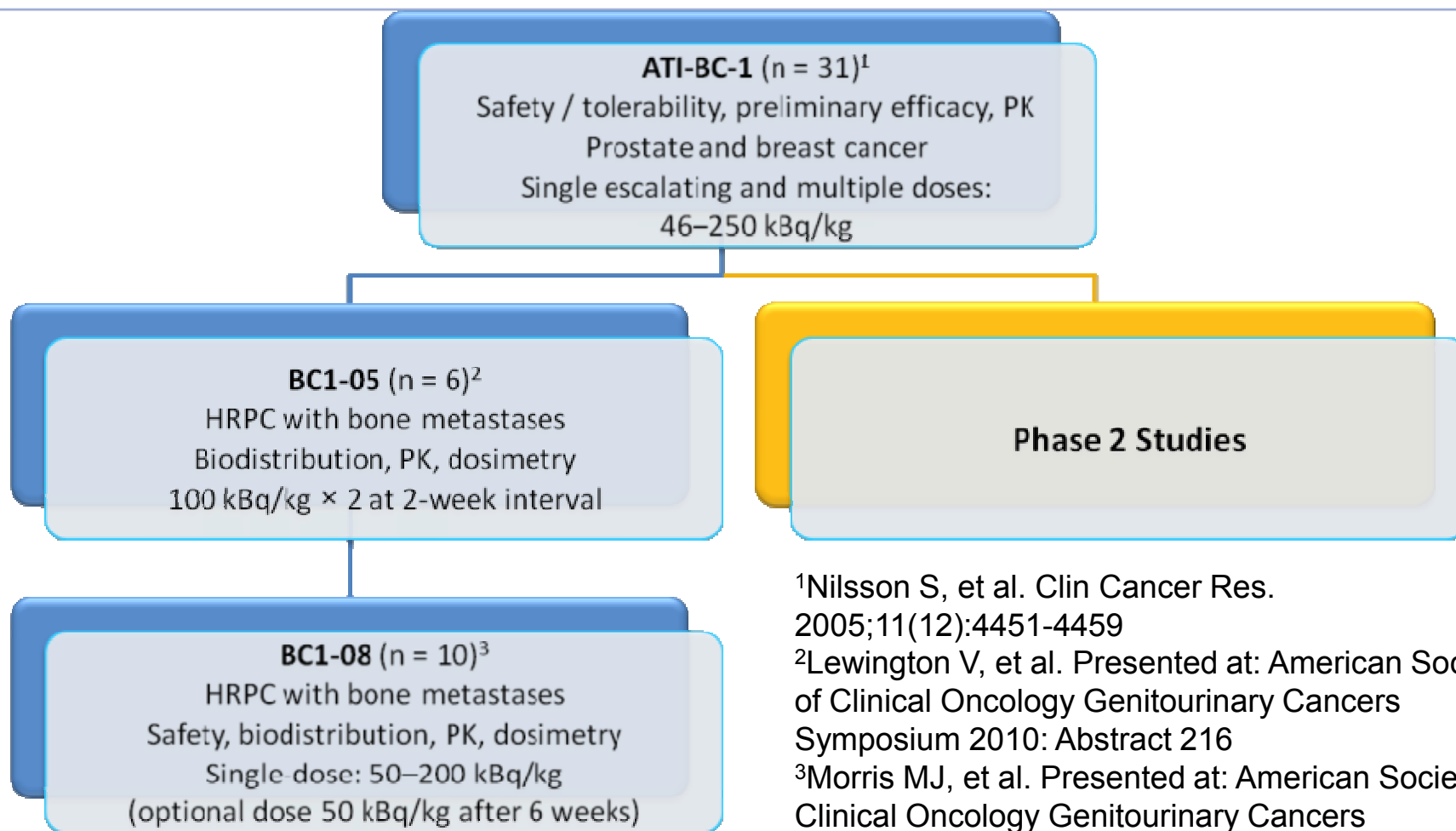
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# Radium-223 Chloride Clinical Data Overview





# Clinical Development Overview of Phase I Studies



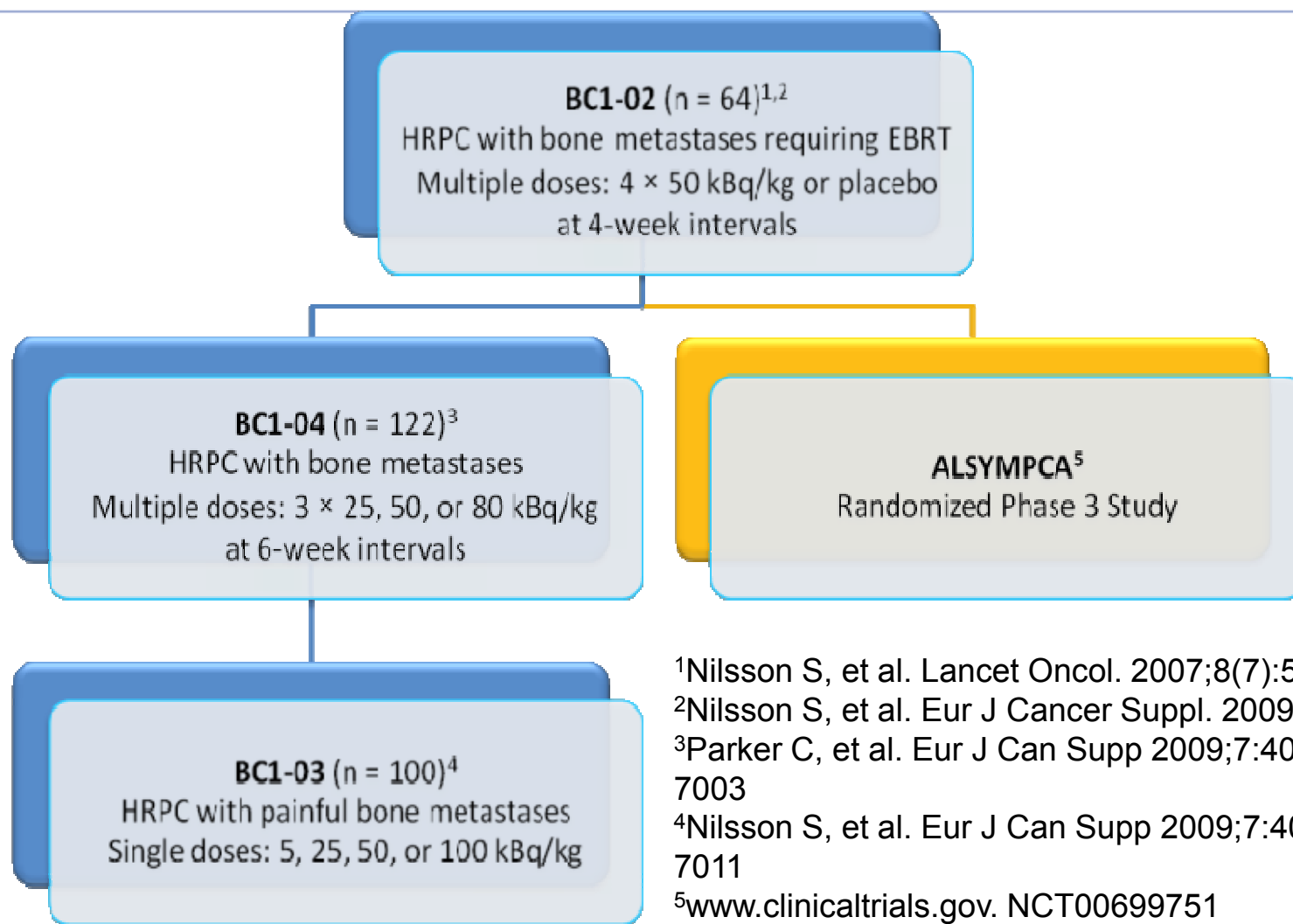
<sup>1</sup>Nilsson S, et al. Clin Cancer Res. 2005;11(12):4451-4459

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

<sup>3</sup>Morris 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



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

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

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

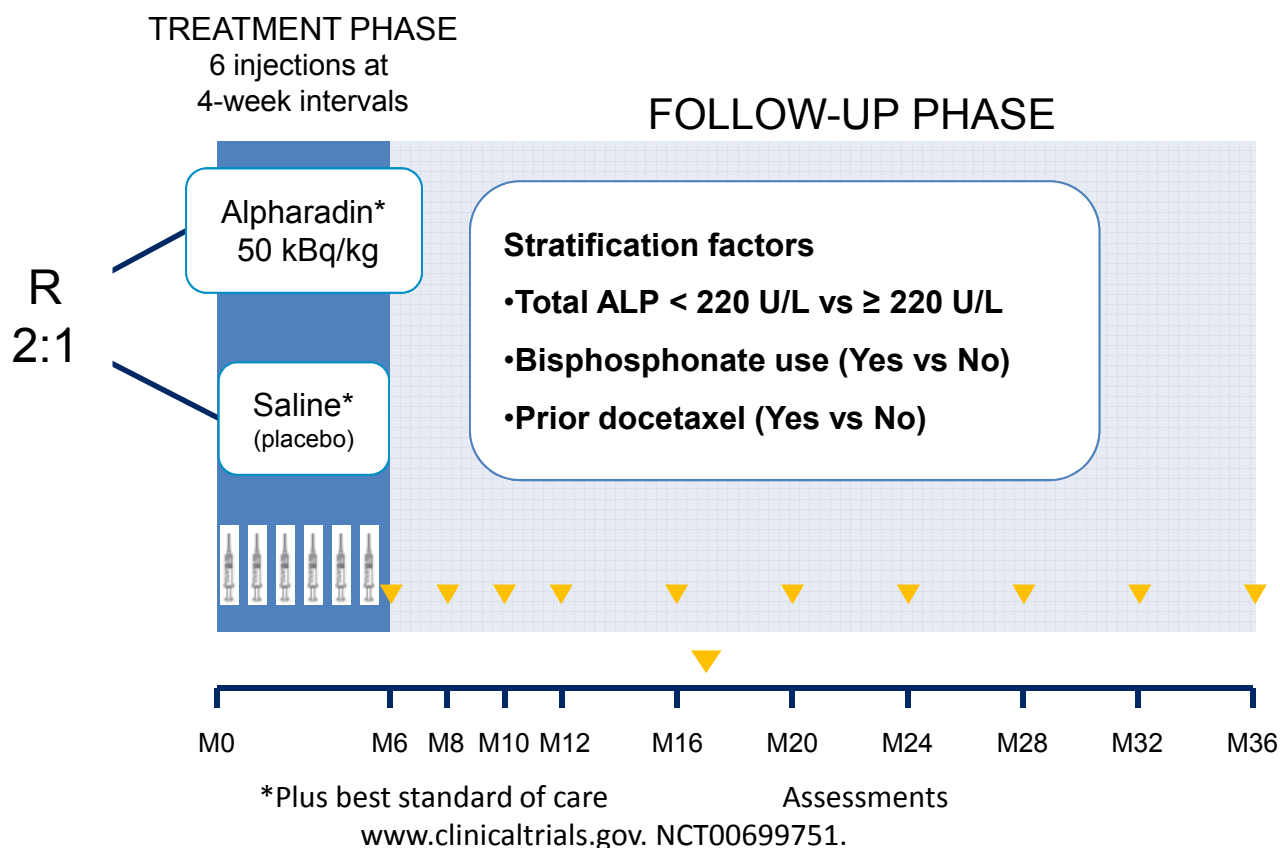
<sup>4</sup>Nilsson S, et al. Eur J Can Supp 2009;7:409 Abstract 7011

<sup>5</sup>[www.clinicaltrials.gov](http://www.clinicaltrials.gov). NCT00699751



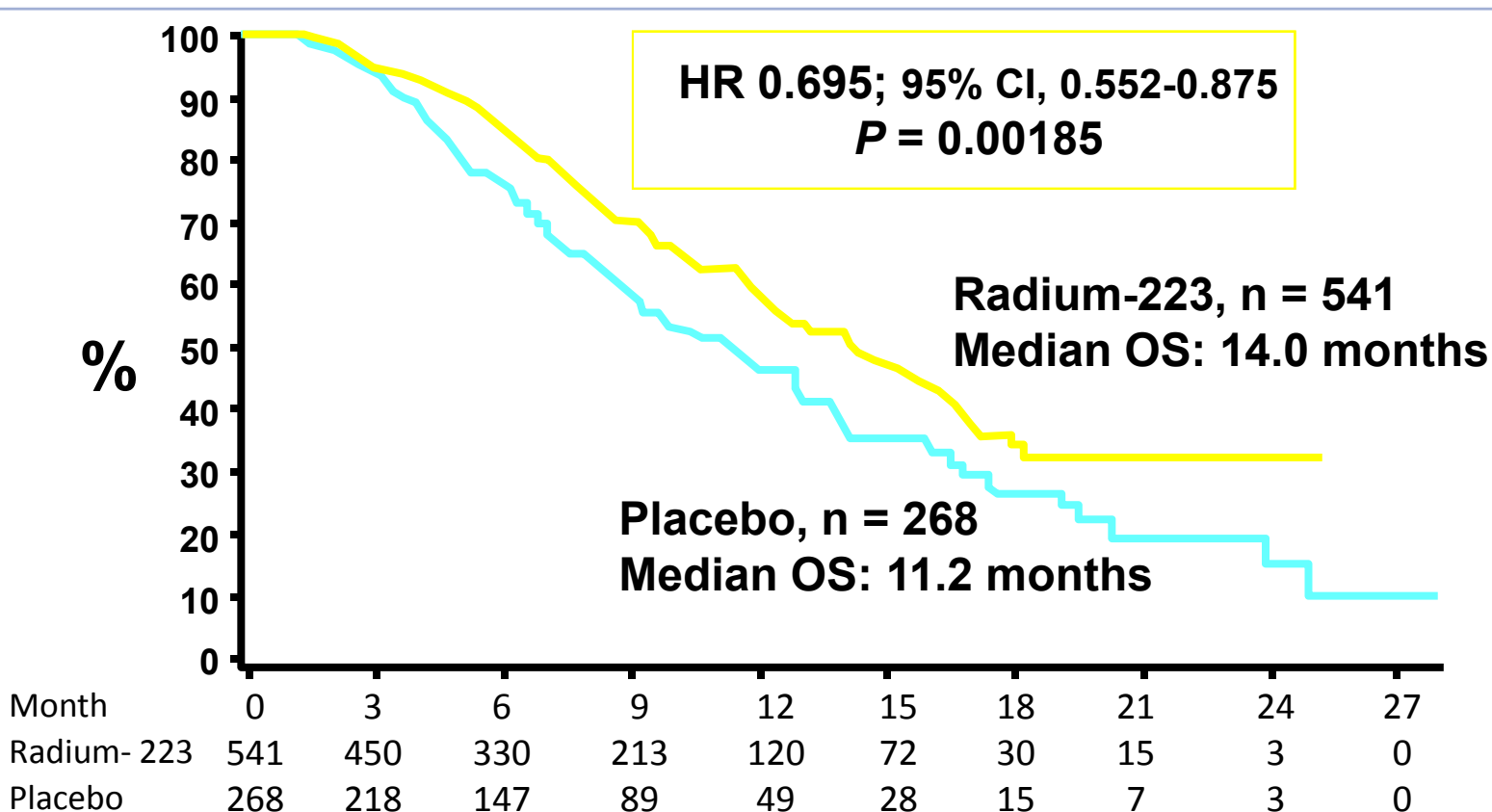
# ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase 3 Study Design

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



# ALSYMPCA Adverse Events of Interest Non-Hematologic

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





## 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  $\alpha$  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  $\mu$ Ci) 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 values<sup>1</sup>  
 (All data presented are unshielded values)

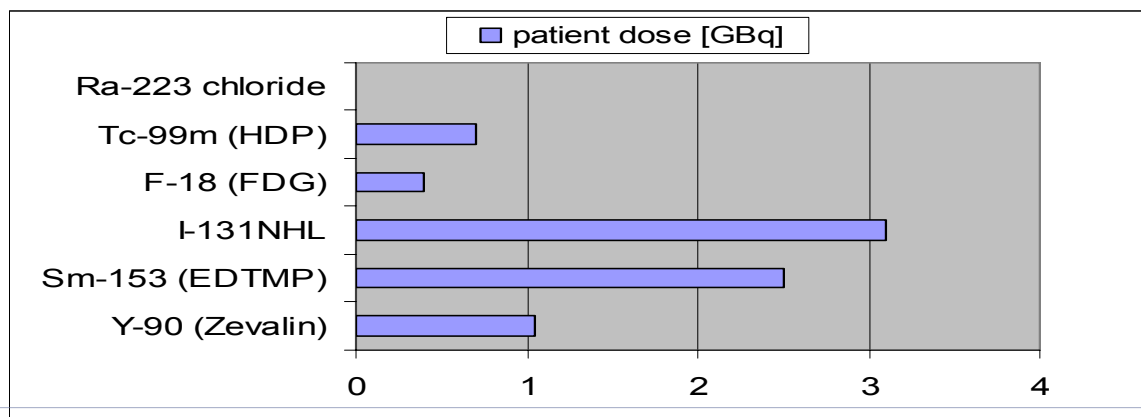
Distance from vial	μSv/h per MBq		μSv/h per patient dose	
	Ra-223	Tc-99m	Ra-223 3.5 MBq (95μCi)	Tc-99m 740 MBq (20000μCi)
one meter	0.02	0.02	0.07	14.8
one centimeter	~ 200	~200	~12*	2460*

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

<sup>1</sup> 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



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

\* 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  $\mu$ 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  $\alpha$ -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  $\mu$ Ci) for a 70 kg patient

## External radiation exposure to others

- Dose rate at 1 m from patient:  
= 0.0002 mrem/hr MBq x 3.5 MBq = 0.007 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 ( $x$  and  $\gamma$ ) 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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## $^{223}\text{Ra}$ : 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,  $^{223}\text{Ra}$ , are similar to any other radiopharmaceutical already regulated under § 35.300
- $^{223}\text{Ra}$  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  $^{223}\text{Ra}$ )



# AUs

## Gray Areas for Licensing of $^{223}\text{Ra}$ Under § 35.300

- Which dosage category for  $^{223}\text{Ra}$  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  
 $^{223}\text{Ra}$  emits betas (~ 4% of E emitted as  $\beta$ 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  $^{223}\text{Ra}$ ? 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  $\alpha$  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  $^{223}\text{Ra}$  requires licensing under § 35.1000 (e.g., if specific risks associated with medical use of  $^{223}\text{Ra}$  warrant additional regulatory requirements) or if this “new” technology is type of use already regulated under § 35.300

- $^{90}\text{Y}$  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)
- $^{90}\text{Y}$  microspheres are brachytherapy devices, unlike  $^{223}\text{Ra}$ , which is a radiopharmaceutical (unsealed source)



# Licensing Proposals for Medical Use of $^{223}\text{Ra}$ 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  $^{223}\text{Ra}$
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  $^{223}\text{Ra}$