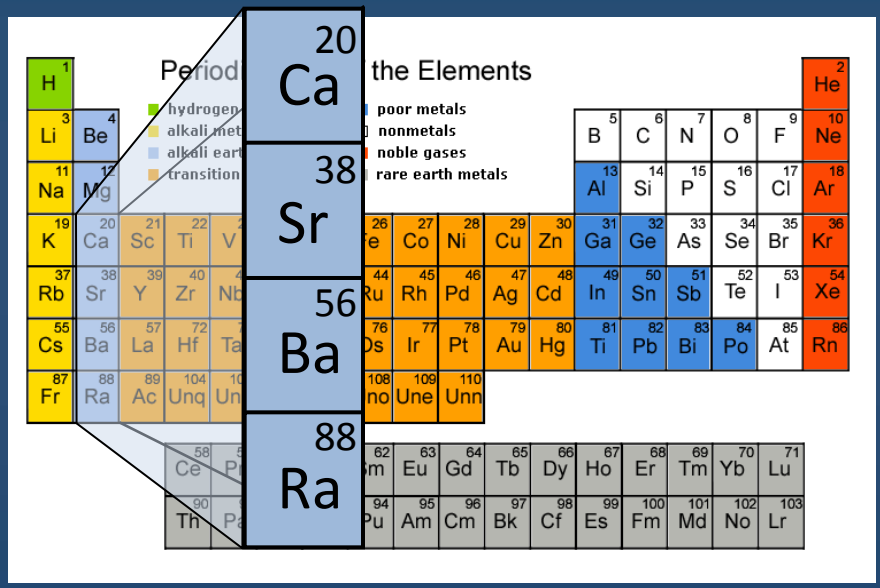
RADIUM-223
MECHANISM OF ACTION AND PRECLINICAL DATA

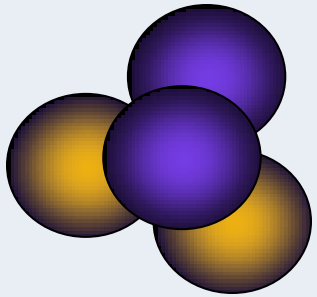
What is Radium-223?

- An alkaline earth metal
- A natural bone seeker[1] because it is a 'calcium mimic'[2]
- An emitter of radioactive α-particles
  - Optimal for a radiopharmaceutical[3]
  - Has a half-life of 11.4 days[3]
- Has a strong tumor-cell killing effect[1]
- α-particles have a short track (2–10 cell diameters)[3]
  - Hence, damage to surrounding healthy tissue is minimized[3]
- Comes as a solution of radium-223 chloride ($^{223}RaCl_2$)



1. Henriksen et al. Can Res. 2002;62:3120. 2. Nilsson et al. Presented at: American Society for Radiation Oncology annual meeting 2010; poster 2385. 3. McDevitt et al. Eur J Nucl Med. 1998;25(9):1341.

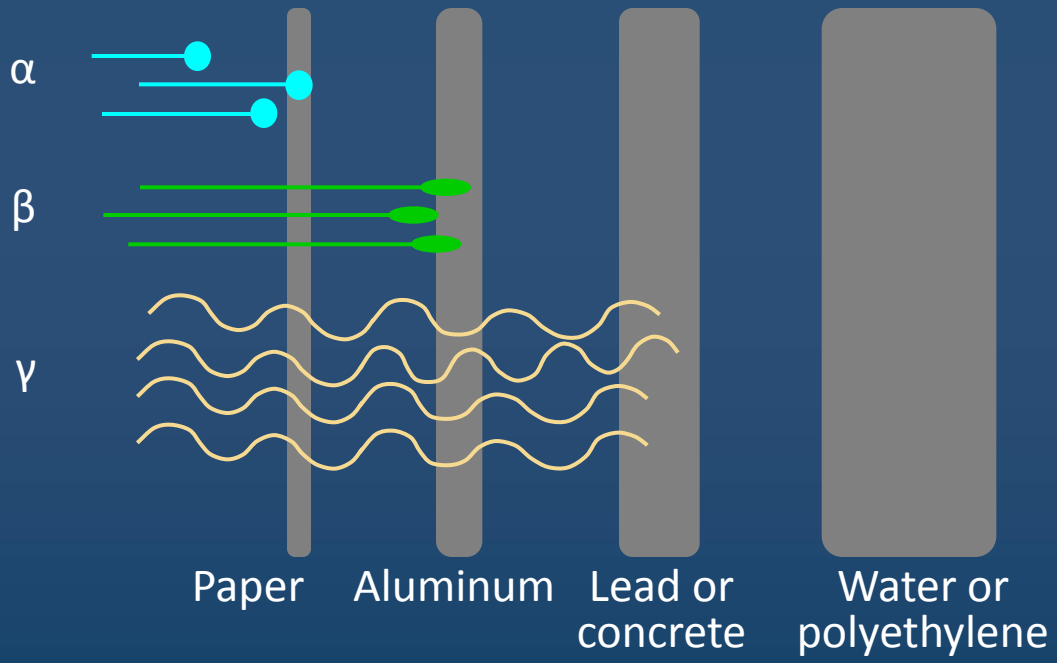
Differences Between α and β Particles[1-3]

	α	β
Example emitters	**Radium-223**	**Strontium-89, Samarium-153**
Size*		
Relative particle mass	7000	1
Initial energy (MeV)	5-9	0.05–2.3
Range in tissue (µm)	40–100	50–12,000
LET (KeV/µm)	60–300	0.1–1.0
Charge	+2	–1
Ion pairs/µm	2000–7000	5–20
DNA hits to kill cell	1–4	>1000

*Orange = protons; purple = neutrons

1. Kassis AI. Semin Nucl Med. 2008;38:358. 2. Brechbiel MW. Dalton Trans. 2007;43:4918. 3. Nilsson et al. Presented at: American Society for Radiation Oncology annual meeting 2010; poster 2385.

Penetration of Ionizing Radiation Types



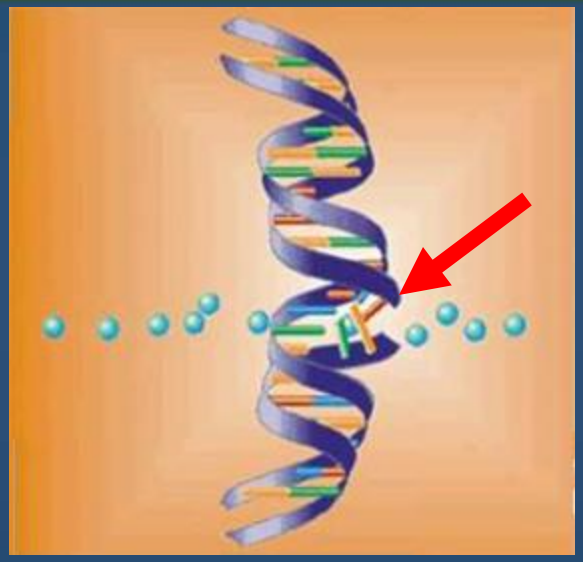
α radiation consists of helium (^4He) nuclei and is stopped by a sheet of paper or skin

β radiation, consisting of electrons, is halted by an aluminum plate or plastic

γ radiation, consisting of energetic photons, is attenuated by dense material

α-particles Cause Lethal Double-strand DNA Breaks

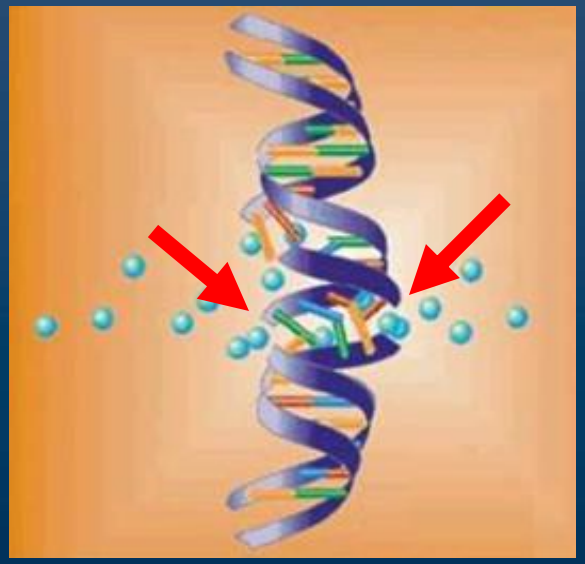
β-emitters



- Low-LET β radiation1 produces single-strand DNA breaks[1]
- Single-strand breaks are easily repaired using the opposite strand as a template[1]
- Single-strand breaks are less likely to induce cell death[1]

α-emitters

- High-LET α–particles produce double-strand DNA breaks[1,2]
- Double-strand breaks are difficult to repair[1,2]
- Failure to repair double-strand breaks leads to apoptosis (programmed cell death)[1]
- Mis-repaired double-strand breaks create chromosomal aberrations that result in mitotic cell death[1]

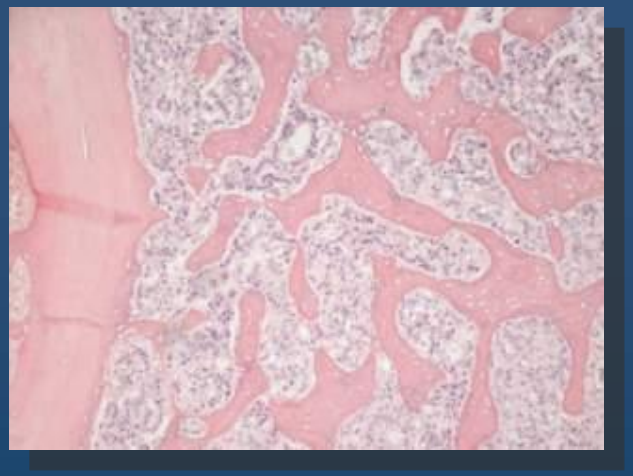


LET, linear energy transfer.

1. Hall and Giaccia. Radiology for the Radiologist. 6th Ed. Philadelphia: J. B. Lippincott William & Wilkins 2006.
2. Bruland et al. Clin Cancer Res. 2006;12(20):6250s.

Radium-223 is a Bone-Seeking Radionuclide

Bone mineral hydroxyapatite is the target: hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$



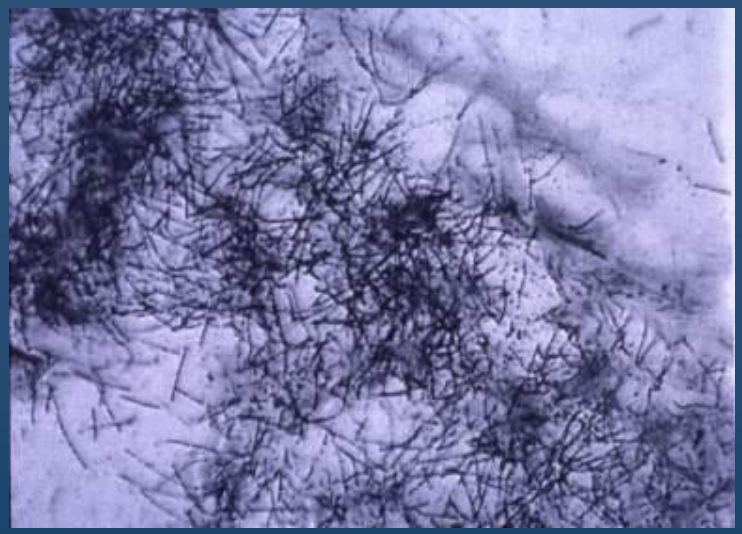
Histologic section of an osteoblastic bone metastasis in a patient with prostate cancer. Note the presence of abundant woven bone distributed as a mesh in between cords of tumor cells

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

Radium-223 has Preferential Uptake in Areas of New Bone Formation

Normal spongious bone

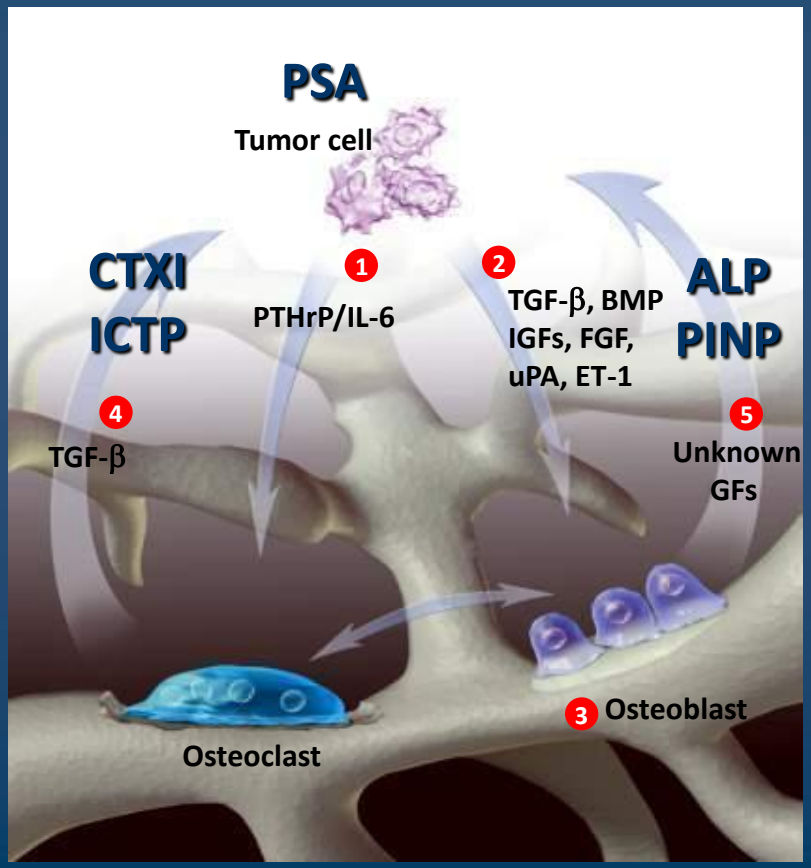
Osteoblastic ('bone forming') zone



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

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

Bone Metastases in Patients with Prostate Cancer



Underlying mechanisms

Factors are released by tumor cells that stimulate both osteoclast 1 and osteoblast 2 activity

Excessive new bone formation 3 occurs around tumor cell deposits, resulting in low bone strength and potential vertebral collapse

Osteoclastic 4 and osteoblastic 5 activity releases growth factors that stimulate tumor cell growth, perpetuating the cycle of bone resorption and abnormal bone growth

Bone biomarkers outlined are elevated

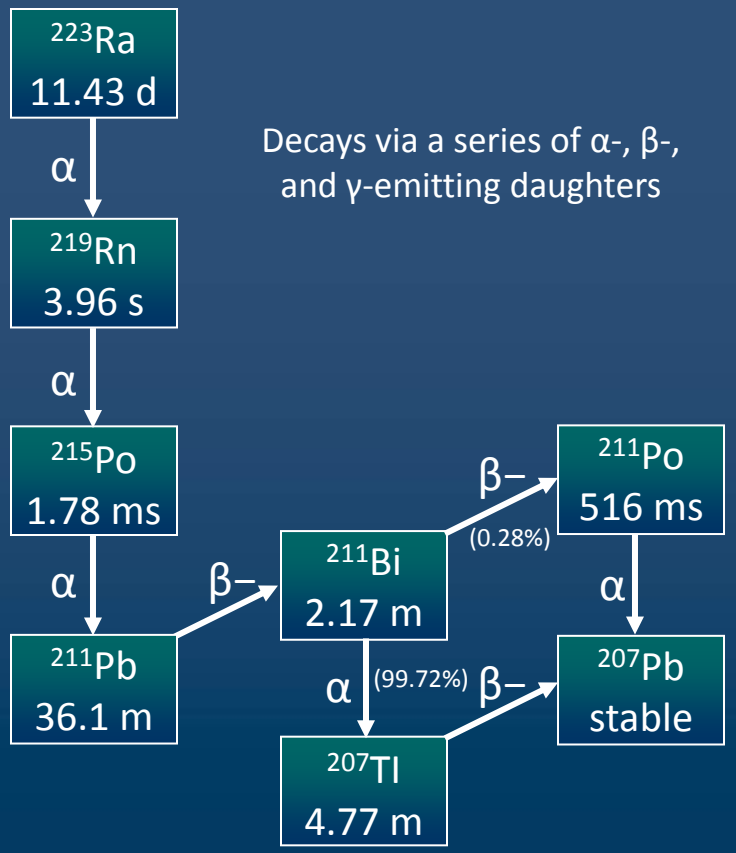
ALP, alkaline phosphatase; BMP, bone morphogenetic protein; CTXI, cross-linked C-terminal telopeptides of type I collagen; ET-1, endothelin-1; FGF, fibroblast growth factor; GF, growth factor; ICTP, C-terminal telopeptides of type I collagen; IGF, insulin-like growth factor; IL-6, interleukin-6; PINP, amino-terminal procollagen propeptides of type I collagen; PSA, prostate-specific antigen; PTHrP, parathyroid hormone-related protein; TGF- β, transforming growth factor β; uPA, urokinase plasminogen activator.

1. Goltzman. Mechanisms of the development of osteoblastic metastases. Cancer, 1997;80:1581. 2. Adami. Bisphosphonates in prostate carcinoma. Cancer, 1997;80:1674. 3. Mundy. Mechanisms of bone metastasis. Cancer, 1997;80:1546. 4. Boyce et al. Factors regulating the growth of metastatic cancer in bone. Endocr Relat Cancer, 1999;6:333.

Majority α Decay, Minimal β and γ Decay

- Of the total decay energy[1]
  - 93.5% emitted as α-particles
  - < 4% emitted as β-particles
  - < 2% emitted as γ- or X-rays
- Measured on standard dose calibrators

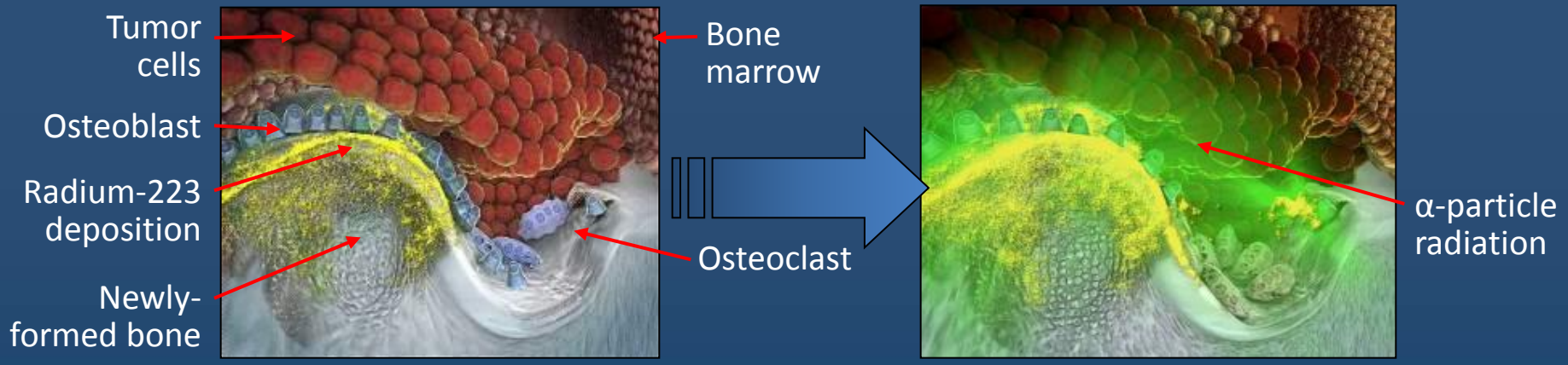
Radium-223 decay chain[2]



Decays via a series of α-, β-, and γ-emitting daughters

1. Bruland et al. Clin Cancer Res. 2006;12(20):6250s. 2. Henriksen et al. Cancer Res. 2002;62:3120.

Radium-223 has a Targeted Mechanism of Action

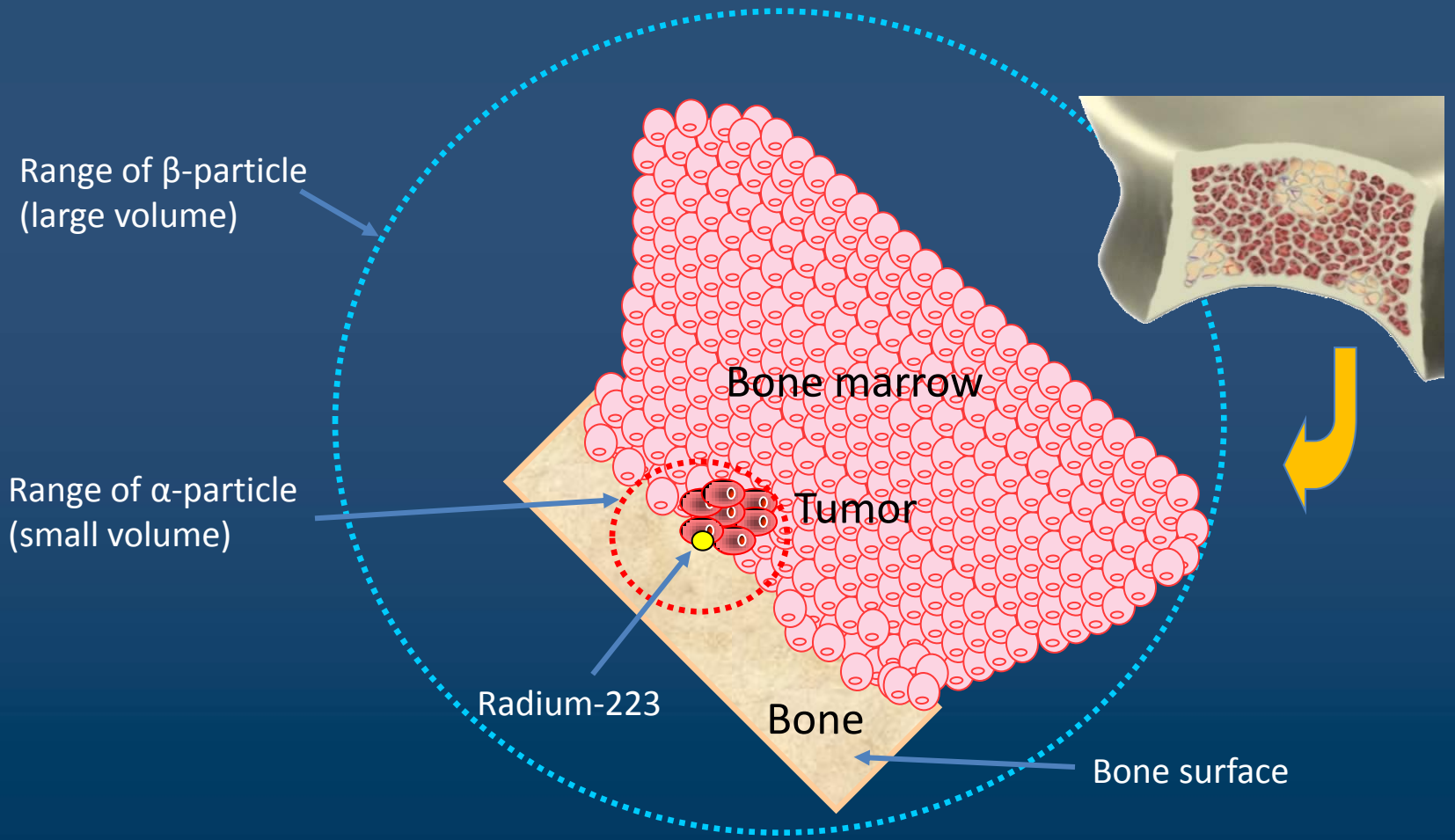


Targets new bone,
e.g. bone metastases

Irradiates adjacent tumor cells leading to highly localized tumor cell killing

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

Radium-223 Mode of Action is Localized (Compared with β-emitters)



1. Henriksen et al. Cancer Res. 2002;62:3120.
2. Nilsson et al. Presented at: American Society for Radiation Oncology annual meeting 2010; poster 2385.

Preclinical Development

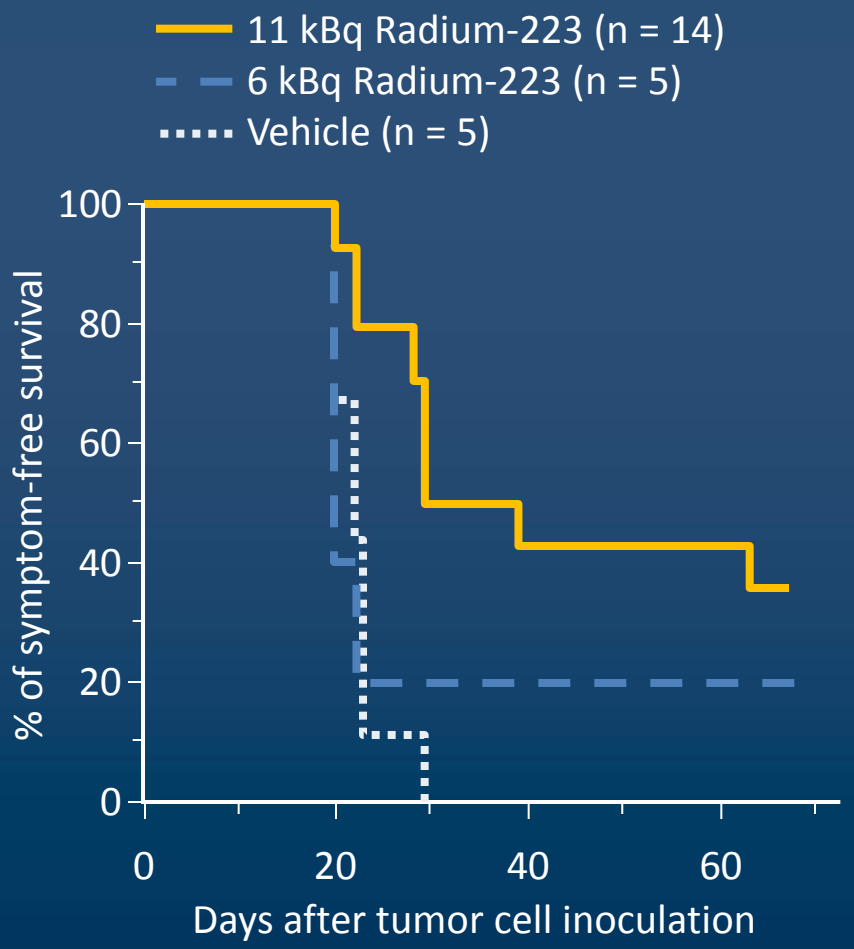
- Radium-223 was studied in an NHIK3025 cervical carcinoma cell line at a high dose (equivalent to 5.8–28 mGy/min) and a low dose (equivalent to 0.12–1.2 mGy/min)
  - Permanent G2 cell cycle arrest was observed in cells exposed to > 0.35 Gy of radiation
  - Cell survival followed a linear–quadratic model
  - Cytotoxicity was independent of dose rate
  - Similar survival curves were observed for irradiation during both log growth and the plateau phase
  - Cellular ATP levels suggested that cells remained metabolically active for at least 48 h after irradiation
  - A multidrug resistant cell line demonstrated identical survival curves to wild-type cells

ATP, adenosine triphosphate.

Dornish et al. Presented at: American Association for Cancer Research Annual Meeting 2008: Abstract 5749.

Preclinical Development Suggested Potential Efficacy

- Nude rats bearing MT1 breast cancer cells (a model for skeletal metastases) were treated with Radium-223 (6 or 11 kBq i.v.) 7 days after tumor induction
- Survival in both treatment groups was increased significantly compared with vehicle (solution minus active ingredient) ($p < 0.05$)
- Symptom-free survivor rates beyond 50 days were 36% and 20% in the 11 and 6 kBq groups, respectively, compared with no survivors by day 30 in the control group

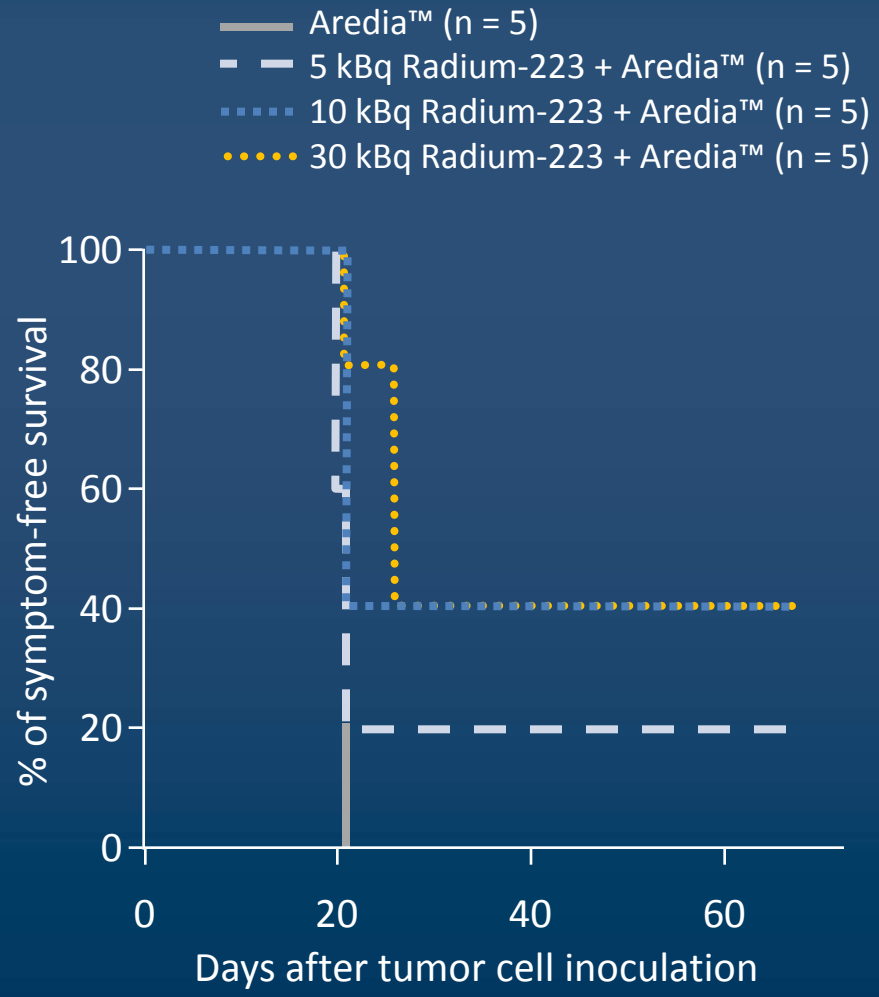


Becquerel (Bq) – SI unit of radioactivity, equivalent to the number of nucleus decays per second in a sample

Henriksen G, et al. Cancer Res. 2002;62:3120–25

Preclinical Development

- An additional group of rats received Aredia™ (1.5 mg/kg) as a supplement to Radium-223 (5, 10 or 30 kBq i.v.) 7 days after tumor induction
- A similar efficacy to Radium-223 therapy alone was observed, with symptom-free survivor rates of 40% in both the 10- and 30-kBq groups, indicating no additive effect of Aredia™



Aredia™, bone resorption inhibitor.

Henriksen et al. Cancer Res. 2002;62:3120.

Summary

- Radium-223 acts as a calcium mimic
- It is incorporated into the bony matrix and preferentially targets new bone formation in and around bone metastases
- Has a half-life of 11.4 and emits high-energy α-particles
- Only one to five hits to DNA are needed to cause cell death
- Due to its short range, it has a highly localized effect (2–10 cell diameters)
- Damage to surrounding normal tissue is therefore minimized