Ra-223 dichloride therapy in castration-resistant prostate cancer and bony metastases

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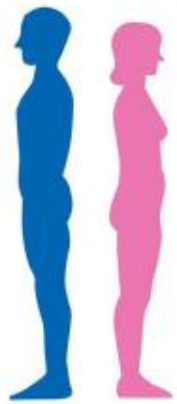
Prostate cancer: incidence

Estimated New Cases

				Males	Females			
Prostate	180,890	21%				Breast	246,660	29%
Lung & bronchus	117,920	14%				Lung & bronchus	106,470	13%
Colon & rectum	70,820	8%				Colon & rectum	63,670	8%
Urinary bladder	58,950	7%				Uterine corpus	60,050	7%
Melanoma of the skin	46,870	6%				Thyroid	49,350	6%
Non-Hodgkin lymphoma	40,170	5%				Non-Hodgkin lymphoma	32,410	4%
Kidney & renal pelvis	39,650	5%				Melanoma of the skin	29,510	3%
Oral cavity & pharynx	34,780	4%				Leukemia	26,050	3%
Leukemia	34,090	4%				Pancreas	25,400	3%
Liver & intrahepatic bile duct	28,410	3%				Kidney & renal pelvis	23,050	3%
All Sites	**841,390**	**100%**				**All Sites**	**843,820**	**100%**

Estimated Deaths

				Males	Females			
Lung & bronchus	85,920	27%				Lung & bronchus	72,160	26%
Prostate	26,120	8%				Breast	40,450	14%
Colon & rectum	26,020	8%				Colon & rectum	23,170	8%
Pancreas	21,450	7%				Pancreas	20,330	7%
Liver & intrahepatic bile duct	18,280	6%				Ovary	14,240	5%
Leukemia	14,130	4%				Uterine corpus	10,470	4%
Esophagus	12,720	4%				Leukemia	10,270	4%
Urinary bladder	11,820	4%				Liver & intrahepatic bile duct	8,890	3%
Non-Hodgkin lymphoma	11,520	4%				Non-Hodgkin lymphoma	8,630	3%
Brain & other nervous system	9,440	3%				Brain & other nervous system	6,610	2%
All Sites	**314,290**	**100%**				**All Sites**	**281,400**	**100%**

Siegel RL, et al. Cancer Statistics, 2016

- The 3rd most diagnosed cancer in Europe
- The 4th most diagnosed cancer in Thailand
- One of the leading cause of cancer-related death in men
- Siriraj Hospital (2015)
  - New cases 5.4% (387)
  - 5th leading cancer

- Incurable advanced or metastatic disease: ~ 10-20%

- Median survival time in metastatic castration-resistant prostate cancer (mCRPC) patients = 22 months.

Bone metastasis in prostate cancer

- Bone metastasis
  - The most frequent metastatic site in prostate cancer
  - affect quality of life
  - increase the risk of bone marrow failure
  - Increase skeletal-related events (SREs)
    - pathological fractures
    - spinal cord compression
    - reduce life expectancy

Treatment: improve OS in mCRPC

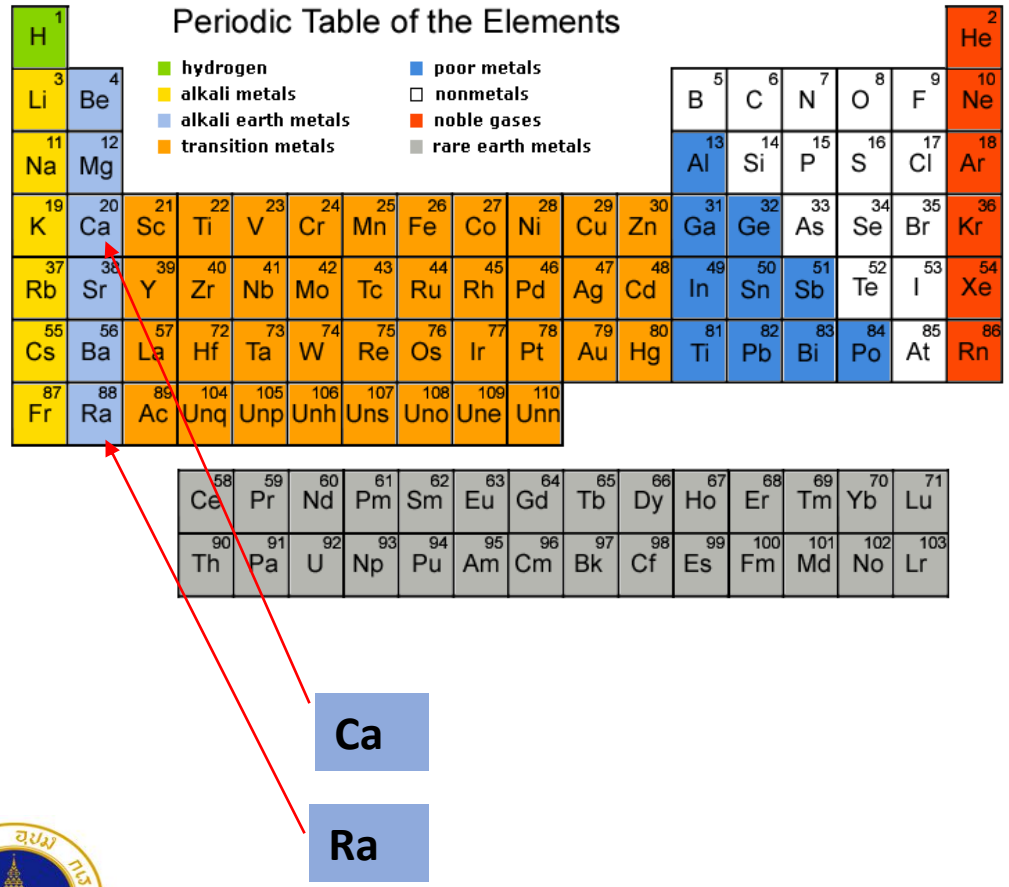
1. Hormonal therapy: Abiraterone acetate (de Bono et al, 2011; Ryan ey al ,2013)
2. Hormonal therapy: Enzalutamide (Scher et al, 2012)
3. Cytotoxic CMT: docetaxel (Petrylak et al, 2004; Tannock et al, 2004)
4. Cytotoxic CMT: cabazitaxel (de Bono et al, 2010)
5. Immunotherapeutic: sipuleucal-T (Kantoff et al, 2010)
6. Radium 223 dichloride

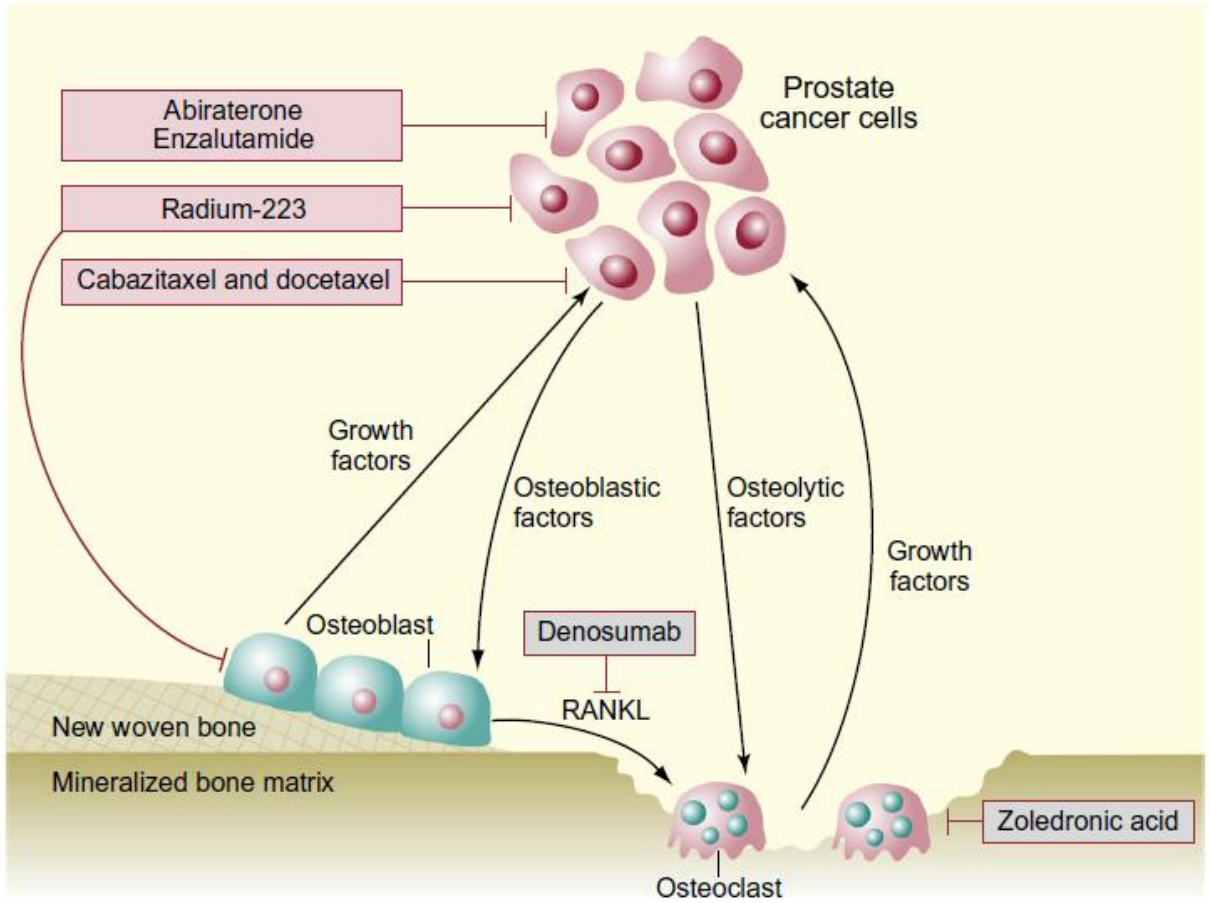
E lien LM et al, 2014

Ra-223

- Radium-223 dichloride
- An alpha particle-emitting pharmaceutical
- An American Food and Drug Administration (FDA) and European Medical Agency (EMA) approved bone targeting agent
  - Approved by FDA (May 2013) and EMA (Nov 2013): clinical use in mCRPC with symptomatic bone metastasis with no visceral disease

Mechanism of Ra-223

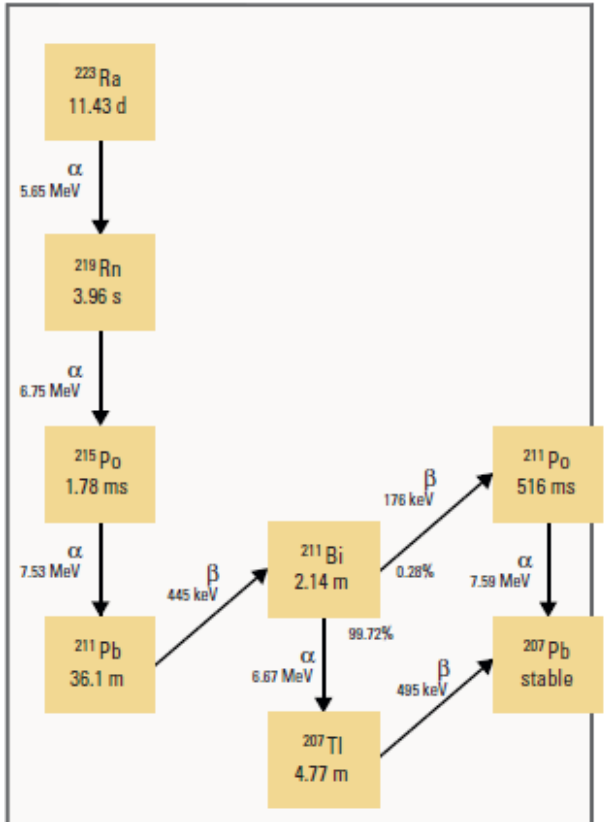




Yong Du, et al. Eur J Nucl Med Mol Imaging (2017) 44:1671–1678

- Ra-223 cause irreversible double-strand DNA breaks in surrounding cells with minimally adjacent cell damage
  - Difficult to repair
  - Failure to repair ➔ apoptosis
  - Misrepaired ➔ chromosomal aberrations ➔ mitotic cell death

Pharmacokinetics and biodistribution

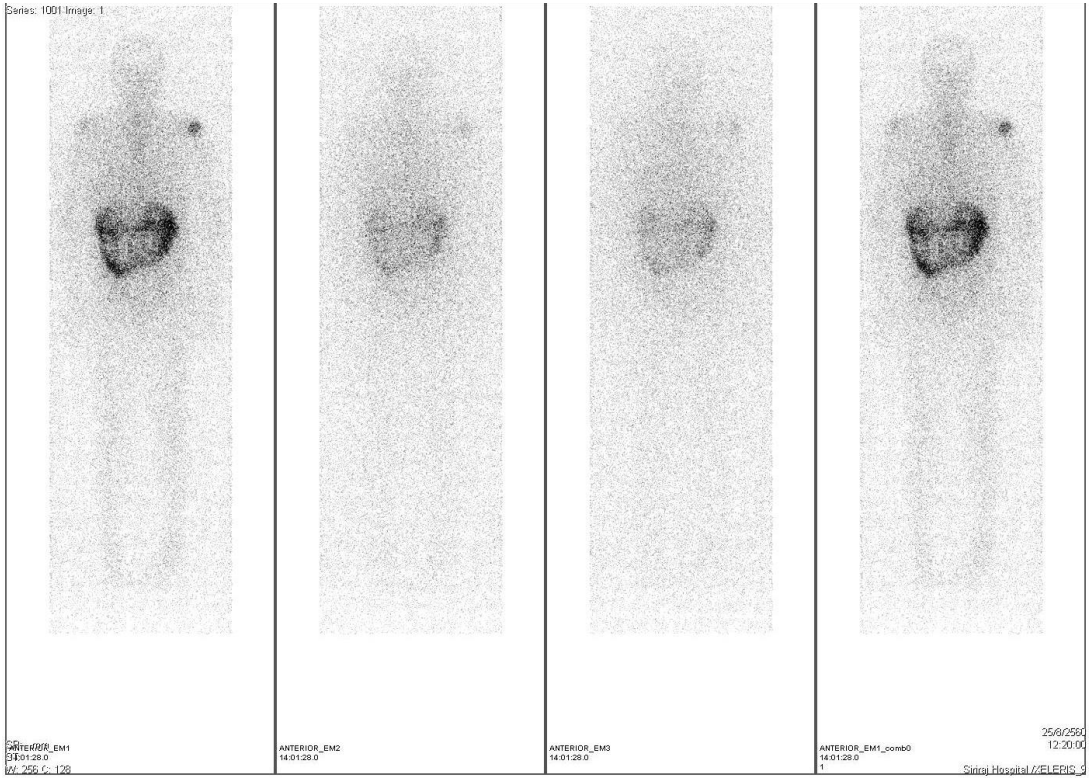


- Emitted mainly by alpha particles
- T1/2 = 11.43 days : allow long distance shipment
- Rapidly eliminated from the blood and accumulates in bone
- >75% clear from the blood at 15th minute after injection
- At 4 hour after injection
  - 61% in bone
  - 49% in small intestine
  - 4% in blood (<1%; 24 hours)
- Excrete into the intestine (~5% excrete in urine, no evidence of hepato-biliary excretion)
- A median of 76% of administrated activity excreted from the body at 7 days

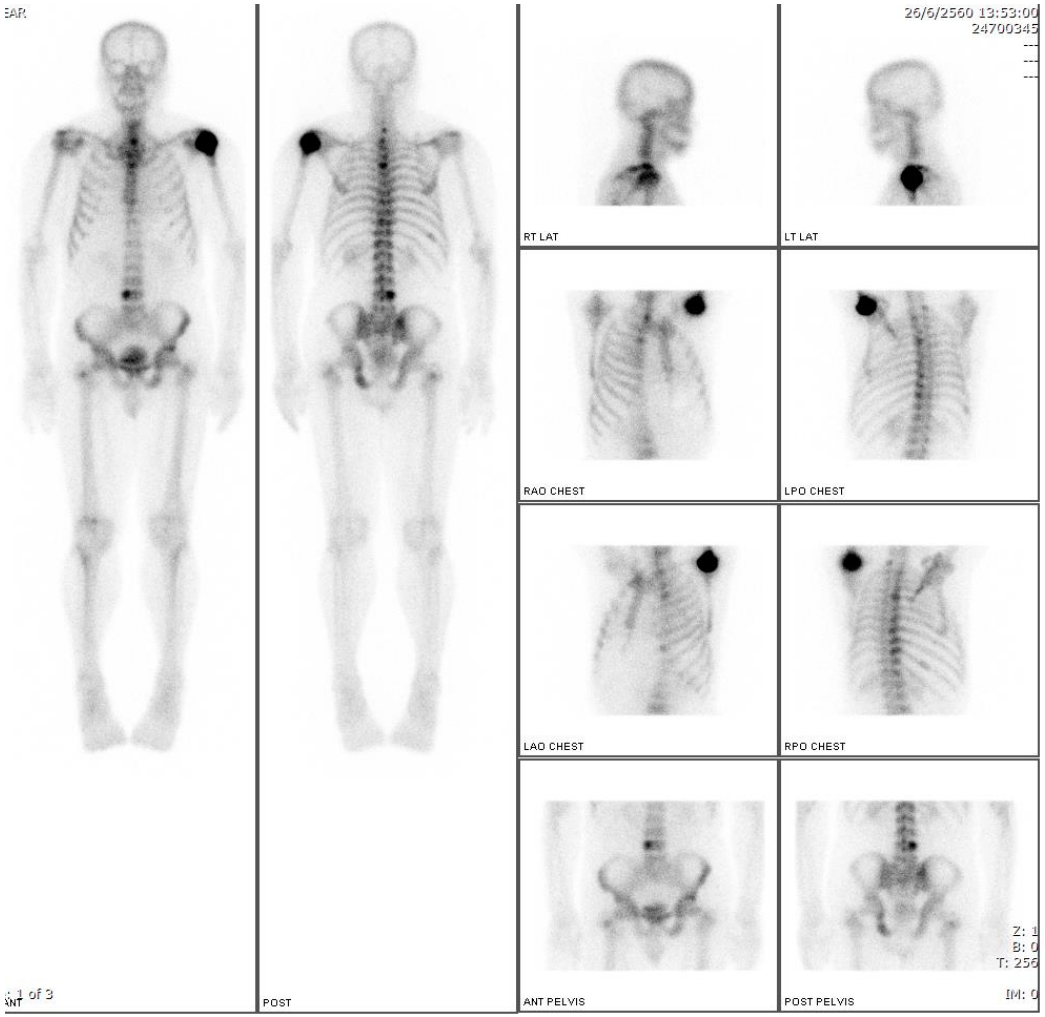
J. Siegel, Radium-223 Therapy: Handling&Radiation Safety issues, 2014 Meeting Mid-Atlantic States Radiation Control Program

Yong Du, et al. Eur J Nucl Med Mol Imaging (2017) 44:1671–1678

Ra-223



Bone scan



Compared with beta emitters

α-emitter

- Ra-223 dichloride

- Delivers high linear energy transfer with a short range (<0.1 mm; 2-10 tumor cell diameters)

B-emitter

- ^{89}Strontium, ^{153}Samarium-EDTMP, ^{188}Rhenium-HEDP
- Longer range (1-10 mm)

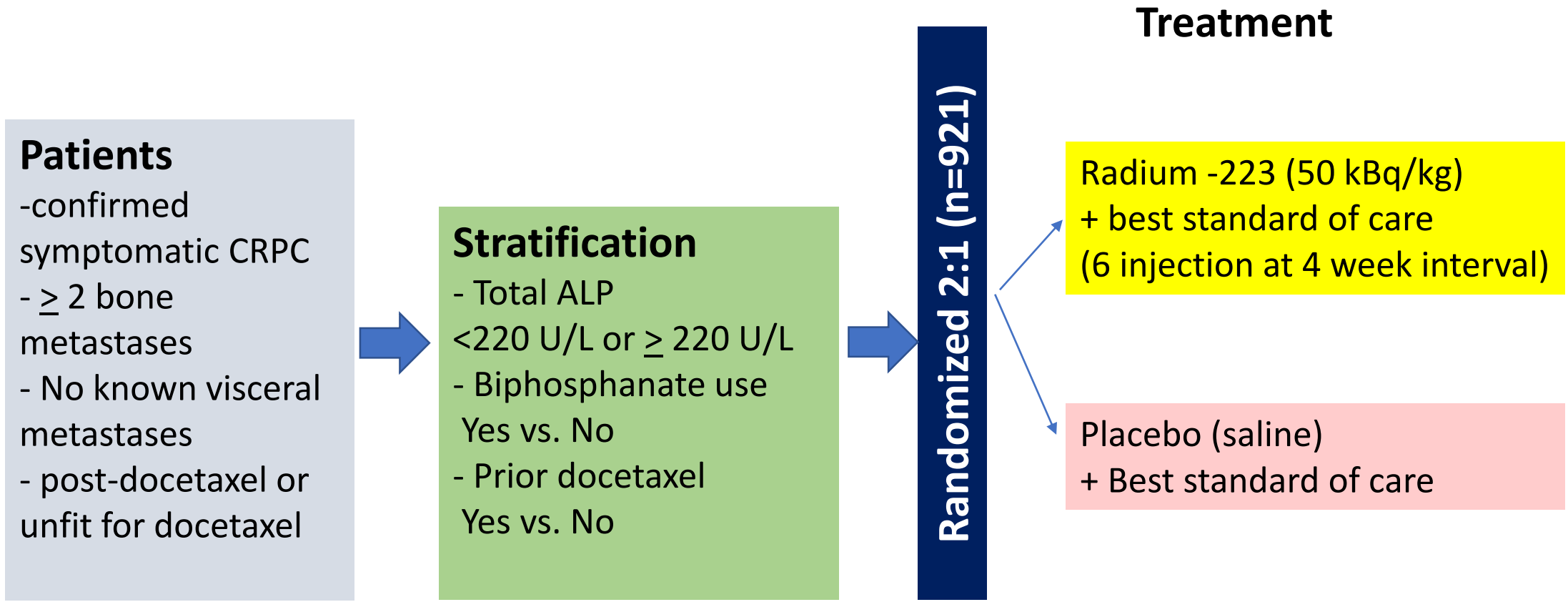
- Bone pain palliation
- No known effect on survival

Tanya et al, 2015

Ra-223

- Phase I study
  - Ra-223 has favorable safety profile with minimal myelotoxicity, evidence of pain relief and decrease in disease-related serum ALP activity in advanced breast or prostate cancer with associated bone metastases (Nilsson et al, 2005)
- Phase II study
  - Favorable safety profiles, reductions in pains and disease-related biomarkers (ALP, PSA) in CRPC patients with bone metastases (Nilsson et al, 2007; Nilsson et al 2012; Parker et al, 2013)
  - Randomized study: a survival benefit in CRPC patients with bony metastases (Ra-223 vs placebo) (Nilsson et al, 2007)

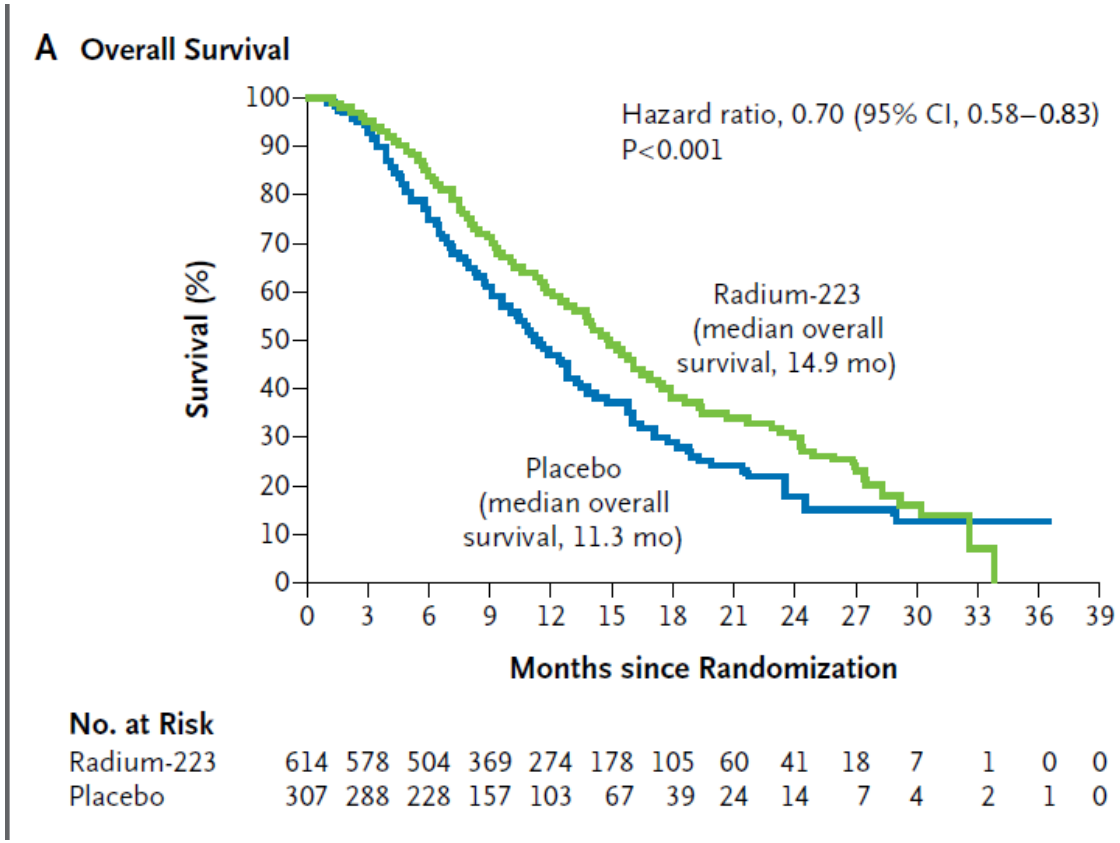
The ALSYMPCA trial

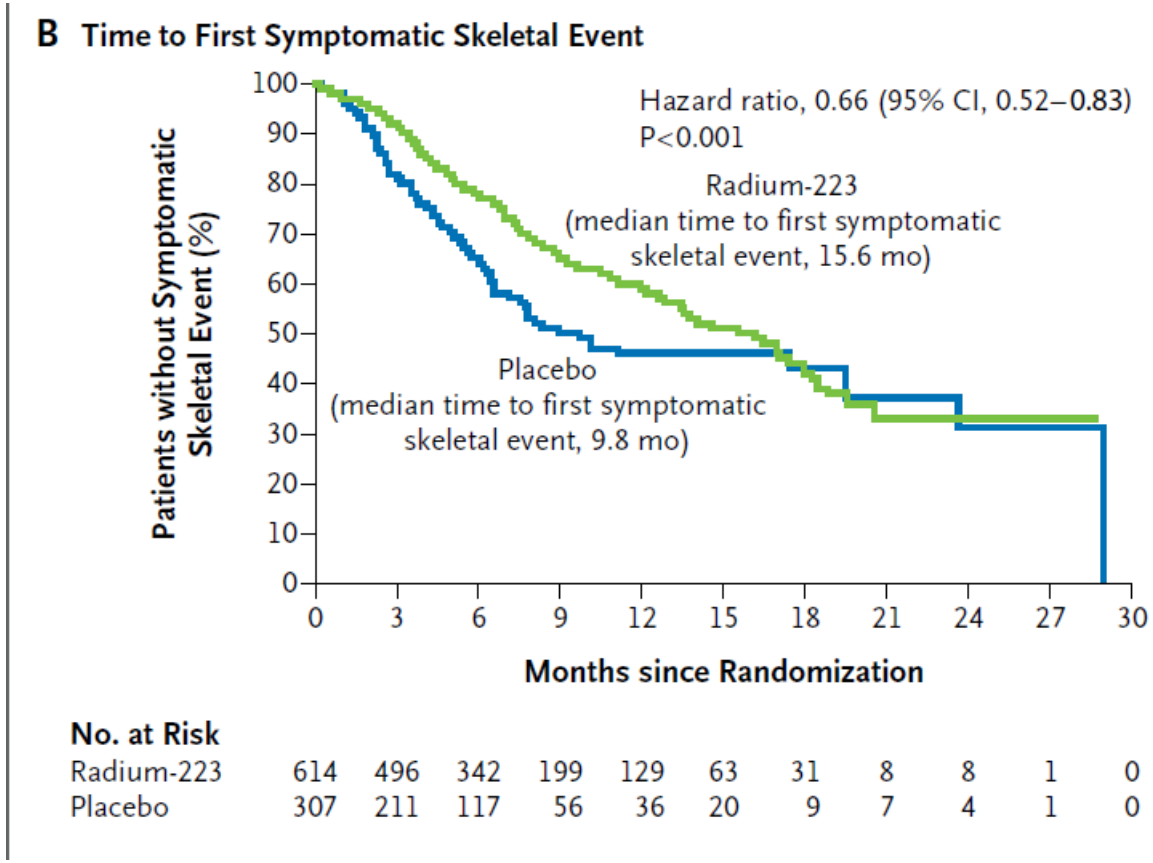


Parker C, N Engl J Med. 2013 Jul 18;369(3):213-23.

End Point	Radium-223 (N = 614)	Placebo (N = 307)	Hazard Ratio (95% CI)	P Value
Median time to first symptomatic skeletal event — mo	15.6	9.8	0.66 (0.52–0.83)	<0.001
Median time to increase in total alkaline phosphatase level — mo	7.4	3.8	0.17 (0.13–0.22)	<0.001
Median time to increase in PSA level — mo	3.6	3.4	0.64 (0.54–0.77)	<0.001
Patients with ≥30% reduction in total alkaline phosphatase response — no. /total no. (%)	233/497 (47)	7/211 (3)		<0.001
Patients with normalization of total alkaline phosphatase level — no./total no. (%)*	109/321 (34)	2/140 (1)		<0.001

Parker C, N Engl J Med. 2013 Jul 18;369(3):213-23.





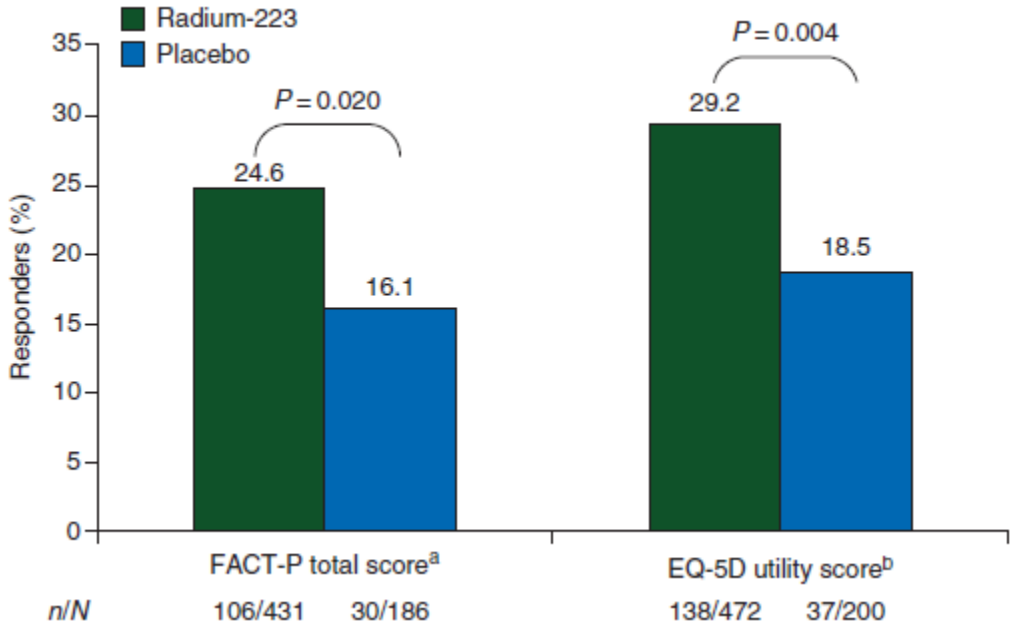
SSE:

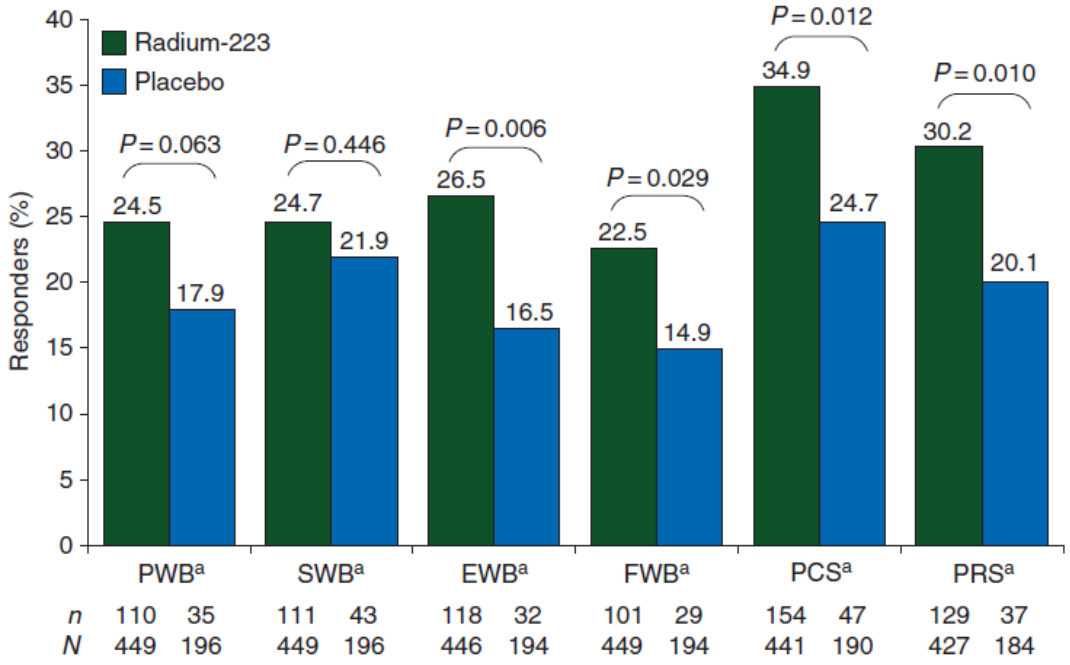
The first use of EBRT to relieve skeletal symptoms
New symptomatic pathologic vertebral or nonvertebral bone fractures
Spinal cord compression
Tumor-related orthopedic surgical intervention

Parker C, N Engl J Med. 2013 Jul 18;369(3):213-23.

ALSYMPCA

- Improve QOL benefits





Nilsson S, et al. Ann Oncol. 2016 May;27(5):868-74.

Adverse events (The ALSYMCA trial)

	All grades		Grade 3 or 4	
	Radium 223 (n=600)	Placebo (n=301)	Radium 223 (n=600)	Placebo (n=301)
Haematological				
Anemia	187(31)	92(31)	76(13)	39(13)
Thrombocytopenia	69(12)	17(6)	38(6)	6(2)
Neutropenia	30(5)	3(1)	13(2)	2(1)
Non-haematological				
Bone pain	300(50)	187(62)	125(21)	77(26)
Diarrhea	151(25)	45(15)	9(2)	5(2)
Nausea	213(36)	104(35)	10(2)	5(2)
Vomiting	111(18)	41(14)	10(2)	7(2)
Constipation	108(18)	64(21)	6(1)	4(1)

Hematologic Safety of Radium-223 Dichloride: Baseline Prognostic Factors Associated With Myelosuppression in the ALSYMPCA Trial

Nicholas J. Vogelzang,[1] Robert E. Coleman,[2] Jeff M. Michalski,[3] Sten Nilsson,[4] Joe M. O'Sullivan,[5] Christopher Parker,[6] Anders Widmark,[7] Marcus Thuresson,[8] Lei Xu,[9] Joseph Germino,[10] Oliver Sartor[11]

- Anemia (grade 2-4)
  - Baseline extent of disease (6-20 vs. < 6 bone metastases; OR = 2.76, p =.022)
  - Elevated baseline PSA (OR=1.65, p =.006)
- Thrombocytopenia (grade 2-4)
  - Prior docetaxel (OR=2.16, p=.035)
  - Decreased baseline hemoglobin (OR=1.35, p=.008) and decreased baseline platelets (OR =1.44, p=.030)
- Neutropenia
  - Too few in placebo patients for a comparative analysis.

Clinical Genitourinary Cancer, Vol. 15, No. 1, 42-52

Ra-223 Retreatment

- Sartor et al, 2016; ASCO GU 2016
- CRPC cases with ≥ 2 bony metastases without experiencing any disease progression in bone
- Total 12 cycles were given.
- 29 from 44 patients completed 12 cycles
  - 1 had bone progression
  - Most progression at soft tissue sites
- AEs (anemia, thrombocytopenia, leukopenia, N/V) are similar to ALSYMPCA trial

Ra223+combination

- Ra-223 + abiratorone (ERA-223 trial)
  - Primary end point: symptomatic skeletal event
- Ra-223 + Enzalutamide (The PEACE-III trial)
  - Primary end point: radiographic progression free survival (rPFS)
- RA-223 + Docetaxel
  - Primary end point: Safety
- Ra-223 + immunotherapy (pembrolizumab)
  - Primary end point: immune changes in the tumor microenvironment (bone biopsy)

Clinical indications

- Treatment in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease
- Phase I&II trials
  - Breast cancer (phase II trial):predominant HER2-negative, hormone receptor-positive and bone metastasis
  - Thyroid cancer (phase II trial): metabolic response of Ra-223 in the treatment of radioiodine refractory bone metastasis
  - Renal cell cancer (phase I trial): combination of Ra-223 and VEGF targeted therapy in bone metastasis

- Phase II&I trials
  - Osteosarcoma (phase I trial): dose escalation trial of Radium-223 (50, 75 and 100 kBq/kg)
  - Multiple myeloma (phase 1b/II trial): safety and efficacy of Radium-223 dichloride in combination with bortezomib and dexamethasone

Radium-223

- Ready-to-use solution
- Shelf life: 28 days
- Half time: 11.4 days
- No particular storage temperature required
- Post administration: decay to non-radioactive daughter product
- No long-lived radioactive waste products

Hematologic evaluation prior to administration of Ra-223

- Before the first administration
  - Hb ≥ 10 g/dL.
  - Absolute neutrophil count (ANC) ≥ 1,500/mm^3
  - Platelet count ≥ 100,000 /mm^3
- Before subsequent administrations,
  - Hb ≥ 10 g/dL.
  - Absolute neutrophil count (ANC) ≥ 1,500/mm^3
  - Platelet count ≥ 50,000 /mm^3

* If hematologic values **do not recover within 6 to 8 weeks** after the last administration, despite receiving supportive care, further treatment with Radium-223 should be continued only after a careful benefit/risk evaluation

Radium-223 [prescribing information]. Bayer healthcare Pharmaceuticals; 2013.

Dosage and administration

- 55 kBq per kg body weight
- 4 week intervals for 6 injections
- Slow intravenous injection over 1 minute
- No dose adjustment in patients with renal and hepatic impairment
- Outpatient treatment
- Contraindication
  - Pregnancy (potential hazard to fetus)

Administration

- Protect area beneath administration site with plastic-backed absorbed bench liner.
- Administer drug as a slow IV injection directly to a 2- or 3-way adapter.
- Verify IV access by flushing with saline before and after drug injection.
- Treat equipment as short-lived radioactive waste; store and dispose in accordance with local regulations.

IPET 2015, Jurgen Gay, Bayer BHC-GCPD Radiopharm

Patient care

- Follow good hygiene practices while **receiving radium-223 and for at least 1 week** after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers.
- Patients should use a toilet and the **toilet should be flushed several times** after each use.
- Clothing soiled with patient fecal matter and urine should **be washed promptly and separately** from other clothing.
- **Wearing gloves and hand washing** will protect caregivers.

Patient care

- There are no restrictions regarding contact with other people after receiving radium-223.
- Patients who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective method of **birth control during treatment and for 6 months** following completion of radium-223 treatment.
- The external radiation exposure associated with handling of patient doses is expected to be low.

Ra-223: Siriraj Hospital, Bangkok

- Ra-223 was introduced in Thailand in March 2015.
- Total numbers of patients in Thailand were 40 cases in both public and private hospitals.
- There were 10 cases treated with Ra-223 in Siriraj Hospital, Bangkok, Thailand between January 2017 and October 2017.
- All patients were castration-resistant prostate cancer with symptomatic skeletal metastasis but no visceral metastasis such as brain, liver or lung metastasis.

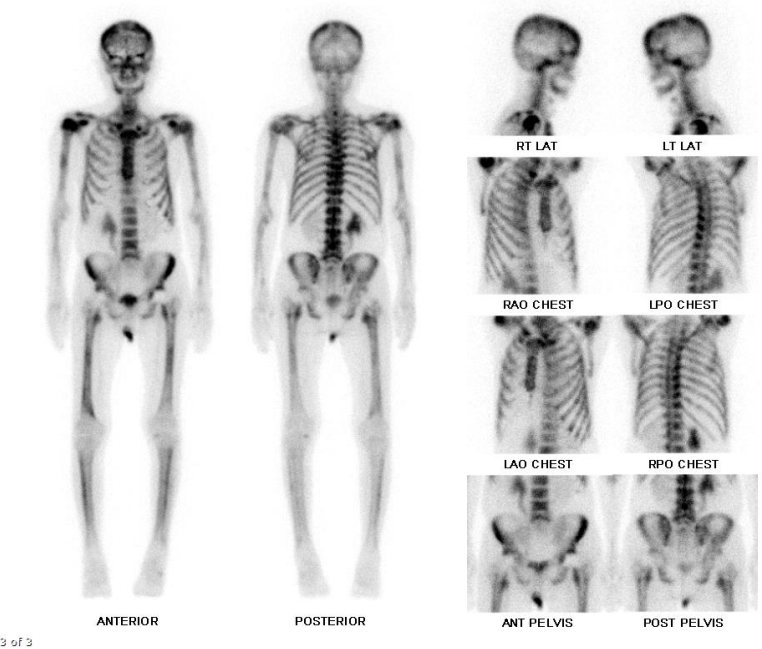
- Four patients had received complete 6 injections while 3 patients have been undergoing Ra-223 treatment.

- In 4 cases who received complete course of Ra-223

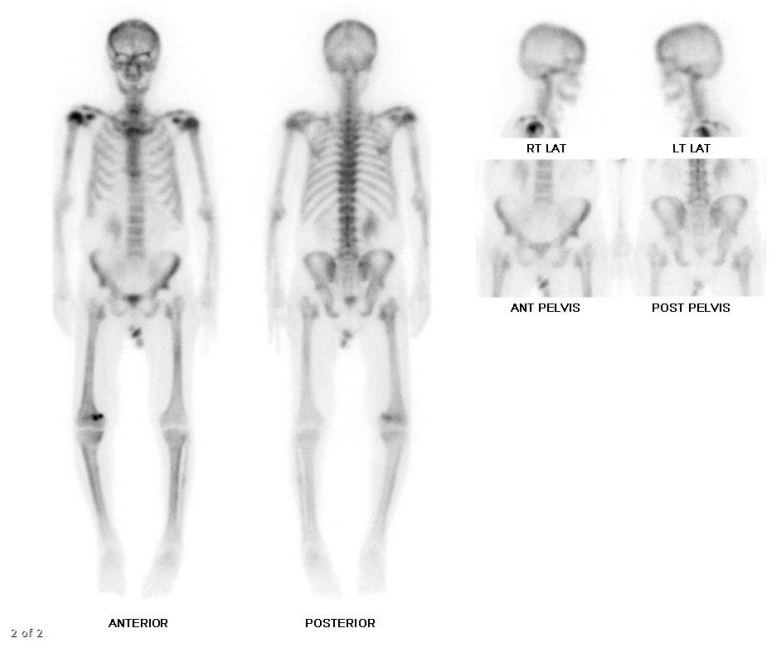
	Before Ra-223	After complete 6 injections of Ra-223
PSA level (ng/ml)	17.89-461.6	8.6-642.5
AP level (U/L)	92-402	49.5-97

- The bone scan

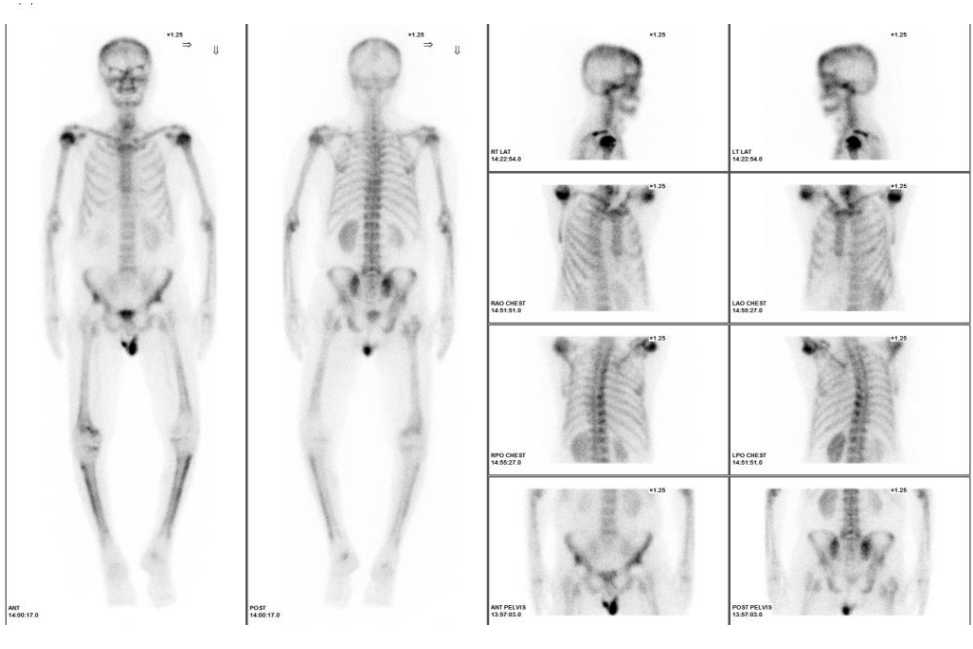
	After 3rd injection of Ra-223 treatment	After 6th injection of Ra-223 treatment
Progression bone scan	5/6 (83.33%)	-
Improvement bone scan	1/6 (16.67%)	1/1 (100%)



Before Ra-223



After 3 injections of Ra-223



After 6 injections of Ra-223

- The pain relief was observed in first injection in 80% (8/10 cases)

	After 1st injection	After 2nd injection	After 3rd injection
No bone pain	2	2	1

3 cases: received Ra-223 less than 6 injections

1: Patient developed spinal cord compression and was referred for surgery (5 doses).

2: Patient developed gross hematuria, thrombocytopenia, and subdural hematoma (2 doses).

3: Patient developed pancytopenia with bone marrow metastasis (1 dose).

Conclusion

- Ra-223 is the novel treatment in symptomatic skeletal metastases in castration-resistant prostate cancer with no known visceral metastasis.
- Ra-223 prolonged overall survival and time to first SSE and improve QOL.
- Most patients have pain relief after the first injection.
- The common adverse effects are hematologic adverse event.
- Alkaline phosphates decreased after Ra-223 treatment.

Acknowledgements

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Thank You

Q&A

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