Radionuclide Therapy of Prostate Cancer

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SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING 1954–2014

CELEBRATING 60 YEARS

Outline

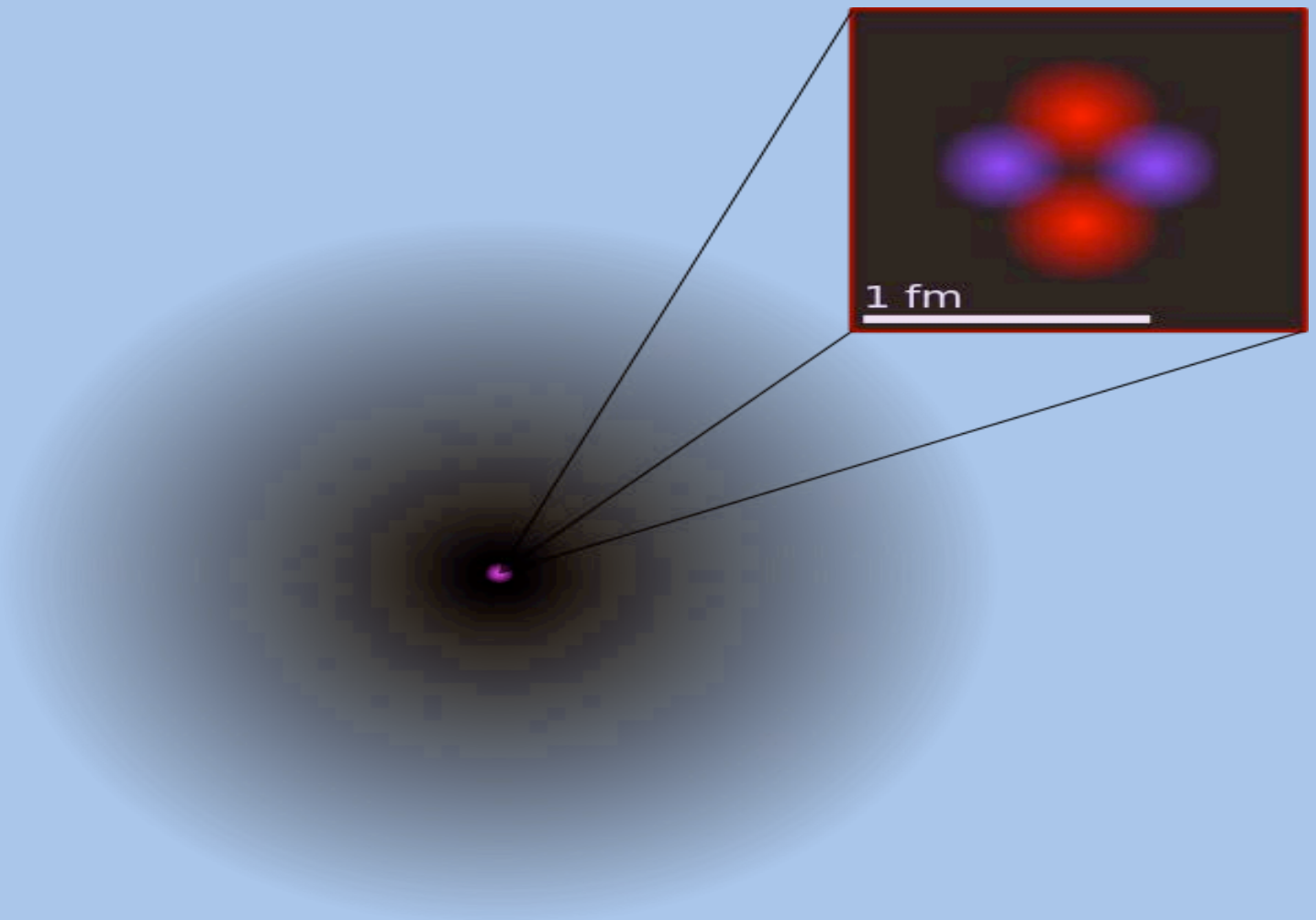
- Alpha particle therapy
- Biology of bone metastases (prostate cancer)
- ALSYMPCA Clinical Trial
- Nuts & bolts of Ra-223 dichloride (Xofigo®) therapy
- NCI-SNMMI TRT Workshops

Alpha Particle Therapy

- >100 alpha-emitting radioisotopes but most decay too fast
- Positively charged helium nuclei
- Short range 50-80 um (vs. several mm's for beta particle)
- High linear transfer energy (LET) 100 keV/um (vs. beta particle 0.2 keV/um) at approximate range of ds DNA diameter (2 nm)
- Relative Biologic Effect (RBE) 3-7 fold > X-Ray reference radiation for cell sterilization
- Targeted beta Rx: "crossfire" or "bystander" effect of antigen-neg. tumor cells due to longer range (several mm) but at cost of nl. tissue toxicity – better for large tumors
- Targeted alpha Rx: more specific tumor cell killing with less damage to surrounding nl. tissue (min. residual dz or uMets)

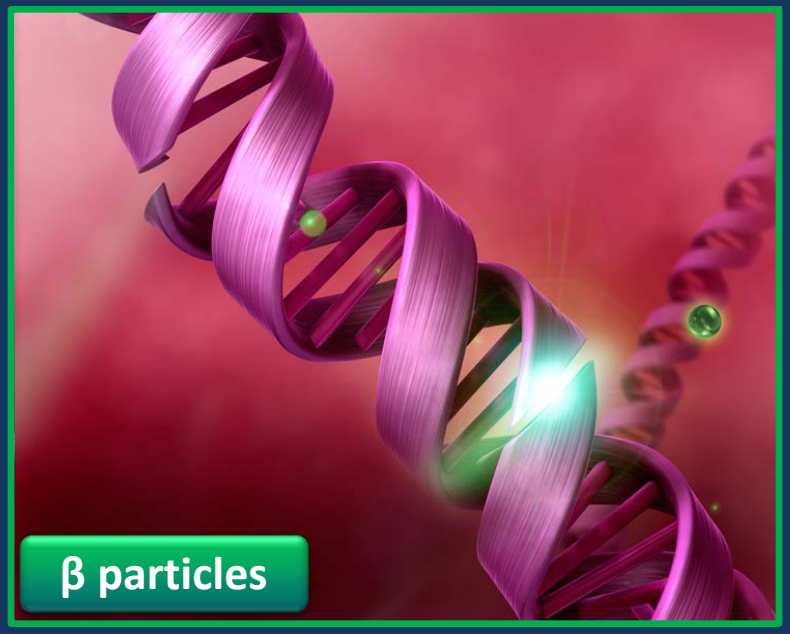
Mulford DA et al. *JNM* 2005.

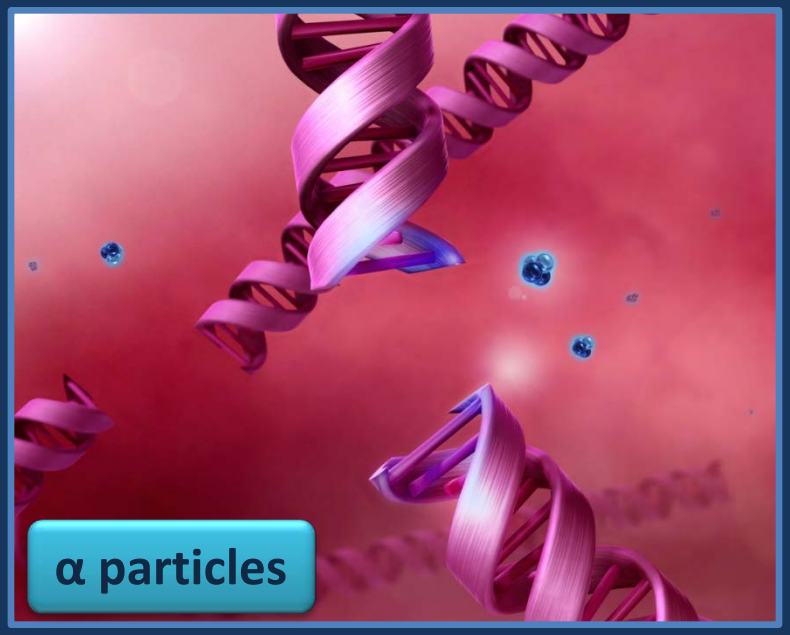
Helium



1 Å = 100,000 fm

Radiation Effects on DNA



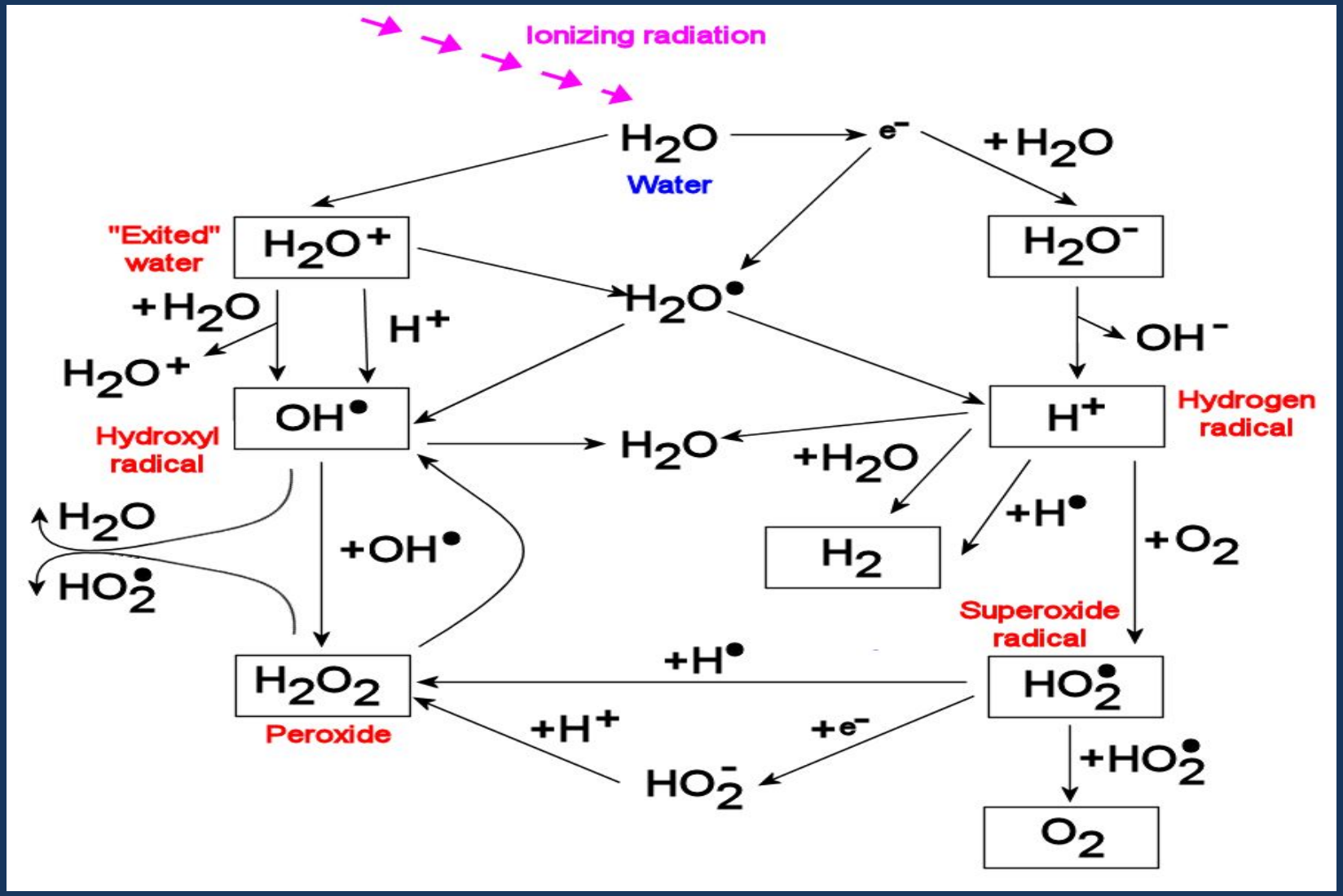


- **Low-LET** β-radiation produces single-strand DNA breaks[1]
- **Single-strand breaks** are easily repaired[1]

- **High-LET** α-particles produce **double-strand** DNA breaks[1]
- Difficult-to-repair double-strand breaks are **lethal**[2]

1. Kassis AI. *Semin Nucl Med* 2008;38:358-366.
2. Ritter MA, et al. *Nature* 1977; 266:653-655.

Radiolysis of Intracellular Water



http://www.mun.ca/biology/scarr/Radiolysis_of_Water.html

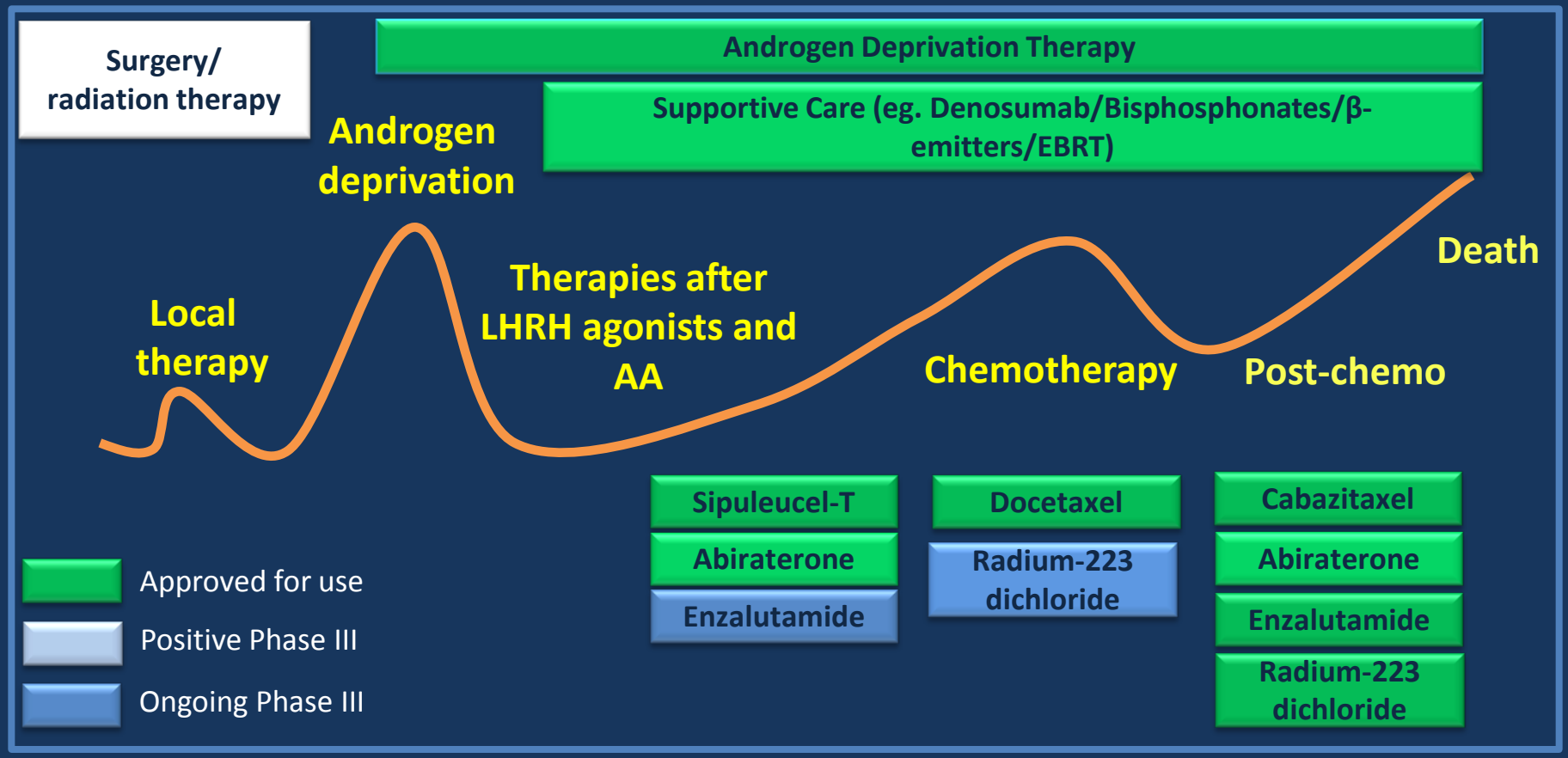
Alpha Emitting Radioisotopes

Mulford DA et al. *J Nucl Med* 2005
Vaidyanathan G, et al. *Curr Radiopharm* 2011

Isotope	Particle(s) emitted	Half-life	Energy of α-particle (MeV)
^{211}At	1 α	7.2 h	6
^{225}Ac	4 α, 2 β	10 d	6–8
^{212}Bi	1 α, 1 β	60.6 min	6
^{213}Bi	1 α, 2 β	46 min	6
^{223}Ra	4 α, 2 β	11.4 d	6–7
^{212}Pb	1 α, 2 β	10.6 h	7.8
^{149}Tb	1 α	4.2 h	4

At: Astatine; Ac: Actinium; Bi: Bismuth, Ra: Radium; Pb: lead; Tb: Terbium

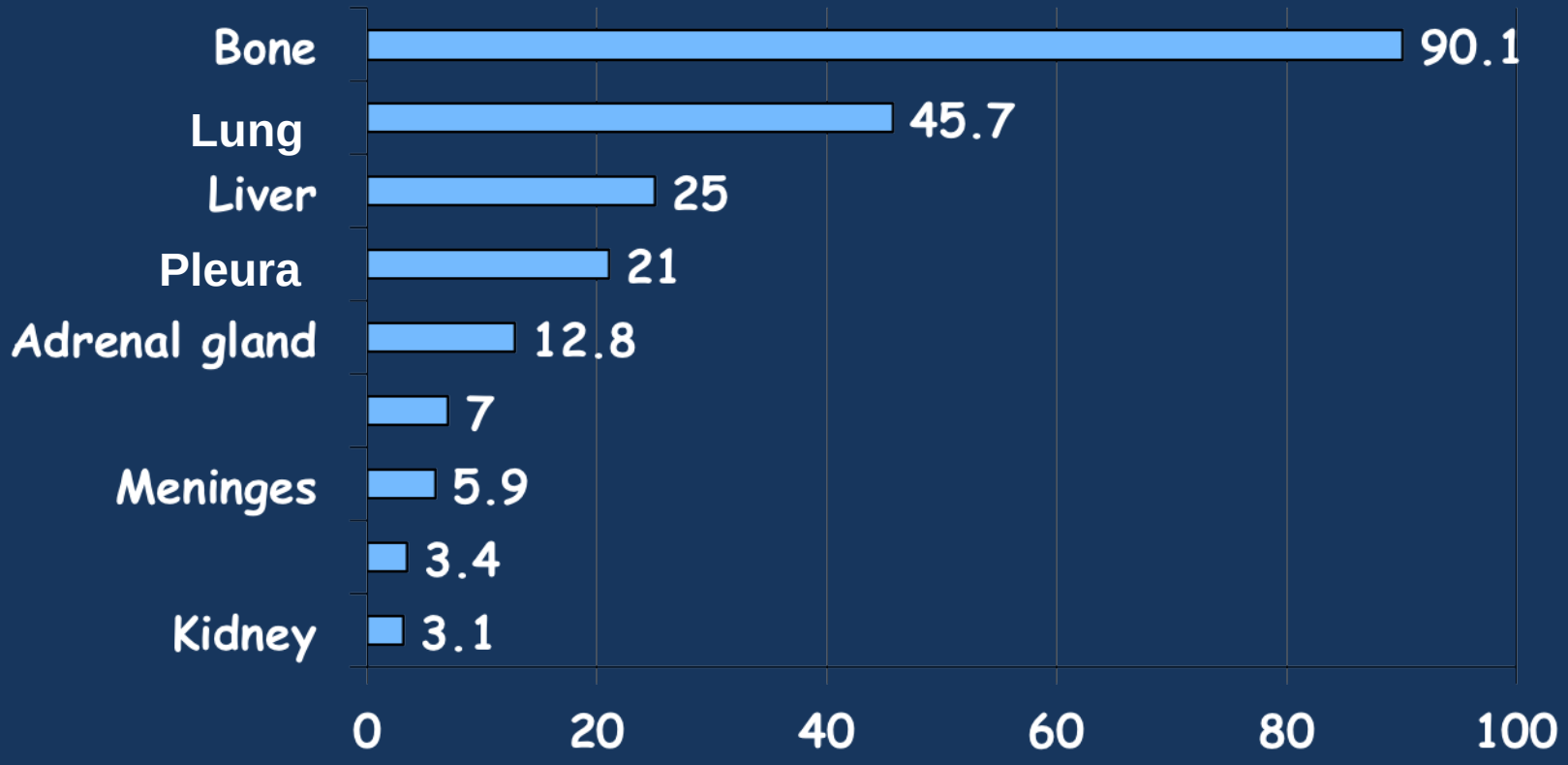
Prostate Cancer
Evolving Treatment Landscape



Typical clinical presentation of patients through different phases of prostate cancer. Time is not proportional.
The line represents the burden of disease at different disease phases.
Adapted from Higano CS. In: Figg WD et al. *Drug Management of Prostate Cancer*. 2010:321.

Sites of prostate metastases at autopsy

n=556 / 1589 (35.0%) patients with CaP



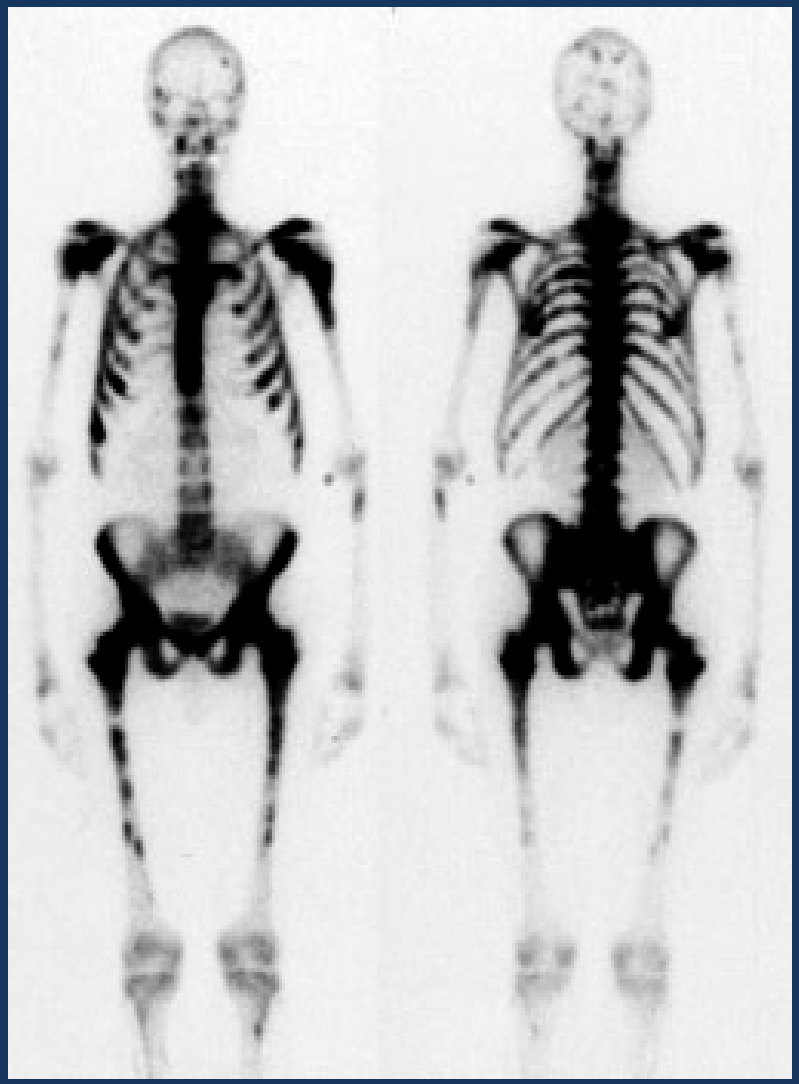
Bubendorf et al, Hum Pathol 2000; 31: 578

Prostate Cancer Bone Metastasis

- > 90% of patients with metastatic CRPC have radiologic evidence of bone metastases[1]
- Skeletal-related events (SREs) include spinal cord compression, pathological fracture, and need for surgery or external beam radiotherapy[2]
- Bone metastases are a major cause of death, disability, decreased quality of life, and increased treatment cost[3]
- Current bone-targeted therapies have not been shown to improve survival (except recently by ALSYMPCA)

1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. Lipton. *Semin Oncol.* 2010;37:S15-S29.
3. Lange and Vasella. *Cancer Metastasis Rev.* 1999;17:331-336.

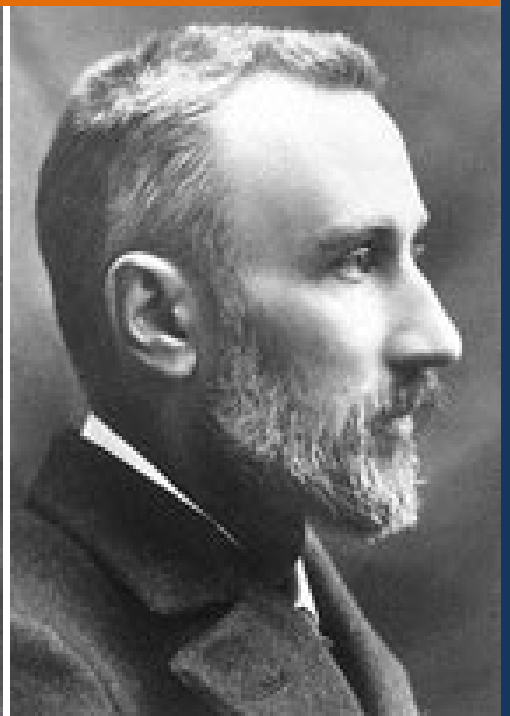
Prostate Cancer Bone Metastases
Skeletal Related Events



- Without treatment, SREs occur about every 8 months
- Median time to first SRE is about 11 months after bone metastases diagnosis
- At >24 months, almost 50% experience SRE
- The longer a patient lives, the more likely chance of SREs
- SREs cause impaired QoL and decreased survival

The Curies: Discovery of Radium

- The Curies informed the *l'Académie des Sciences*, on December 26, 1898, that they had come upon an additional very active substance that behaved chemically almost like pure barium. They suggested the name of *radium* for the new element.
- 25 known isotopes, 4 found in nature; ^{226}Ra most common; ^{223}Ra generated naturally through decay of Uranium (U) or Thorium (Th)



1903 Madame Curie presented her doctoral thesis and shared the Nobel Prize with her husband, Pierre Curie (and Henri Becquerel)

1748 THE BRITISH MEDICAL JOURNAL] [DEC. 18, 1909.

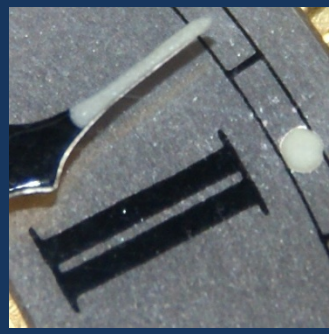
IS RADIUM A CURE FOR CANCER?*

BY DR. LOUIS WICKHAM,

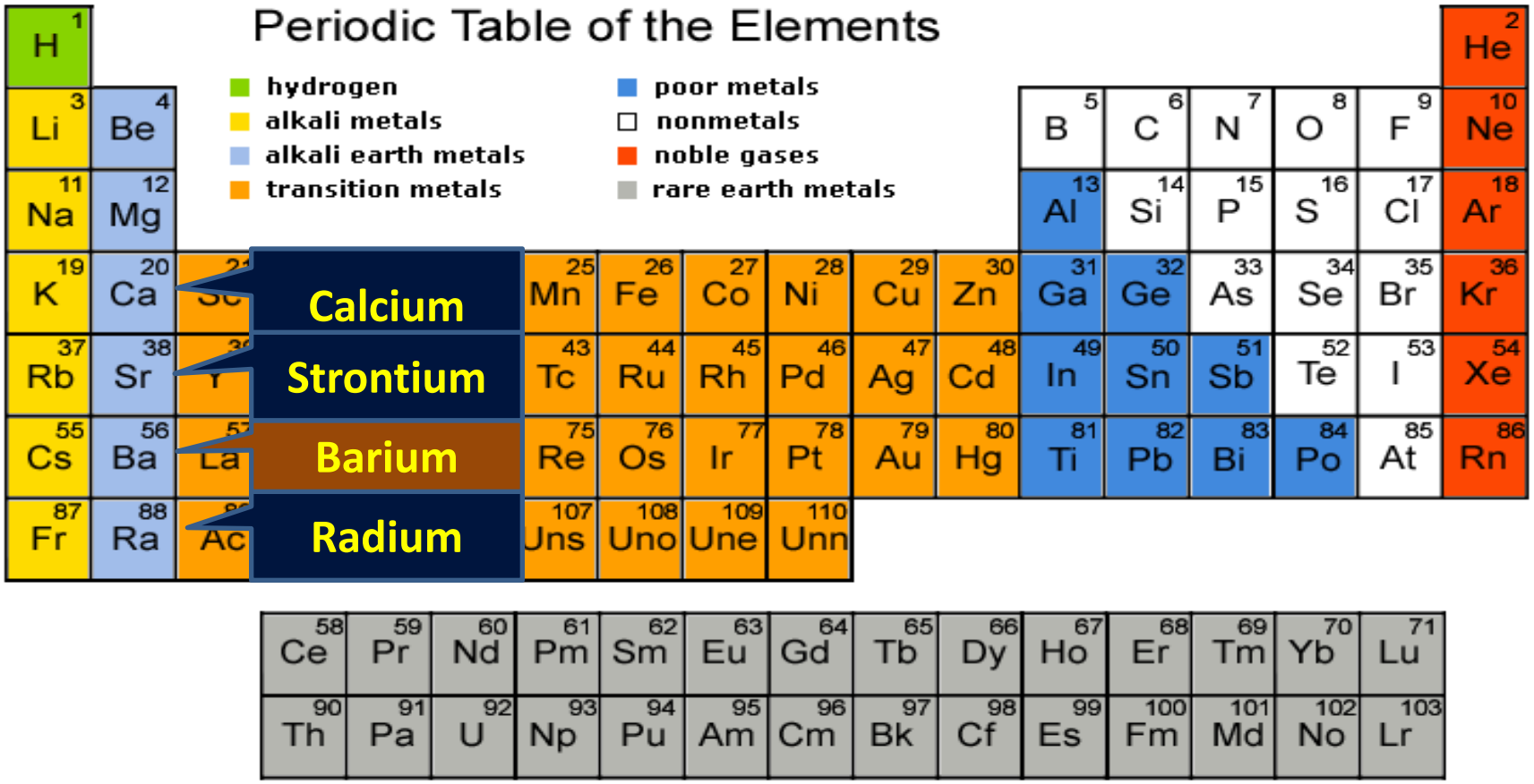
DIRECTOR OF THE RADIUM INSTITUTE, PARIS.

[redacted] it is difficult, without any exaggeration, not to recognize that radium-therapy, as I have often repeated, has won its place in the therapeutic armamentarium, that the fine French discovery of Curie and of Madame Curie has borne definite and certain fruit in the medical field.

- "Alpha particles in medicine may be newly explored 115 years after their discovery" – Vapiwala N, Glatstein E. *NEJM* 2013.
- US Labor law change after lawsuit filed against US Radium Corp. by dying "Radium Girls" dial painters in mid 1920's; Nasal Radium irradiation administered to children to prevent middle ear problems or enlarged tonsils 1940's-early 1970's.



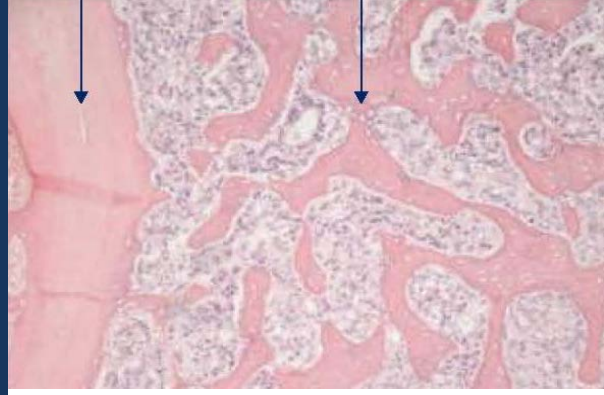
Radium Targets Osteoblastic Bone Metastases by Acting as a Calcium Mimetic

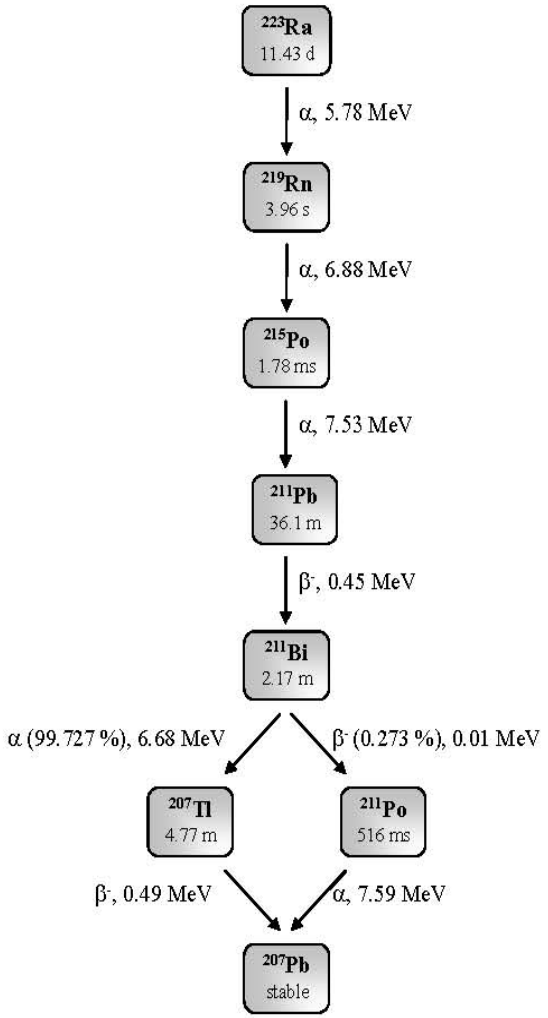


McDevitt et al. *Eur J Nucl Med* 1998;25:1341-1351.

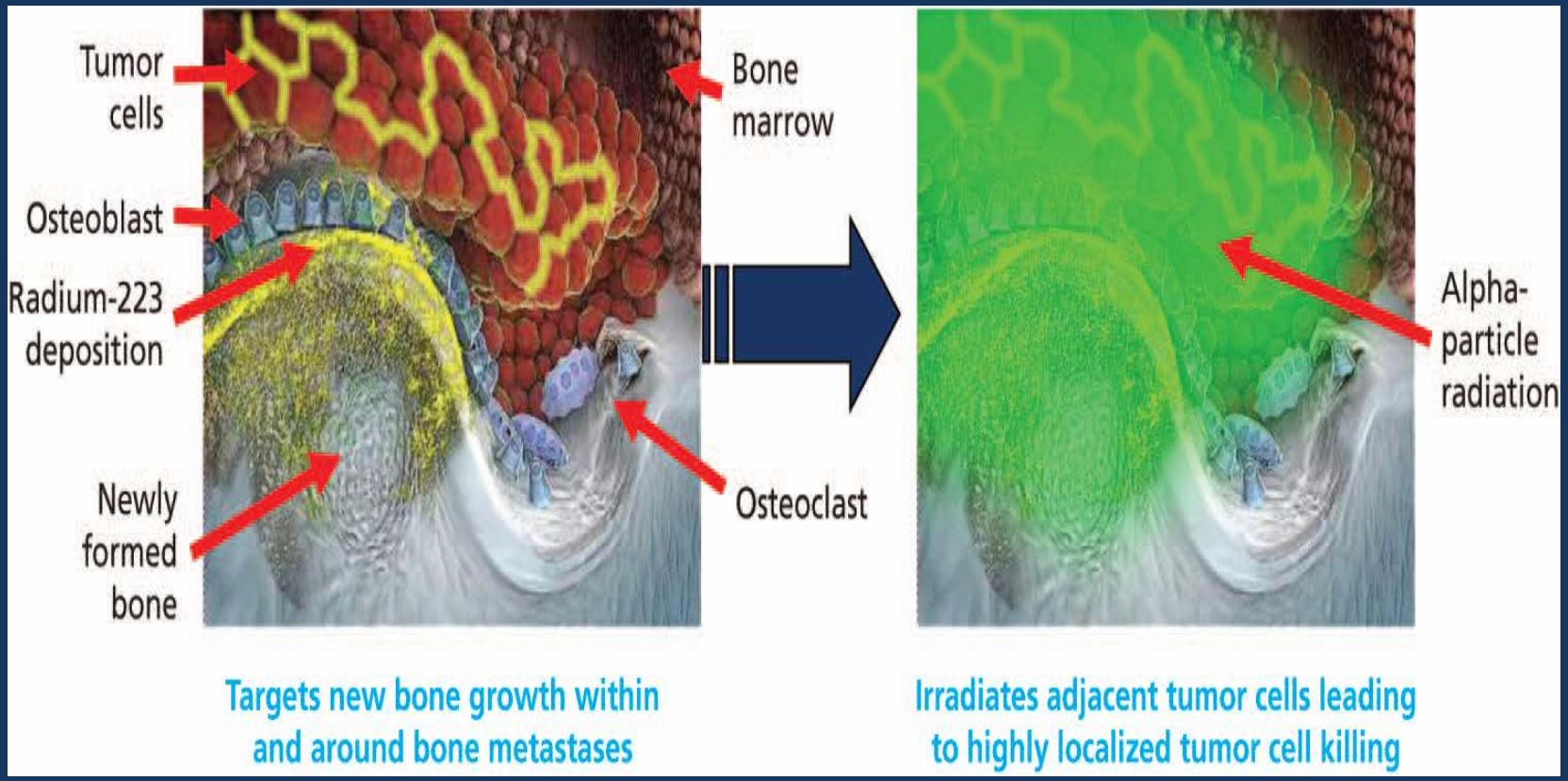
Radium-223

- Calcium mimetic (bone-seeking) with Hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ as target
- Provided from uranium mill tailings or in generator form from ^{227}Ac ($t_{1/2}$=21.8 y) parent
  - $^{227}Ac \Rightarrow {}^{227}Th \Rightarrow {}^{223}Ra$
- $T\frac{1}{2}$= 11.43 days
- Emitted energy distribution
  - 93.5% α particle, 5.78 MeV (avg.)
  - <3.6% as β particle
  - <1.1% as γ radiation
  - 28MeV combined energy for complete decay including 0.9 MeV as γ radiation





As calcium-mimetic, Radium-223 dichloride self-targets to osteoblastic zones near bone metastases

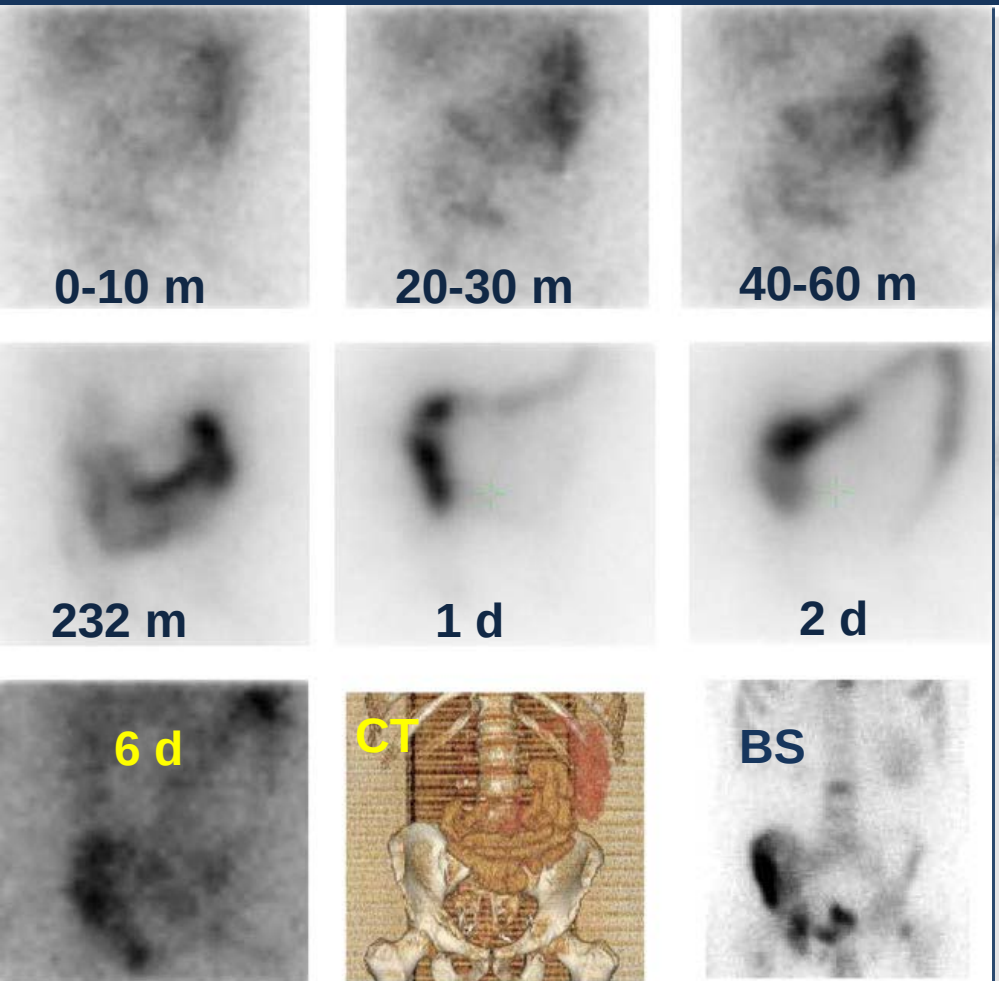


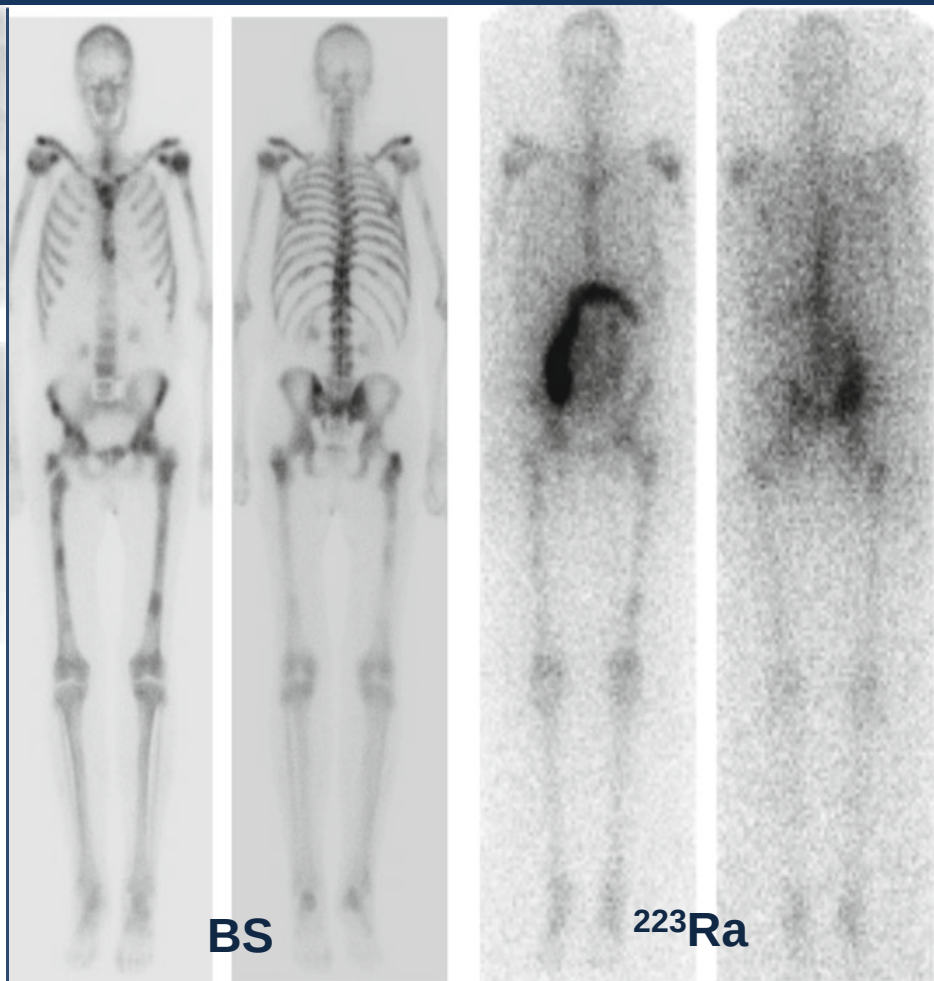
Nilsson S. Alpha-Emitter Radium-223 in the management of Solid Tumors: Current Status and Future Directions. *ASCO eBook* 2014.

^{223}Ra Dichloride Biodistribution

Carrasquillo JA et al. *EJNMMI* 2013

- High Energy General Purpose collimator with 20% energy windows centered on 82, 154, 269, 351, 402 Kev





Estimated equivalent dose after iv injection of 50 kBq/kg of ^{223}Ra

Target organs	Dose equivalents (Sv)
Adrenals	5.60×10^{-2}
Urinary bladder	5.70×10^{-2}
Brain	5.55×10^{-2}
Breast	5.55×10^{-2}
Gall bladder	5.60×10^{-2}
Heart wall	5.55×10^{-2}
Kidneys	5.60×10^{-2}
Liver	6.35×10^{-1}
Muscle	5.60×10^{-2}
Ovaries	5.65×10^{-2}
Pancreas	5.60×10^{-2}
Testes	5.55×10^{-2}
Thyroid	5.55×10^{-2}
Bone surface	13.05
Stomach	5.60×10^{-2}
Small intestine	5.65×10^{-2}
Upper large intestine	1.68×10^{-1}
Lower large intestine	3.67×10^{-1}
Skin	5.55×10^{-2}
Spleen	5.55×10^{-2}
Thymus	5.55×10^{-2}
Uterus	5.60×10^{-2}
Expiratory tract	5.55×10^{-2}
Lung	5.55×10^{-2}
Colon	2.54×10^{-1}
Thoracic lymph node	5.55×10^{-2}
Esophagus	5.55×10^{-2}
Gonads	5.65×10^{-2}
Remainder	5.60×10^{-2}

^{223}Ra-dichloride

- indication, bone scan, labs, signed consent (MD present)
- well hydrated, good running i.v.
- check blood work
  - ANC ≥1.5 × 10^9/L
  - platelet count ≥100 × 10^9/L
  - hemoglobin ≥10 g/dL.
  - Prior to subsequent administrations, ANC ≥1 × 10^9/L. platelet count ≥50 × 10^9/L
  - ^{223}Ra should be discontinued if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care
- double gloves; packaging surveyed after vial removal
- Dispose in clinical waste stream after decay-in-storage (10 CFR 35.92)

^{223}Ra-dichloride

Courtesy of A. Iagaru, MD, Stanford

- 1 min i.v. injection in an arm vein *(95 uCi for 70kg)*
- underpad chux on floor, chair, and table without arms
- double bagged red biohazard bag
- IV pole with 500 ml saline and tubing primed
- connect the 3-way stopcock to the patient i.v.
- MD will push dose from vial
- Pull i.v. and place contaminated materials in a latex glove and tape-shut
- put in red biohazard bag; measure for residual using standard meter
- Survey technologist's and MD's hands and feet
- prior to release, check HR and BP, then call MD to clear the patient

^{223}Ra-dichloride
patient instructions

- Minimal exposure to others below regulatory limit (0.007 mrem/h <<0.5)
- drink plenty of fluids
- use medical gloves when wiping up blood, urine, stool or vomit and when touching or washing dirty clothes; *(~75% of activity excreted within 1 week, mainly feces)*
- urinate as frequently as possible, while sitting; Flush toilet twice; If any urine splattered, wipe with toilet paper and flush down toilet
- If diarrhea or urinary incontinence, use disposable underwear or diaper pants during first week after each injection
- If cut yourself or vomit, wipe up with toilet paper and flush in toilet
- Underwear worn during the first week after each injection should be washed separately; same applies to bed linen and any clothing soiled with urine, stool or blood (otherwise no need for separation; no salivary/sweat excretion)
- Avoid prolonged contact with pregnant women and small children during first week after each injection; avoid fathering child until 6m post Rx

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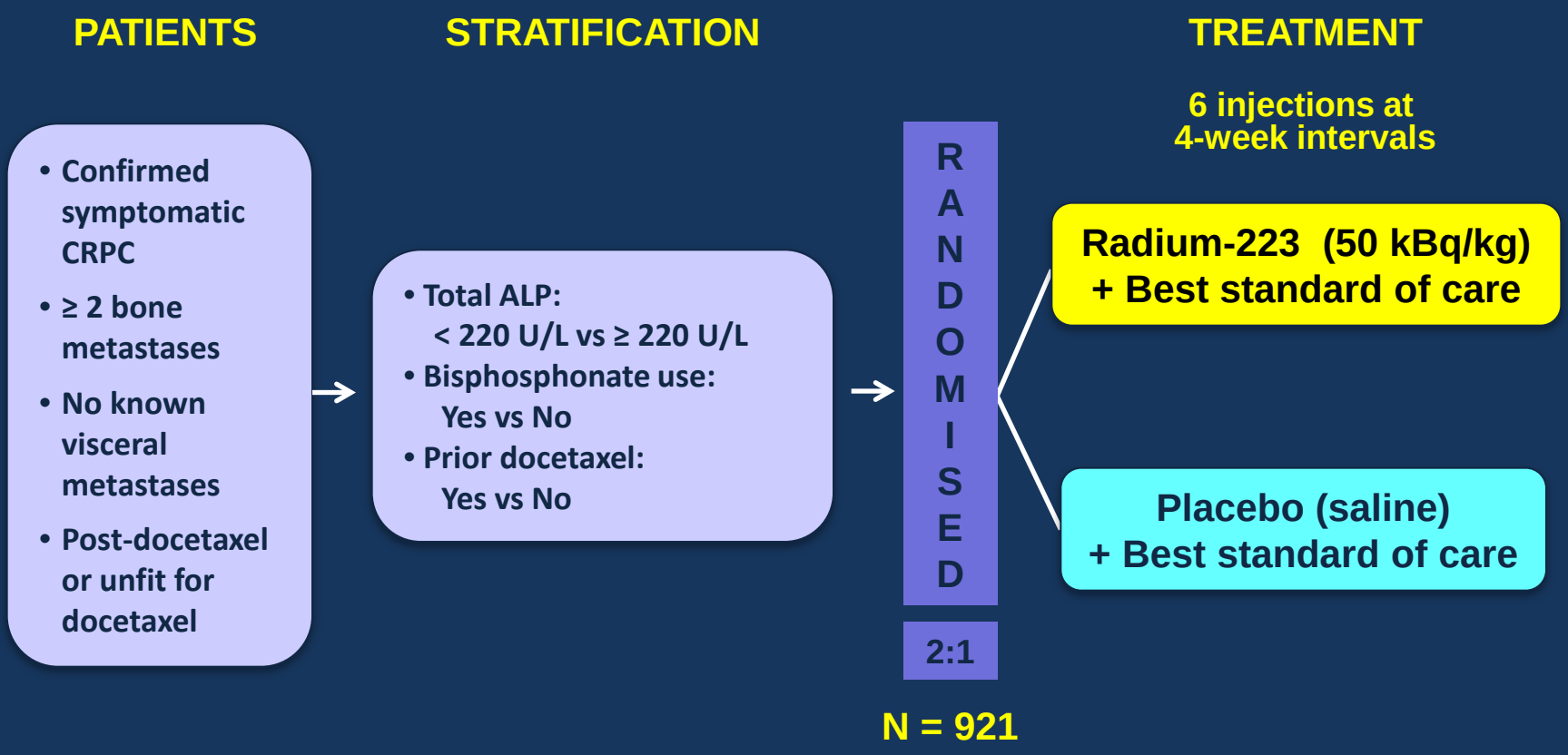
Updated analysis of the phase III, double-blind, randomized, multinational study of radium-223 chloride in castration-resistant prostate cancer (CRPC) patients with bone metastases (ALSYMPCA)

C. Parker,[1] S. Nilsson,[2] D. Heinrich,[3] J.M. O'Sullivan,[4] S. Fosså,[5] A. Chodacki,[6] P. Wiechno,[7] J. Logue,[8] M. Seke,[9] A. Widmark,[10] D.C. Johannessen,[11] P. Hoskin,[12] D. Bottomley,[13] R. Coleman,[14] N. Vogelzang,[15] C.G. O'Bryan-Tear,[16] J. Garcia-Vargas,[17] M. Shan,[17] and O. Sartor[18]

[1]The Royal Marsden NHS Foundation Trust, Sutton, UK; [2]Karolinska University Hospital, Stockholm, Sweden; [3]Akershus University Hospital, Lørenskog, Norway; [4]Centre for Cancer Research and Cell Biology, Queen's University, Belfast, Northern Ireland; [5]Radiumhospitalet, Oslo, Norway; [6]Hospital Kochova, Chomutov, Czech Republic; [7]Centrum Onkologii – Instytut im Sklodowskiej-Curie, Warsaw, Poland; [8]Christie Hospital, Manchester, UK; [9]Centrallasarettet Växjö, Växjö, Sweden; [10]Umeå University, Umeå, Sweden; [11]Ullevål University Hospital, Oslo, Norway; [12]Mount Vernon Hospital Cancer Centre, Middlesex, UK; [13]St. James Hospital, Leeds, UK; [14]Weston Park Hospital, Sheffield, UK; [15]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [16]Algeta ASA, Oslo Norway; [17]Bayer Healthcare Pharmaceuticals, Montville, NJ, USA; [18]Tulane Cancer Center, New Orleans, LA, USA

ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer) Phase III Study Design



Planned follow-up 3 years

Clinicaltrials.gov identifier: NCT00699751

ALSYMPCA Study Endpoints

- Primary Endpoint
  - Overall survival (OS)
- Secondary Endpoints
  - Time to first SRE
  - Time to total ALP progression
  - Total ALP response
  - Total ALP normalization
  - Time to PSA progression
  - Safety
  - Quality of life

ALSYMPCA
Patient Demographics (n = 921)

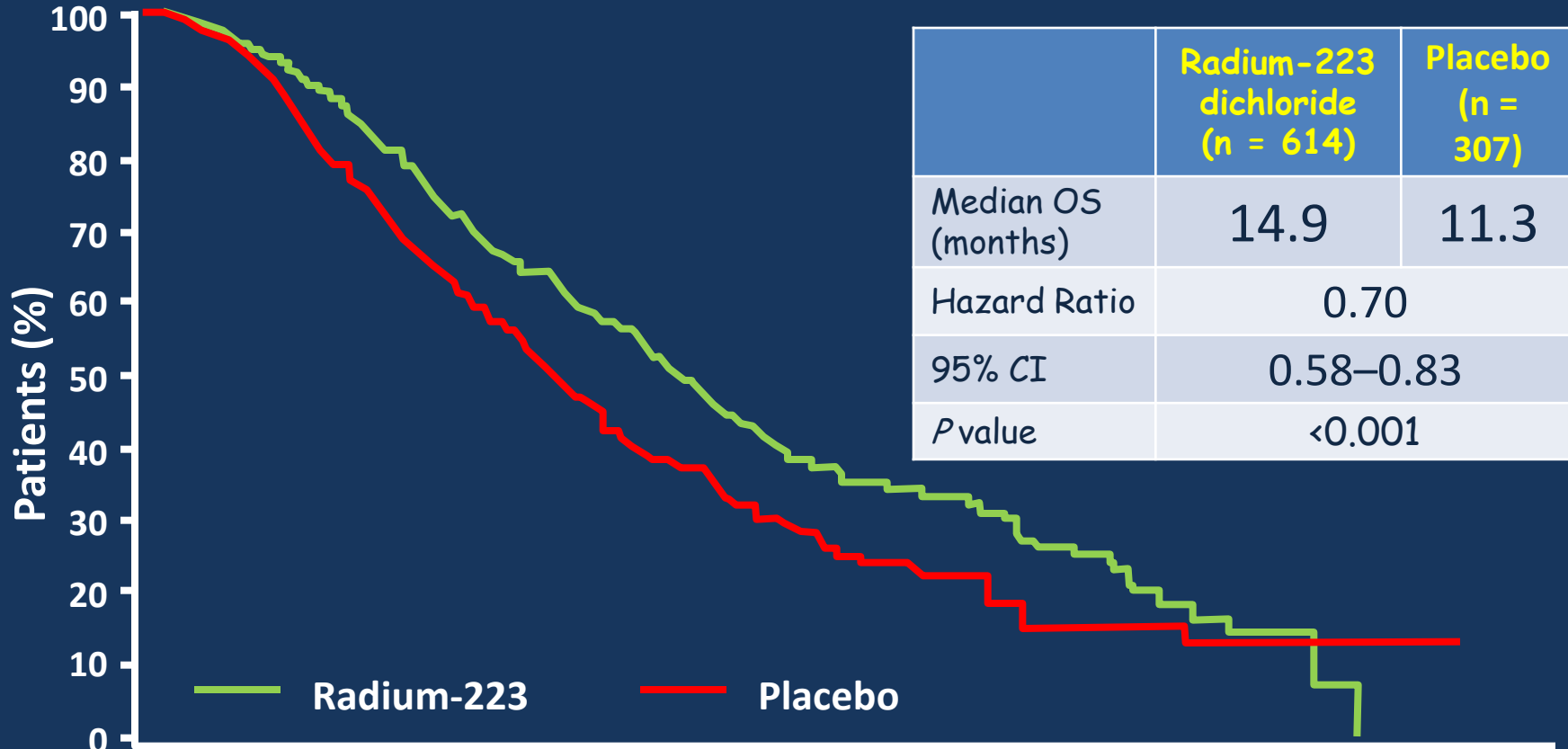
Parameter	Radium-223 n = 614	Placebo n = 307
Age, y		
Mean	70.2	70.8
Race, n (%)		
Caucasian	575 (94)	290 (95)
Baseline ECOG score, n (%)		
≤ 1	536 (87)	265 (86)
2	76 (12)	40 (13)
Extent of disease, n (%)		
< 6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
> 20 metastases/superscan	249 (41)	121 (40)
WHO ladder, cancer pain index ≥ 2, n (%)	345 (56)	168 (55)

ALSYMPCA
Patient Baseline Characteristics (n = 921)

Parameter Median (min, max)	Radium-223 (n = 614)	Placebo (n = 307)
Hemoglobin, g/dL	12.2 (8.5-15.7)	12.1 (8.5-16.4)
Albumin, g/L	40 (24-53)	40 (23-50)
Total ALP, µg/L	211 (32-6431)	223 (29-4805)
LDH, U/L	315 (76-2171)	336 (132-3856)
PSA, µg/L	146 (3.8-6026)	173 (1.5-14500)
Current bisphosphonates Yes, n (%)	250 (40.7)	124 (40.4)
Prior docetaxel Yes, n (%)	352 (57.3)	174 (56.7)

ALSYMPCA: Overall Survival

3.6 month OS benefit



	Radium-223 dichloride (n = 614)	Placebo (n = 307)
Median OS (months)	14.9	11.3
Hazard Ratio	0.70	
95% CI	0.58–0.83	
P value	<0.001	

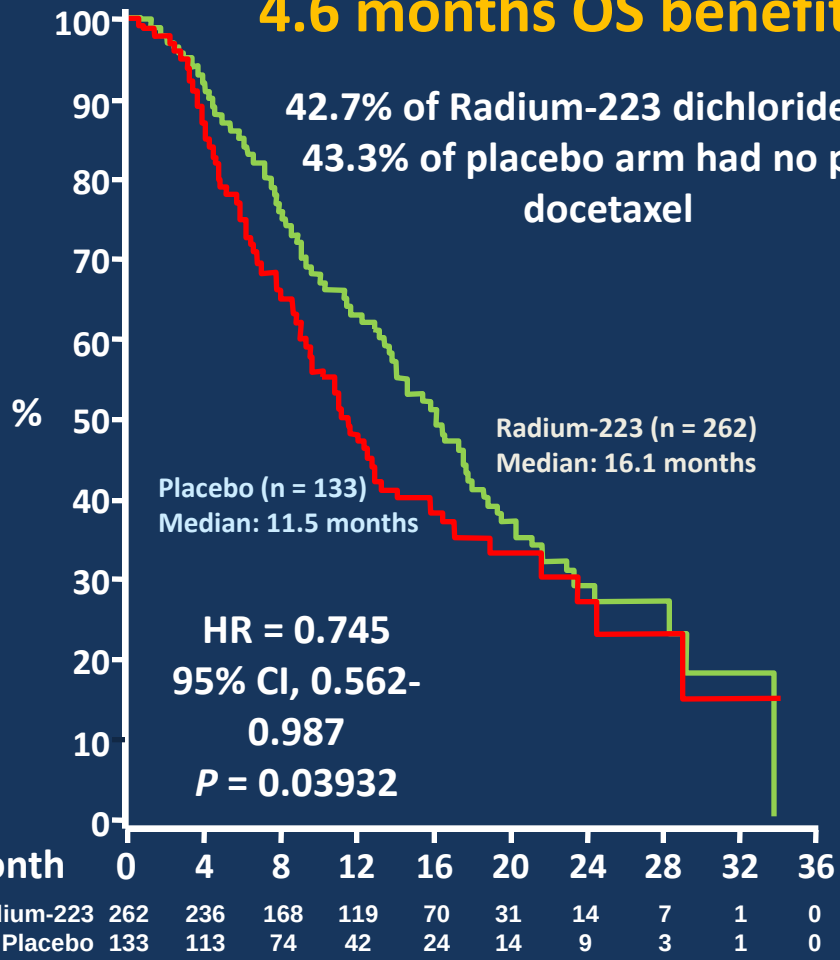
Month	0	3	6	9	12	15	18	21	24	27	30	33	36	39
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

Parker C et all. *New Engl J Med* 2013.

ALSYMPCA : Overall Survival Stratified by Prior Docetaxel Use

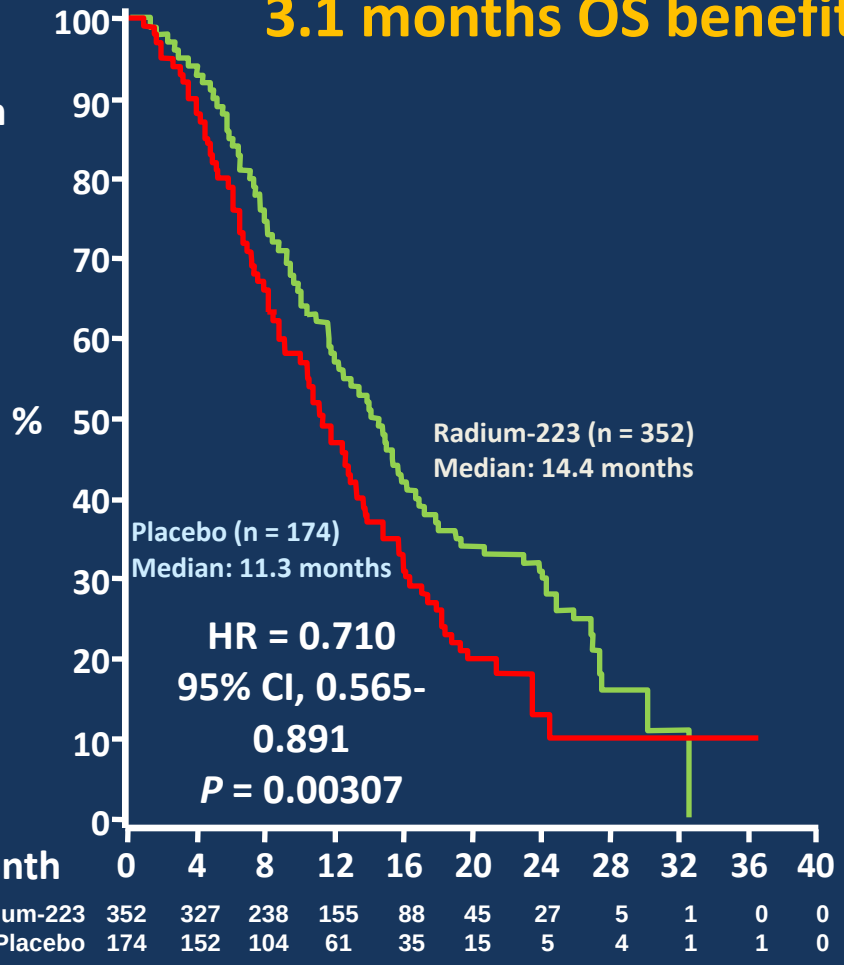
No prior docetaxel use:

4.6 months OS benefit



Prior docetaxel use:

3.1 months OS benefit

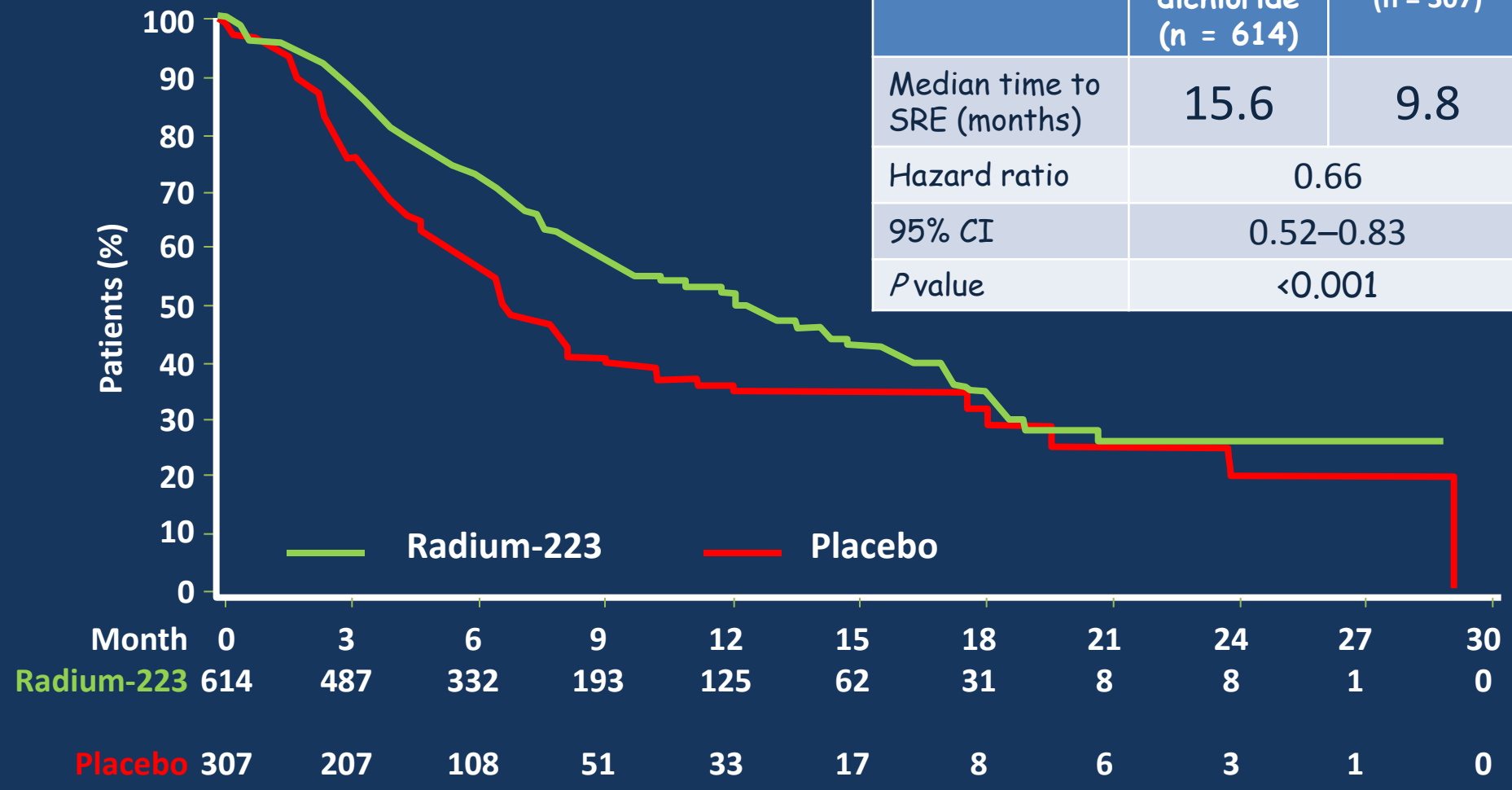


Parker et al. *J Clin Oncol.* 2012; 30(suppl): abstract LBA4512. Presented at ASCO 2012.

ALSYMPCA: Time to First SRE

5.8 month benefit

	Radium-223 dichloride (n = 614)	Placebo (n = 307)
Median time to SRE (months)	15.6	9.8
Hazard ratio	0.66	
95% CI	0.52–0.83	
P value	<0.001	



Parker C et all. *New Engl J Med* 2013.

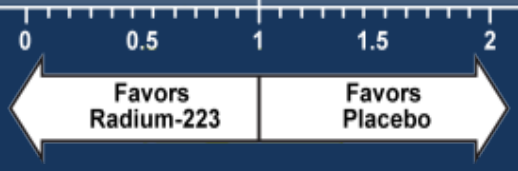
ALSYMPCA: Time to First SRE Components

	N (%) of Events		Time to Event (Radium-223 dichloride vs. Placebo)	
SRE Component	**Radium-223 dichloride (n = 614)**	**Placebo (n = 307)**	***P* value**	**HR (95% CI)**
External-beam radiotherapy	186 (30.3)	105 (34.2)	0.00117	0.67 (0.52-0.85)
Spinal cord compression	25 (4.1)	21 (6.8)	0.025	0.51 (0.28-0.93)
Pathologic bone fracture	32 (5.2)	20 (6.5)	0.09	0.62 (0.35-1.09)
Surgical intervention	12 (2)	7 (2.3)	0.479	0.71 (0.28-1.8)

Sartor et al. *J Clin Oncol.* 2012;30 (suppl): abstract 4551. Presented at ASCO 2012.

ALSYMPCA: Survival Benefit Across Patient Subgroups

Variable	Subgroup	N	HR	95% CI
Overall Survival		921	0.695	0.581–0.832
Total ALP #	< 220 U/L	517	0.825	0.635–1.072
	>= 220 U/L	404	0.619	0.486–0.788
Current Use of Bisphosphonates #	Yes	374	0.699	0.525–0.931
	No	547	0.736	0.587–0.923
Prior Use of Docetaxel #	Yes	526	0.710	0.565–0.891
	No	395	0.745	0.562–0.987
Baseline ECOG Status	0 or 1	801	0.675	0.555–0.821
	2 or Higher	118	0.820	0.498–1.351



Parker et al. *J Clin Oncol.* 2012;30(suppl): abstract LBA4512. Presented at ASCO 2012.

ALSYMPCA: Adverse Events

no clinically meaningful differences in frequency of Grade 3/4 AEs

	All Grades		Grades 3 or 4	
	Radium-223 dichloride (n = 600; %)	Placebo (n = 301, %)	Radium-223 dichloride (n = 600, %)	Placebo (n = 301, %)
Hematologic				
Anemia	187 (31.2)	92 (31)	**77 (13)**	**40(13)**
Neutropenia	30 (5)	3 (1)	**13 (2)**	**2 (1)**
Thrombocytopenia	69 (11.5)	17 (5.6)	**39 (6.5)**	**6 (2)**
Non-hematologic				
Bone pain	300 (50)	187 (62)	**125 (21)**	**77 (26)**
Diarrhea	151 (25)	45 (15)	**9 (1.5)**	**5 (1.7)**
Nausea	213 (35.5)	104 (35)	**10 (2)**	**5 (2)**
Vomiting	111 (18.5)	41 (14)	**10 (2)**	**7 (2)**
Constipation	108 (18)	64 (21)	**6 (1)**	**4 (1)**

Parker et al. *New Engl J Med* 2013.

ALSYMPCA: Summary

Parker C et al. *New Engl J Med* 2013.

- In CRPC patients with symptomatic bone metastases , Radium-223 dichloride vs. placebo:
  - significantly prolonged OS compared with BSC alone by 3.6 months (HR=0.7; *P*=0.001) → 30.5% reduction in risk of death
  - significantly prolonged median time to first SRE compared with BSC alone by 5.8 months (HR=0.66, *P*<0.001)
  - had relatively similar frequency of grade 3/4 AEs (bone pain, anemia) of 57% compared to 63% from BSC alone
  - Common adverse events
    - Non-hematologic: bone pain, nausea, diarrhea, vomiting
    - Hematologic: anemia, thrombocytopenia (no 2nd CA yet)
  - Clinical trials of retreatment with Ra-223 or in combination with either docetaxel, enzalutamide, or abiraterone

Ra-223 provides a new standard of care for the treatment of CRPC with bone metastases; incorporated into updated NCCN Guidelines v3.2013

One-Year Clinical Experience at USC

Jadvar H et al. *Cancer Biother Radiopharm* 2015

- 25 patients with met CRPC receive total of 91 doses
  - 6 patients received all 6 scheduled doses
  - 2 completed 5 doses, 6 received 4 doses, 2 completed 3 doses, 6 patients had 2 doses, 3 patients received one dose
- 9 patients discontinued after receiving at least one dose due to progressive disease
- 5 required blood transfusions (prior to Ra to increase Hgb to 10)
- 5 developed GI symptom; 4 worsening bone pain; 1 developed dermatitis
- Downward trends in serum Alk Phos and PSA in 11 and 5 pts, respectively
- About 25% of cohort completed entire 6-dose regimen; advancing soft tissue disease primary reason for cessation; adverse events mild and manageable; decline in serum bALP more common than decline in PSA

Remaining Issues

- Timing, sequencing, combination and abbreviated therapies
  - Any benefit from incomplete course (< 6 treatments)
  - If used earlier, what will be effect on subsequent therapies (dosing, efficacy, risks)
  - Can higher dosses and cycles be used? (NCT02023697)
  - maximize synergistic clinical efficacy with other therapies
    - 13 D vs 33 D+Ra223 (favorable impact on bALP > PSA declines; NCT01106352) - Morris MJ et al. ASCO 2015 Abstract 5012
  - minimize cross resistance, side effects (adverse events)
  - strive for cost-effective care
- Use in other cancers
  - Hormone-refractory bone-dominant metastatic breast cancer (Takalkar A et al. Exp Hematol Oncol 2014; Coleman R et al. Breast Cancer Res Treat 2014)
  - Osteosarcoma (Anderson PM et al. Adv Exp Med Biol 2014)
- Need for clinical trials and adaptation to individual patients

Targeted Radionuclide Therapy - Prostate Cancer

- 89Sr-chloride and 153Sm-EDTMP (bone pain palliation) - D' angelo QJNMMI 2012
- 223Ra dichloride - Parker, *NEJM* 2013
- 177Lu-labeled anti-PSMA monoclonal antibody 3/F11 (177Lu-DOTA-3/F11) – Behe, *In Vivo* 2011
- 90Y-labeled anti-PSMA J591 antibody - Vallabhajosula, Clin Cancer Res 2005
- 213Bi-labeled anti-PSMA J591 antibody - Li, *PCPD* 2002
- Anti-PSMA liposomes loaded with 225Ac - Bandekar, *JNM* 2014
- 177Lu-labeled GRPr antagonist - Dumont, *JNM* 2013
- 177Lu-labeled RGD-BBN heterodimer - Jiang, Nucl Med Commun 2013
- 188Re-MAG2-RGD-BBN - Cui, *Nucl Med Biol* 2013

PSMA=Prostate Specific Membrane Antigen, GRPr= gastrin-releasing peptide receptor
RGD=Arg-Gly-Asp ; BBN=bombesin

The NIH-SNMMI Summit on Targeted Radionuclide Therapy, Bethesda, MD – March 2013, October 2014

J Nucl Med 2014, 55:337-348; J Nucl Med 2015, 56:1119-1129

Targeted Radionuclide Therapy: Proceedings of a Joint Workshop Hosted by the National Cancer Institute and the Society of Nuclear Medicine and Molecular Imaging

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Overarching Targeted Radionuclide Therapy Goal

- *"Give the right target-radionuclide combination as part of the right "multi-step" treatment strategy to the right patient by the right "provider team" at the right time to achieve the right outcome at the right price"*

Jadvar

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