CURRENT STATUS AND POTENTIAL OF ALPHA-EMITTING RADIOPHARMACEUTICALS

Chaitanya Divgi, MD

crdivgi@gmail.com

NO DISCLOSURES

Objectives

- **Aware of the types of radionuclides with therapeutic potential.**
- **Familiar with the relative therapeutic properties of radionuclides.**
- **Aware of terminology used in radiopharmaceutical therapy, with particular reference to dosimetry and efficacy.**
- **Aware of the nature of alpha-particle radiopharmaceuticals currently in clinical trials/practice.**
- **Aware of challenges and potential, including regulatory issues, of alpha-particle radiopharmaceutical therapy.**

SYSTEMIC RADIOTHERAPY

- The first targeted therapy was I-131 in thyroid disorders
- Principle: Accumulation in specific cells
  - of radioactivity
    - (I-131, Sr-89, Ra-223)
  - of ligands carrying radioactivity
    - (Sm-153 EDTMP, Y-90 Zevalin)

RADIOTHERAPY IN CANCER

Radionuclides with therapeutic potential

- ^{131}I*# $T_{1/2}$ 8 days; ß$^-_{ave}$ 191 KeV
- ^{90}Y# $T_{1/2}$ 2.67 days; ß$^-_{ave}$ 934 KeV
- ^{177}Lu* $T_{1/2}$ 6.7 days; ß$^-_{ave}$ 150 KeV
- ^{67}Cu# $T_{1/2}$ 62 h; ß$^-_{ave}$ 141 KeV
- ^{186}Re* $T_{1/2}$ 3.78 days; ß$^-_{ave}$ 362 KeV
- ^{188}Re* $T_{1/2}$ 17 h; ß$^-_{ave}$ 795 KeV

http://nucleardata.nuclear.lu.se/Database/nudat/

RADIOTHERAPY IN CANCER

Alpha-emitting Radionuclides

Nuclide	T-half	Energy	
		HALIDE	
^{211}At*	7 hrs	7.5 MeV	Conjugation complex; Production fraught. Stable iodine block.
		METAL/lanthanide	
^{213}Bi*	46 mins	8.4 MeV	Chelation chemistry not universally applicable. DOTA most reliable and versatile chelator. Linkers not necessarily required.
^{225}Ac*	10 days	22+ MeV	
^{223}Ra*	12 days	22+ MeV	
^{227}Th*	19 days	27+ MeV	
			** All may be imaged, not high quality*

http://nucleardata.nuclear.lu.se/Database/nudat/

Cytotoxic radionuclides

- Beta emitters
  - I-131
  - Y-90
  - Lu-177
    - Cu-67
    - Re-186; Re-188
  - Deposition of low energy over variable lengths (0.5 – 3 mm)

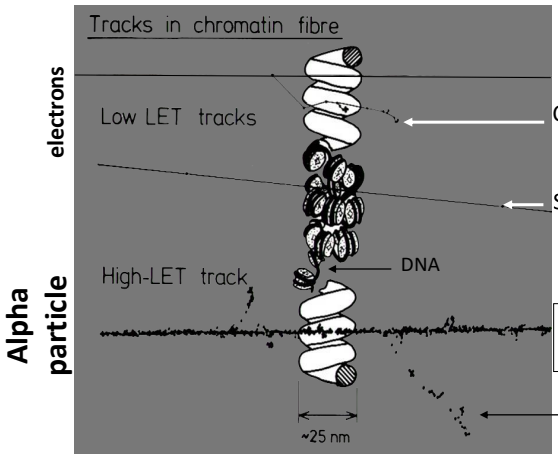
Cytotoxic radionuclides

- **Auger emitters**
  - **Deposition of high energy over VERY short path lengths (1-2 cell diameters).**
- **Alpha emitters**
  - **Bi-213**
  - **At-211**
  - **Ac-225**
  - **Ra-223**
  - **Deposition of high energy over short path lengths (10-50 cell diameters).**

Therapy with alpha-, Auger- and beta-emitting nuclides

- **Auger emission – one cell diameter – for cytoplasmic/intranuclear decay – high LET**
- **Alpha emission – 5-15 cell diameters – for small tumor clusters <200 μ – high LET**
- Beta emission – deposition (function of energy) over several mm. – for established disease – low LET

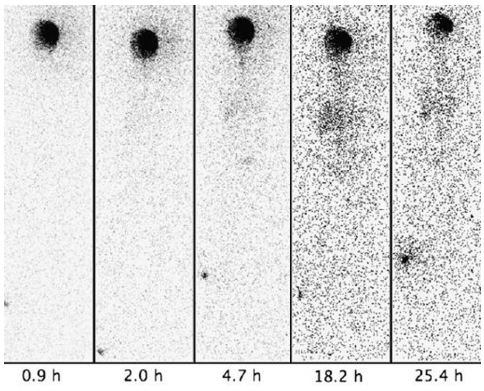
Linear Energy Transfer (LET)



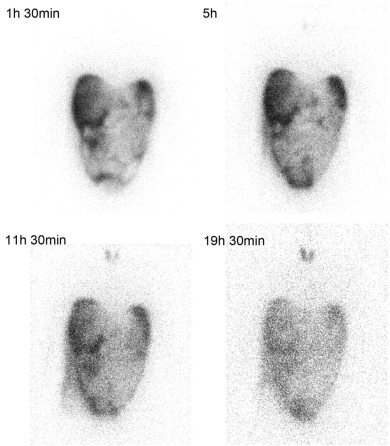
RBE >20

(D.T.Goodhead, CERRIE Workshop 2003)

At-211 labeled antibodies



J. Nucl. Med. 2008; 49:30



J. Nucl. Med. 2009; 50: 1153

CRPC and bone metastases

Prostate cancer is the most bone tropic solid tumor

- **Bone/soft tissue ratios are exceptionally high for metastatic prostate cancer**
- **More than 90% of metastatic prostate cancer (mCRPC) patients have osseous metastases**

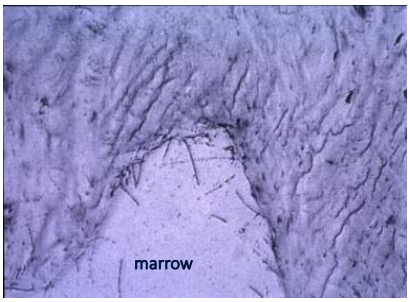
Limitations of β- emitters used for bone metastases

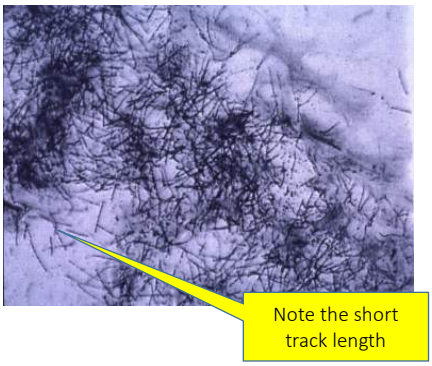
- **Approved only for pain palliation**
- **Toxicity dose-limiting**
  - **May overlap with chemo-toxicity**
- **Hematopoietic toxicity**
  - **Thrombocytopenia**
  - **Usually reversible**
  - **Interval (≥12 weeks) between therapies**
- **No effect on natural course of disease**
  - **When used as monotherapy**

Alpha-particle Radiopharmaceutical therapy in castration-resistant prostate cancer

- Unique opportunity to use radiopharmaceutical therapy in CRPC to
  - EXTEND SURVIVAL
  - Palliate pain
- Safe agent with minimal toxicity
- Universal precautions ALONE sufficient

Ra-223: Preferential Uptake in Lesion Stroma





Ra-223 Emissions

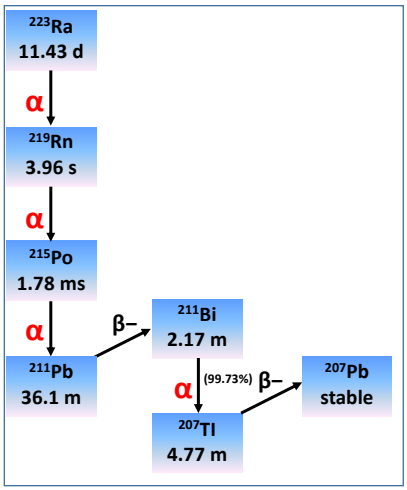
Ra-223 Main Branch

4 α particles

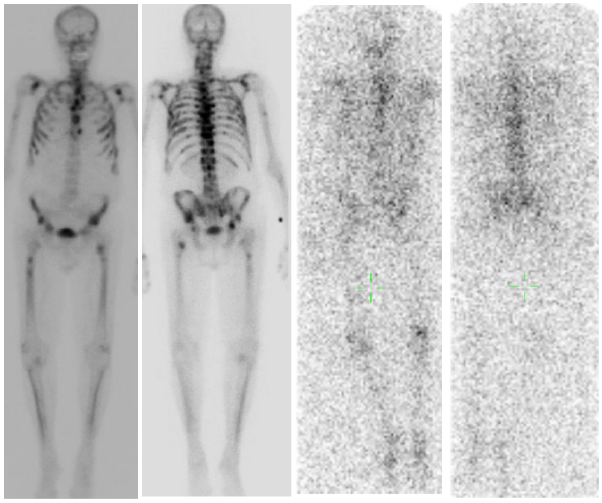
(~28 MeV,~ 95%)

2 β particles

Multiple X/γ particles allow imaging & PK



Ra-223 Imaging



EJNMMI. 2013; 40: 1384

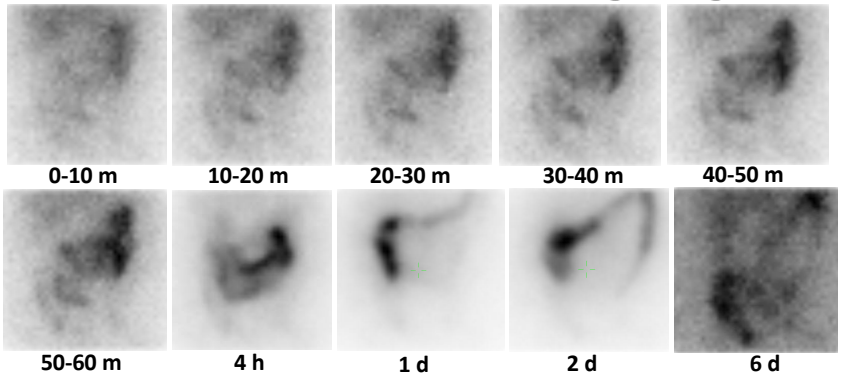
200kBq/kg

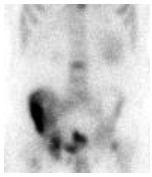
13 MBq (0.36 mCi)

all energy windows combined

Shows very long retention in bone

Ra-223 Imaging



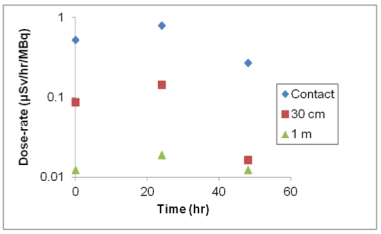


EJNMMI. 2013; 40: 1384

Safety: Dose rates to Public

Administered activities are low
50 kBq/kg (1.3 µCi/kg): (~ 3.5 MBq (95 µCi) for 70 kg patient)
Exposure rates to staff and public from patients undergoing treatment are very low.

Median dose-rate (µSv/hr/MBq)			
Time	Contact	30 cm	1 m
~0	0.52	0.086	0.012
24 h	0.80	0.14	0.019
48 h	0.27	0.016	0.012



(Dose-rate from patient with 444 MBq (12) mCi ^{18}F-FDG ~ 40 µSv/h at 1m)

Dauer L et al, Health Physics 2014

SPECIAL CONTRIBUTION

MIRD Pamphlet No. 22 (Abridged): Radiobiology and Dosimetry of α-Particle Emitters for Targeted Radionuclide Therapy*

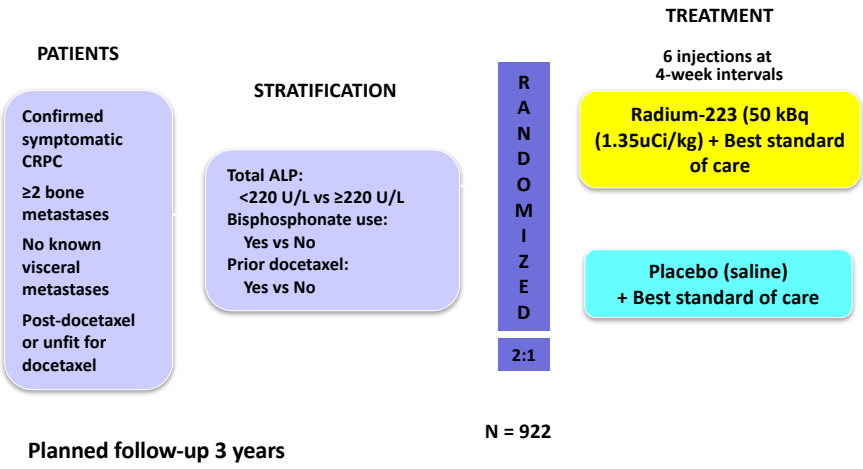
George Sgouros[1], John C. Roeske[2], Michael R. McDevitt[3], Stig Palm[4], Barry J. Allen[5], Darrell R. Fisher[6], A. Bertrand Brill[7], Hong Song[1], Roger W. Howell[8], and Gamal Akabani[9]

In collaboration with the SNM MIRD Committee: Wesley E. Bolch, A. Bertrand Brill, Darrell R. Fisher, Roger W. Howell, Ruby F. Meredith, George Sgouros (Chair), Barry W. Wessels, and Pat B. Zanzonico

[1]Department of Radiology and Radiological Science, Johns Hopkins University, Baltimore, Maryland; [2]Department of Radiation Oncology, Loyola University Medical Center, Maywood, Illinois; [3]Departments of Medicine and Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York; [4]Dosimetry and Medical Radiation Physics Section, International Atomic Energy Agency, Vienna, Austria; [5]Centre for Experimental Radiation Oncology, St. George Cancer Centre, Kogarah, Australia; [6]Radioisotopes Program, Pacific Northwest National Laboratory, Richland, Washington; [7]Department of Radiology, Vanderbilt University, Nashville, Tennessee; [8]Division of Radiation Research, Department of Radiology, New Jersey Medical School Cancer Center, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; and [9]Department of Nuclear Engineering, Texas A&M University, College Station, Texas

J Nucl Med 2010

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

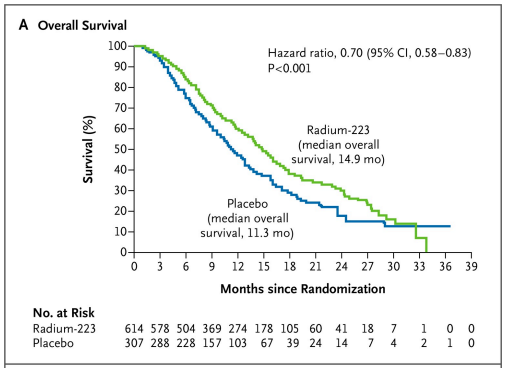


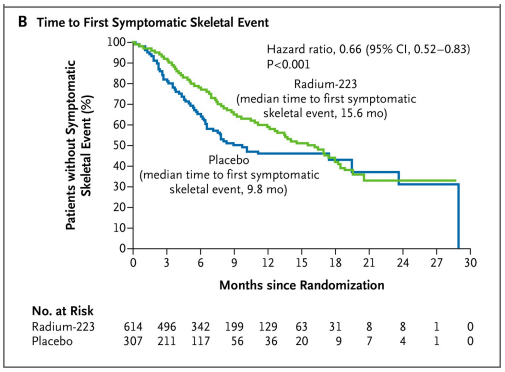
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 18, 2013 VOL. 369 NO. 3

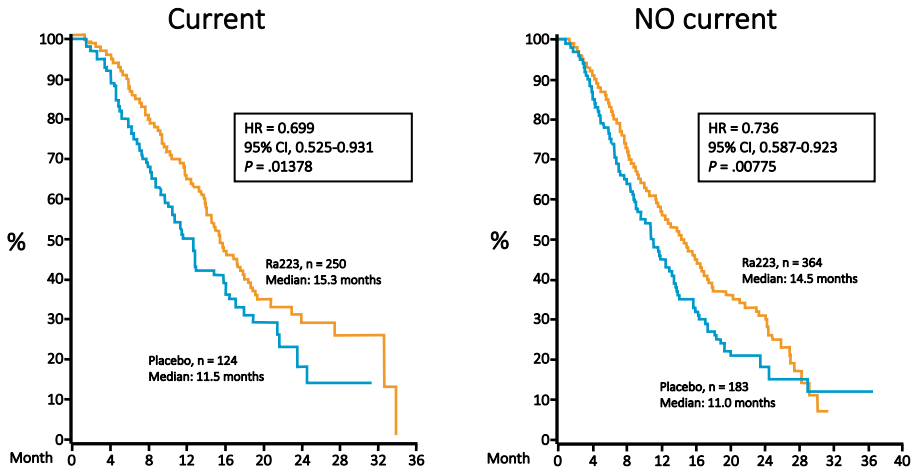
Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fosså, A. Chodacki, P. Wiechno, J. Logue, M. Seke, A. Widmark, D.C. Johannessen, P. Hoskin, D. Bottomley, N.D. James, A. Solberg, I. Syndikus, J. Kliment, S. Wedel, S. Boehmer, M. Dall'Oglio, L. Franzén, R. Coleman, N.J. Vogelzang, C.G. O'Bryan-Tear, K. Staudacher, J. Garcia-Vargas, M. Shan, Ø.S. Bruland, and O. Sartor, for the ALSYMPCA Investigators*





Overall Survival & Bisphosphonate Use



Parker C, et al. *J Clin Oncol.* 2012;30(15S): Abstract 8.

Nuclear Medicine aspects of Ra-223 therapy

- **Safe, easy to administer**
- **Out-patient**
- **Therapy q4weeks x 6 (~6 months total)**
  - **Unless other therapy initiated for PoD**
- **Hematologic toxicity comparable to placebo**

Logistics

- Verify measurable/evaluable disease
- Verify adequate hematologic parameters
  - ANC >1.5, Plt >100K, Hgb >10 *recommended*
- NO radiation safety directions/isolation
  - Plastic gloves adequate for shielding
- Imaging possible
  - Poor quality
    - Targeting demonstrable
  - Bowel significant

No deleterious effects precluding subsequent therapy

- Post-hoc analysis (Sartor et al) of 147 patients who received therapy after Ra-223 or placebo
  - Similar toxicity
  - Similar overall survival

Licensing issues: 10CFR Part 35

- Facility license amendment for Ra-223 (Z=88)
- 35.300 – Use of unsealed product for which a written directive is required
  - Physicians already authorized to parenterally administer therapeutic radiopharmaceuticals for medical use under § 35.396
  - United States NRC. Notice of Licensing decisions on radium-223 dichloride (FSME-13-002). January 10, 2013.

http://pbadupws.nrc.gov/docs/ML1300/ML13008A149.pdf

ALSYMPCA Conclusions

In CRPC patients with bone metastases

- Radium-223 significantly prolongs
  - Overall Survival
    - *P* value = .00185; HR = 0.695; 95% CI, 0.552-0.875
  - Time to first clinically relevant SSE
    - *P* value = .00046; HR = 0.610; 95% CI, 0.461-0.807
- Radium-223 is very well tolerated
  - (Hematologic) Toxicity comparable to placebo

Conclusions

FDA & NRC – making Ra-223 easy
Rapid blood clearance
    Little or no urinary excretion
Rapid targeting to bone
Slow clearance via the gut – fecal excretion
Little or no redistribution from Ra-223 decay site
No requirement for written directive
Very low dose-rates to staff and public

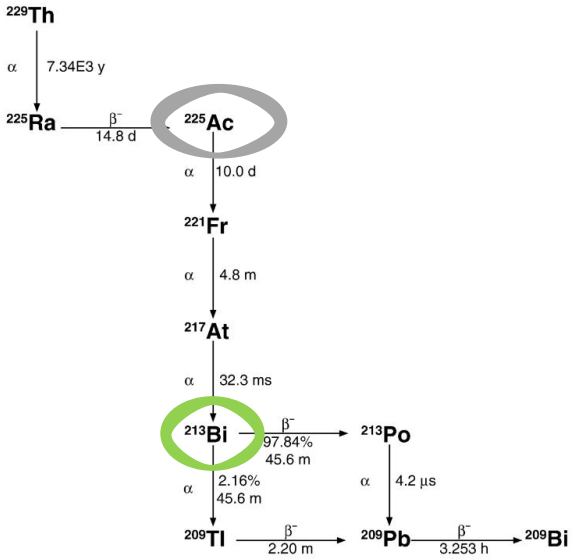
Overall Conclusions

- Ra-223, a bone-targeting alpha emitter, has been demonstrated to prolong survival in CRPC
  - Therapy is safe, convenient, and out-patient
  - Side effects are reversible
  - Therapy is effective regardless of past/current therapy, and does not preclude future therapy
- Future directions include combination therapies

Ra-223 therapy in CRPC

- Opportunity for Nuclear Medicine physicians to rejuvenate radiopharmaceutical therapy
- Work closely with referring clinician to manage the patient over a 6-month period to assess
  - Toxicity
  - Performance status
  - Quality of life

Actinium-225

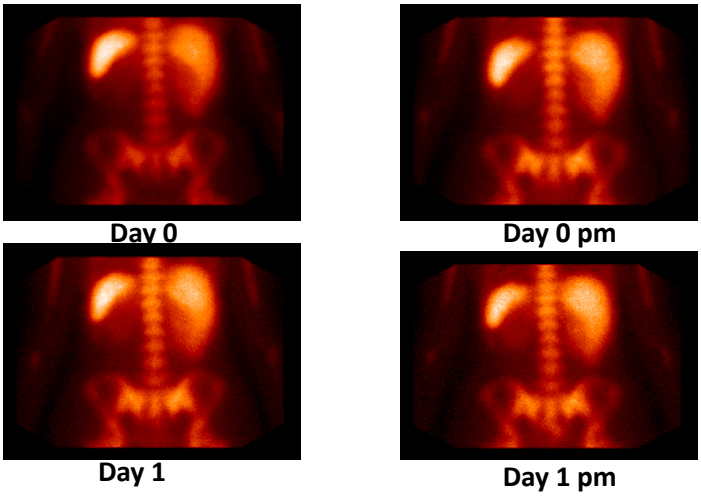


HuM195 Blast Targeting Model

Antibody binds to all targets not only those in the marrow

Time dependent labeled ^{213}Bi-HuM195 activity distribution between spleen, liver and marrow

Bi-213 gammas (~440 KeV)



Clin Cancer Res. 2010; 16: 5303

Actimab-A Phase 1 – Safety

In advanced age patients with high risk factors Actimab-A was safe with low mortality and few side effects

- **Patients treated at 4 dose levels**
- **No early mortality at 28 days from treatment start**
- **56 days early mortality 11% (2 of 18 patients)**
- **MTD not reached**
- **2 DLTs**, one each at 1 µCi/kg/fraction (1/6) and 2 µCi/kg/fraction dose level (1/6)
  - Patient treated at 1 µCi/kg/fraction had late recovery and achieved CR and long term survival (3 years plus), patient treated at 2 µCi/kg/fraction too early to tell
  - 1 DLT was G4 thrombocytopenia and 1 DLT G4 leukopenia
- **No extramedullary DLTs**
- As expected in this group of older patients with high risk factors, all but one patient experienced SAEs
  - **Most SAEs were expected consequences of AML: infections and cytopenias**
  - SAEs other than infection and cytopenia related were observed in one patient each across dose levels (no discernible trend)

Actimab-A Phase 1 Efficacy

Actimab-A showed significant efficacy in patients with very limited treatment options

- **18 patients (median age, 77 years; range, 68-87 years) completed therapy**
  - **14 (78%) 75 and older**
  - **5 (28%) 80 and older**
  - **12 (67%) had prior MDS**
  - **9 (75%) had prior therapy (8 HMA, 1 allo-SCT)**
  - **11 (67%) had intermediate-risk and 7 (33%) had unfavorable cytogenetics**
- **4 out of 5 responses were seen at two highest dose levels (4/9 treated patients)**

Response	Dose Level (µCi/kg/fraction)				Total (n=18)	Total 1+ (n=15)
	0.5 (n=3)	1 (n=6)	1.5 (n=3)	2 (n=6)		
CR/CRp/CRi	0	1 (17%)	2 (67%)	2 (33%)	5 (28%)	5 (33%)

Impact of PB Burden – Phase 1 Trial

*Improved dose response observed in patients with low **peripheral blast** burden*

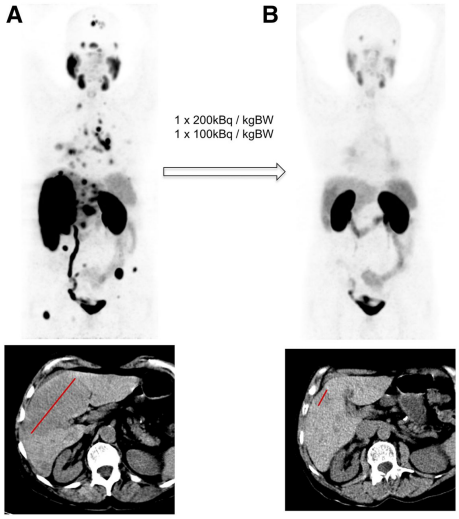
Fractionated dose & LDAC

Dose level	µCi/kg	Pts #	CRc	DLTs
1	2 x 0.5	3	0%	-
2	2 x 1	6	17%	1
3	2 x 1.5	3	67%	-
4	2 x 2	6	33%	1

Fractionated dose & LDAC – low PB only

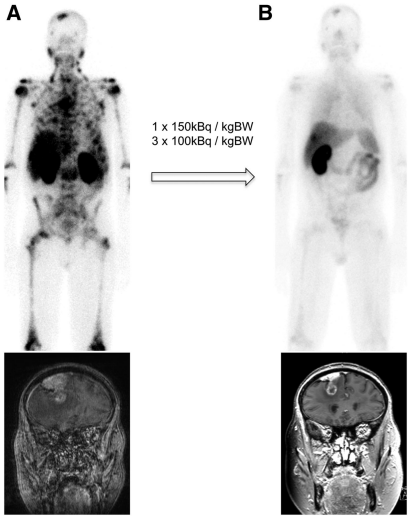
Dose level	µCi/kg	Pts #	CRc	DLTs
1	2 x 0.5	1	**0%**	-
2	2 x 1	3	**33%**	1
3	2 x 1.5	3	**67%**	-
4	2 x 2	4	**50%**	1

^{225}Ac-PSMA-617 in CRPC



Kratochwil et al. J Nucl Med 2017;58:1624-1631

^{225}Ac-PSMA-617 in CRPC



Kratochwil et al. J Nucl Med 2017;58:1624-1631

Alpha-radiopharmaceutical therapy

- High linear energy transfer (LET) produces irreparable DNA strand breaks
- Short path length minimizes off-target radiation
- Potential therapeutic radioactivity window without dose-limiting toxicity
- Minimal radiation safety precautions

- Off-target binding
- Daughter nuclides
- Dosimetry estimates
- Radiochemical features

Conclusions

- Ra-223 prolongs survival in mCRPC
- Bi-213 anti-CD33 mAb has shown significant responses in CML
  - Ac-225 Actimab-A® Phase 2 ongoing
- Ac-225 anti-PSMA small molecules have shown dramatic responses in mCRPC

- EFFICACY WITH MANAGEABLE TOXICITY
- CONVENIENT AND SAFE ADMINISTRATION