FMU-ICRP Workshop on Radiological Protection in Medicine

"Current Status in Radionuclide Therapy"

Tuesday, October 3, 2017

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Kindai University Faculty of Medicine, Osaka, Japan

Current Status in Radionuclide Therapy

- Prologue
- Conventional RNT
- Radium-223 dichloride
- Theranostic approach
  - ✓ Somatostatin Receptor Radionuclide Therapy
  - ✓ Prostate-specific membrane antigen (PSMA ligands)
  - ✓ Hematology
  - ✓ Hypoxia (Cu-64 ATSM)
- Targeted Alpha-Particle Immunotherapy
- Pretargeting: how to enhance tumor-to-normal

Kawamata town, Fukushima

Population: 15,352 (as of May 1, 2011)
Industry: Silk Products, Chicken, IT Products

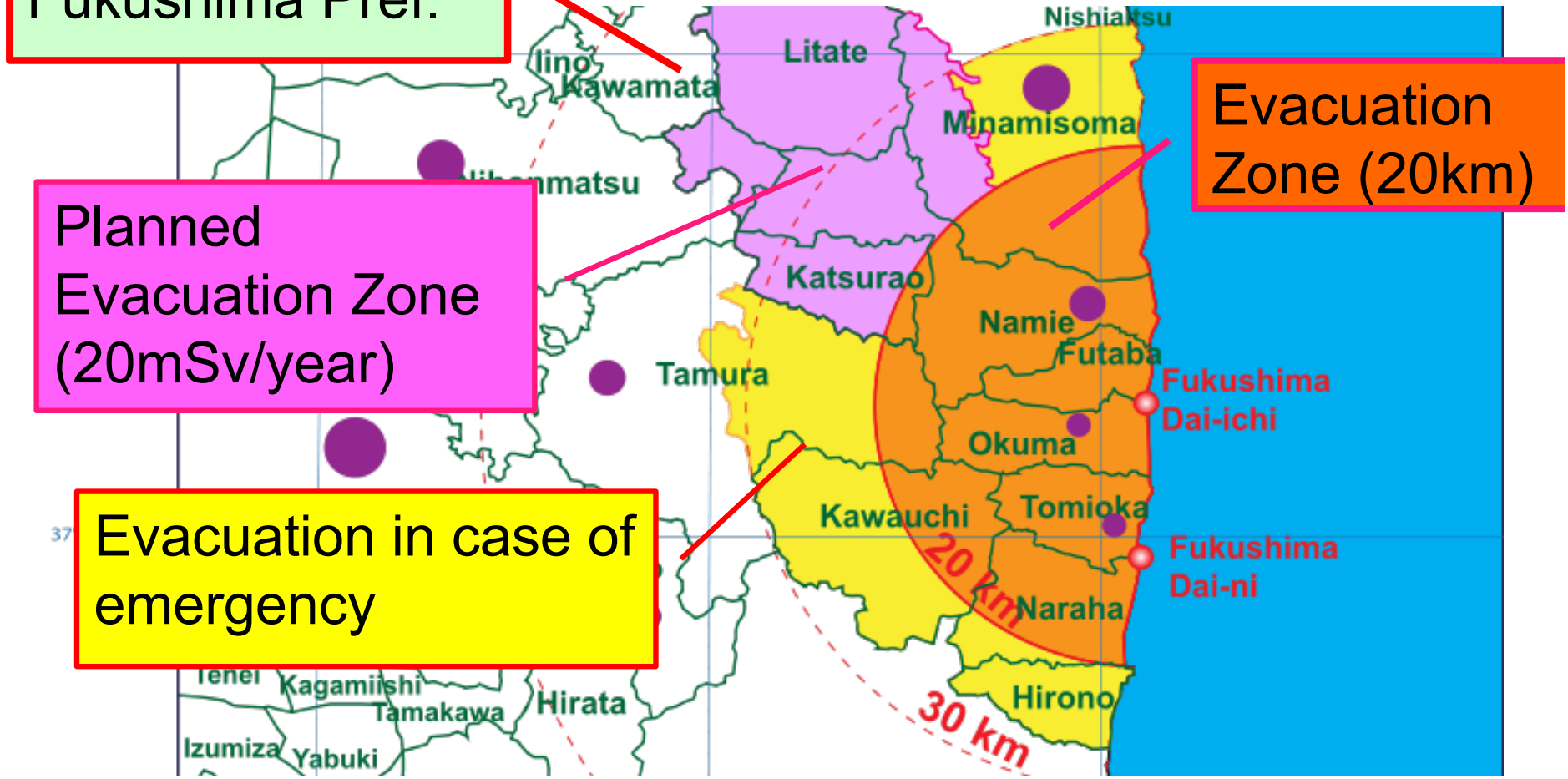
Collaboration with Kindai University for Reconstruction from Disaster and Protection of Children

Silk Products

Chicken

Kawamata town

Kawamata town, Fukushima Pref.

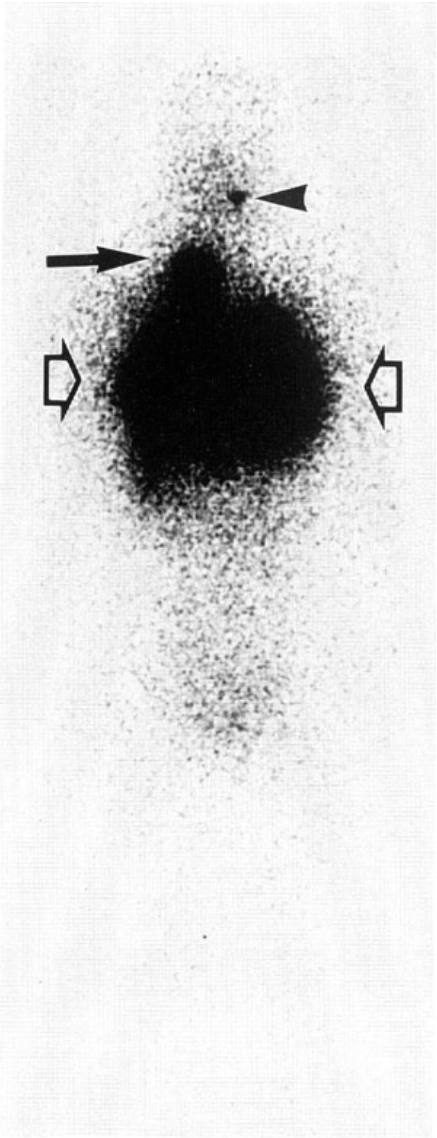


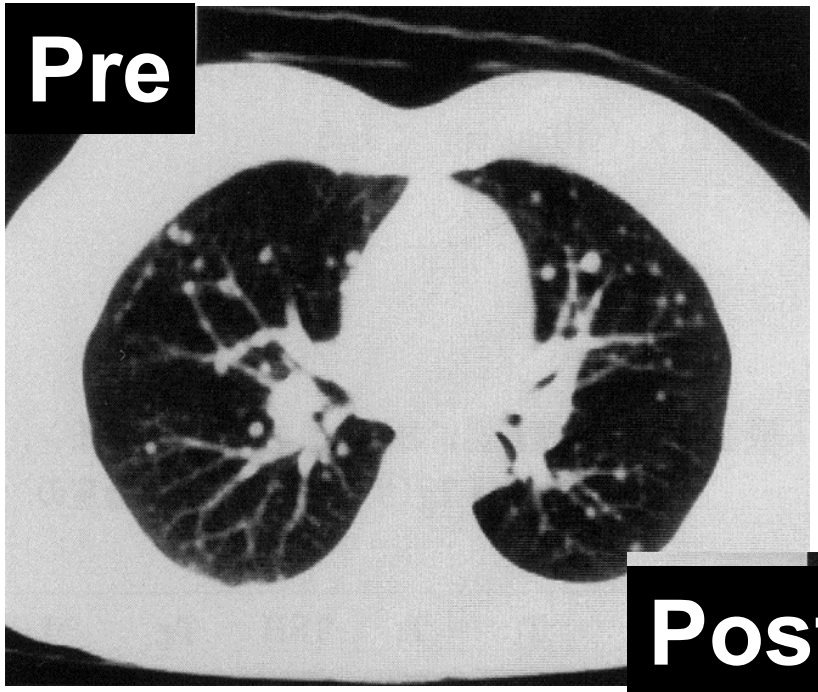
Planned Evacuation Zone (20mSv/year)

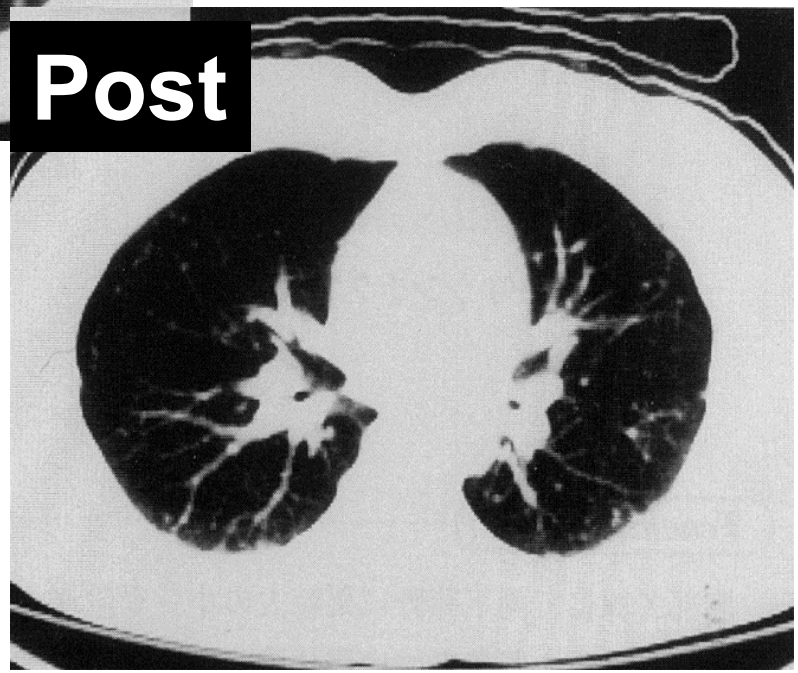
Evacuation Zone (20km)

Evacuation in case of emergency

^{131}I Therapy for Thyroid Cancer



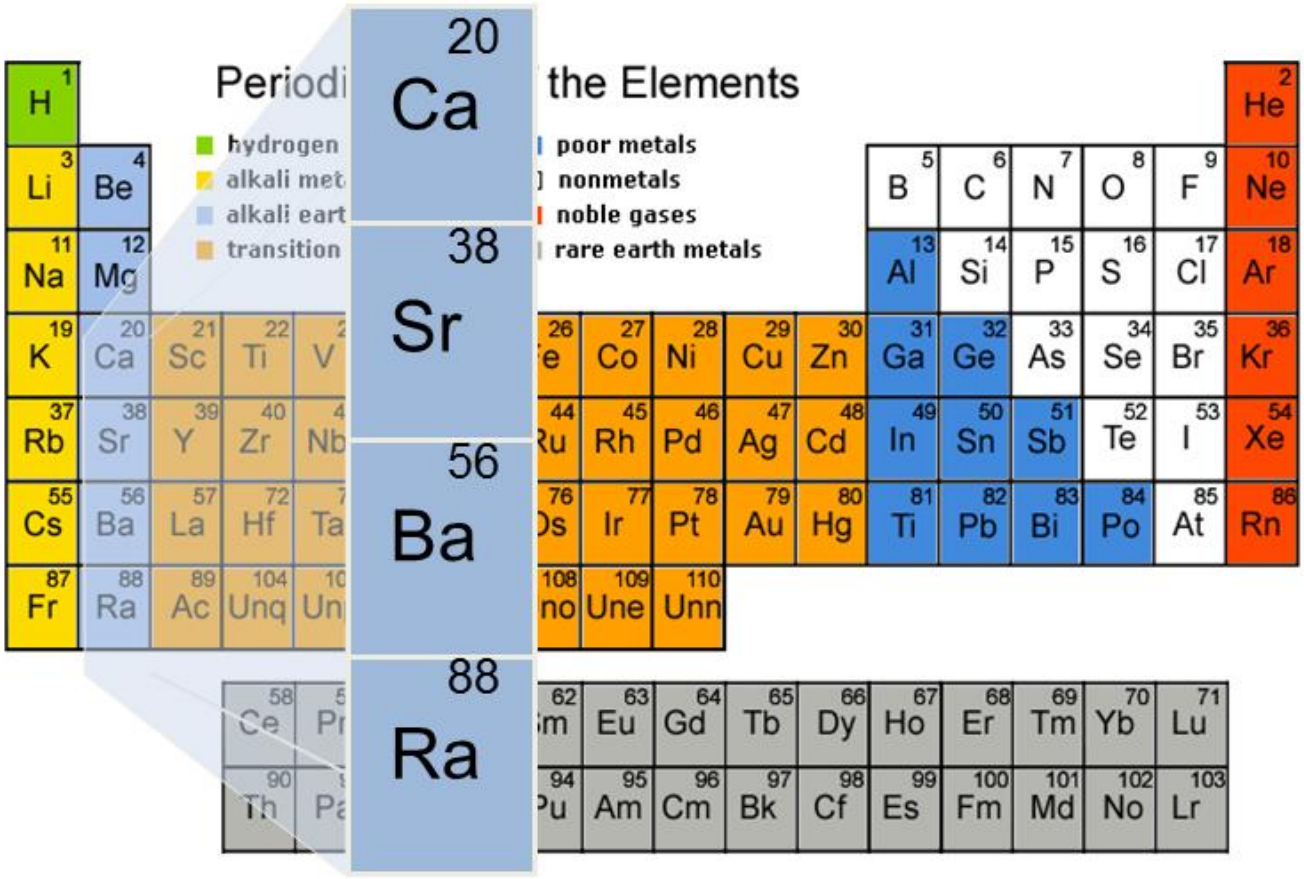




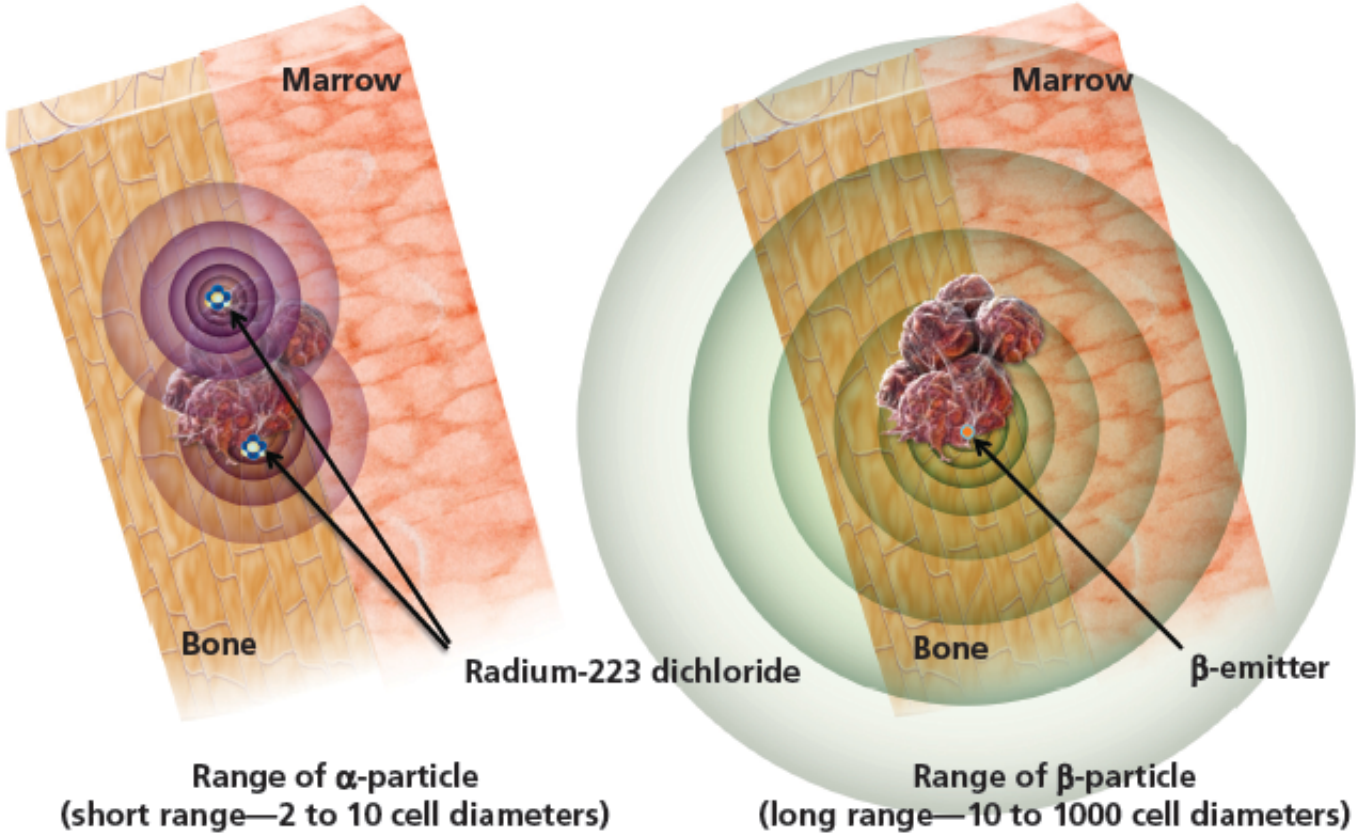
^{131}I Therapy in Shanghai Hospitals

Radium-223 Dichloride for Treatment of Bone Metastases

Radium is alkaline earth as Calcium.



Comparison of Radium-223 and Beta-Emitting Radioactive Therapeutic Agents

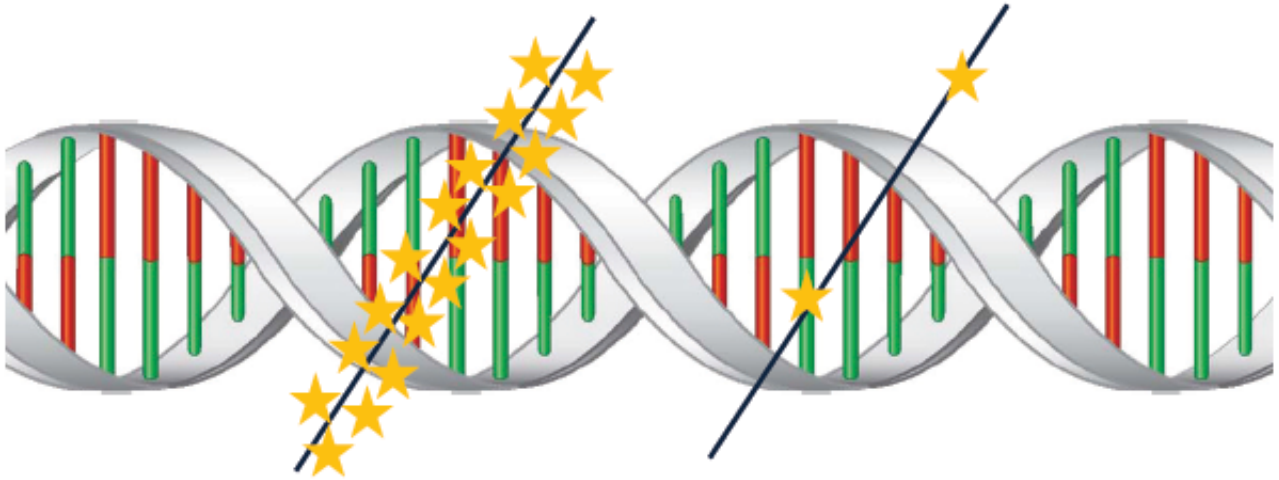


Note: image portrays relative ranges of alpha- and beta-particles, which are not drawn to scale.

Alpha-particles have a much shorter range of action than beta-particles (such as strontium-89 and samarium-153), permitting more selective cancer cell killing and less bone marrow toxicity

Parker C et al. ESMO 2013 Abstr. 2.878

Radiation Effects of Alpha-Particles Versus Beta-Particles on DNA

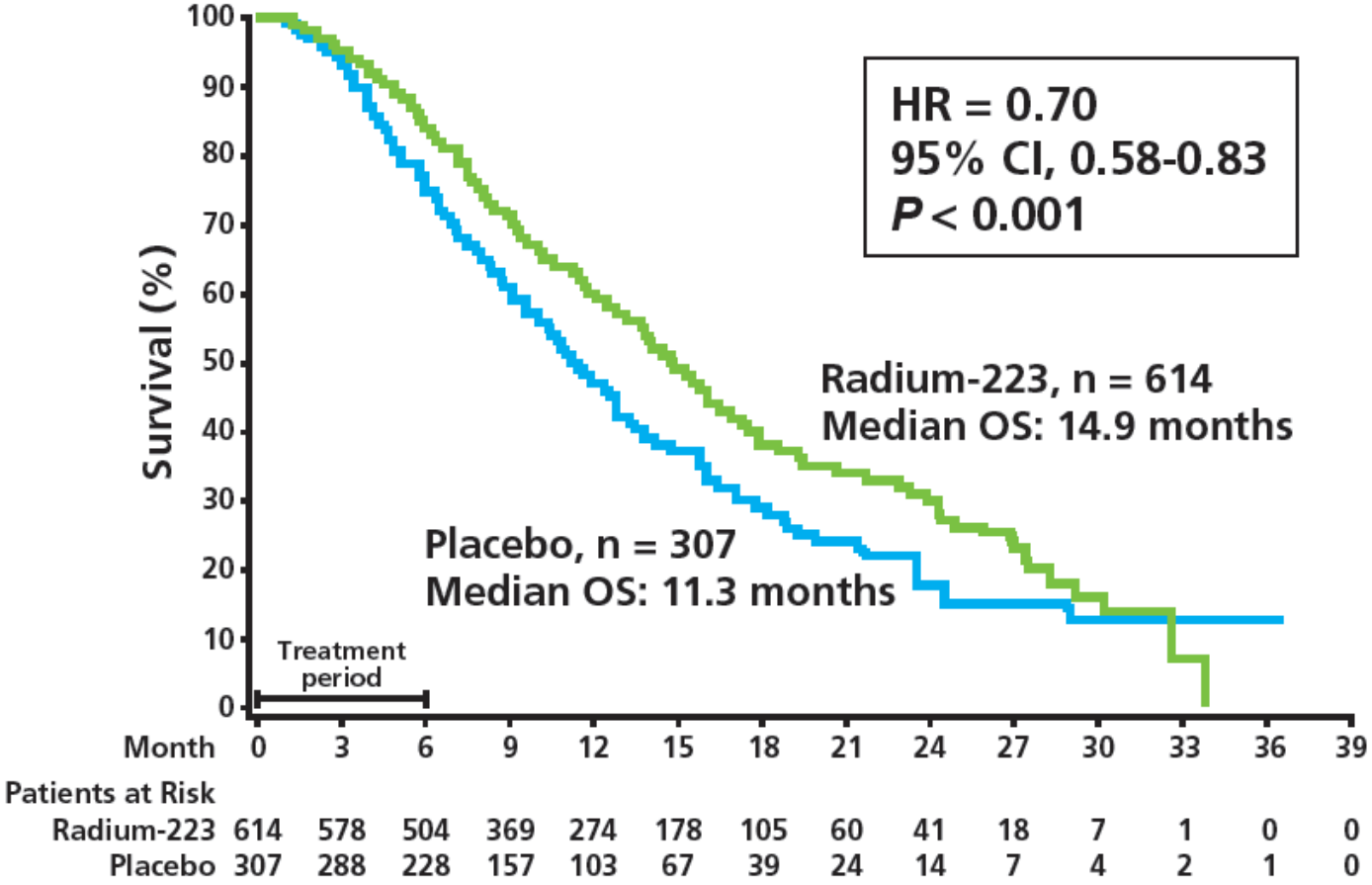


α-particles	β-particles
• High linear-energy transfer	• Low linear-energy transfer
• Double-strand DNA breaks	• Single-strand DNA breaks
• Lethal, difficult to repair	• Repairable

The high linear-energy transfer (LET) radiation produced by alpha-particles induces double-strand DNA breaks in adjacent tumor cells and is more effective at killing cancer cells than the low-LET radiation produced by beta-particles

Parker C et al. ESMO 2013 Abstr. 2.878

ALSYMPCA
Overall Survival in Patients with CRPC and Symptomatic Bone Metastases

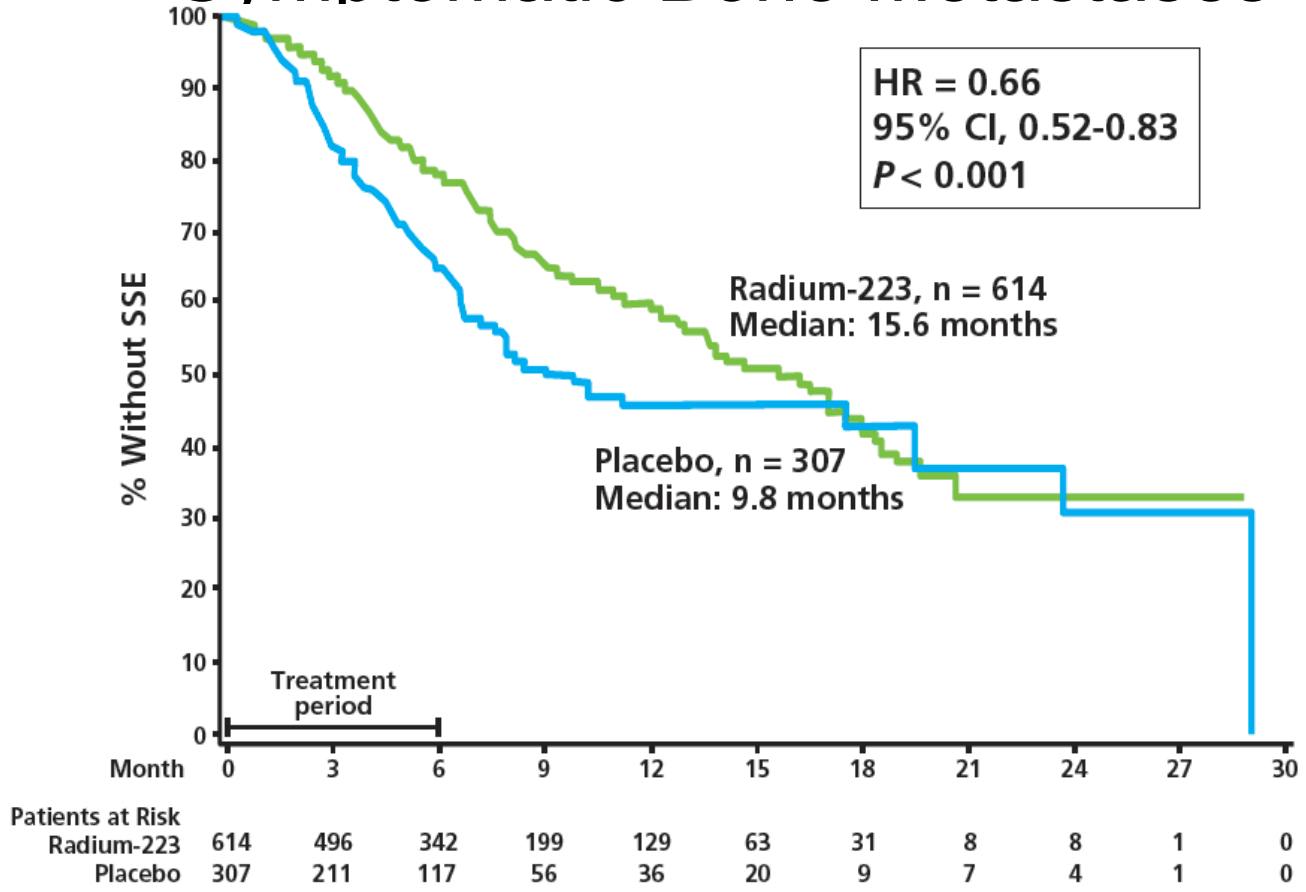


In an updated analysis of ALSYMPCA, radium-223 significantly improved OS by 3.6 months versus placebo

P value is for descriptive purpose only.

Parker C et al. ESMO 2013 Abstr. 2.878

ALSYMPCA
Time to First SSE in Patients With CRPC and Symptomatic Bone Metastases

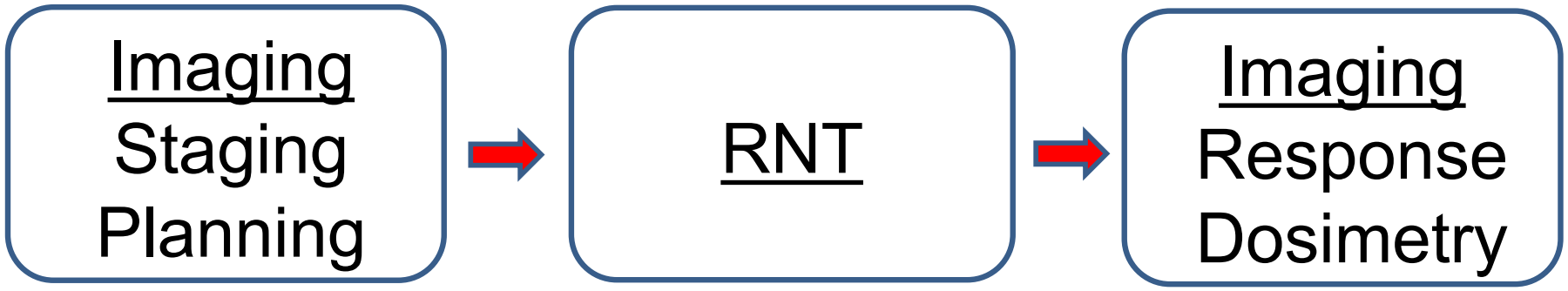


- In ALSYMPCA, radium-223 significantly improved time to first symptomatic skeletal event (SSE) versus placebo
- SSEs included only clinically relevant pathologic bone fractures, not asymptomatic compression fractures

P value is for descriptive purpose only.

Parker C et al. ESMO 2013 Abstr. 2.878

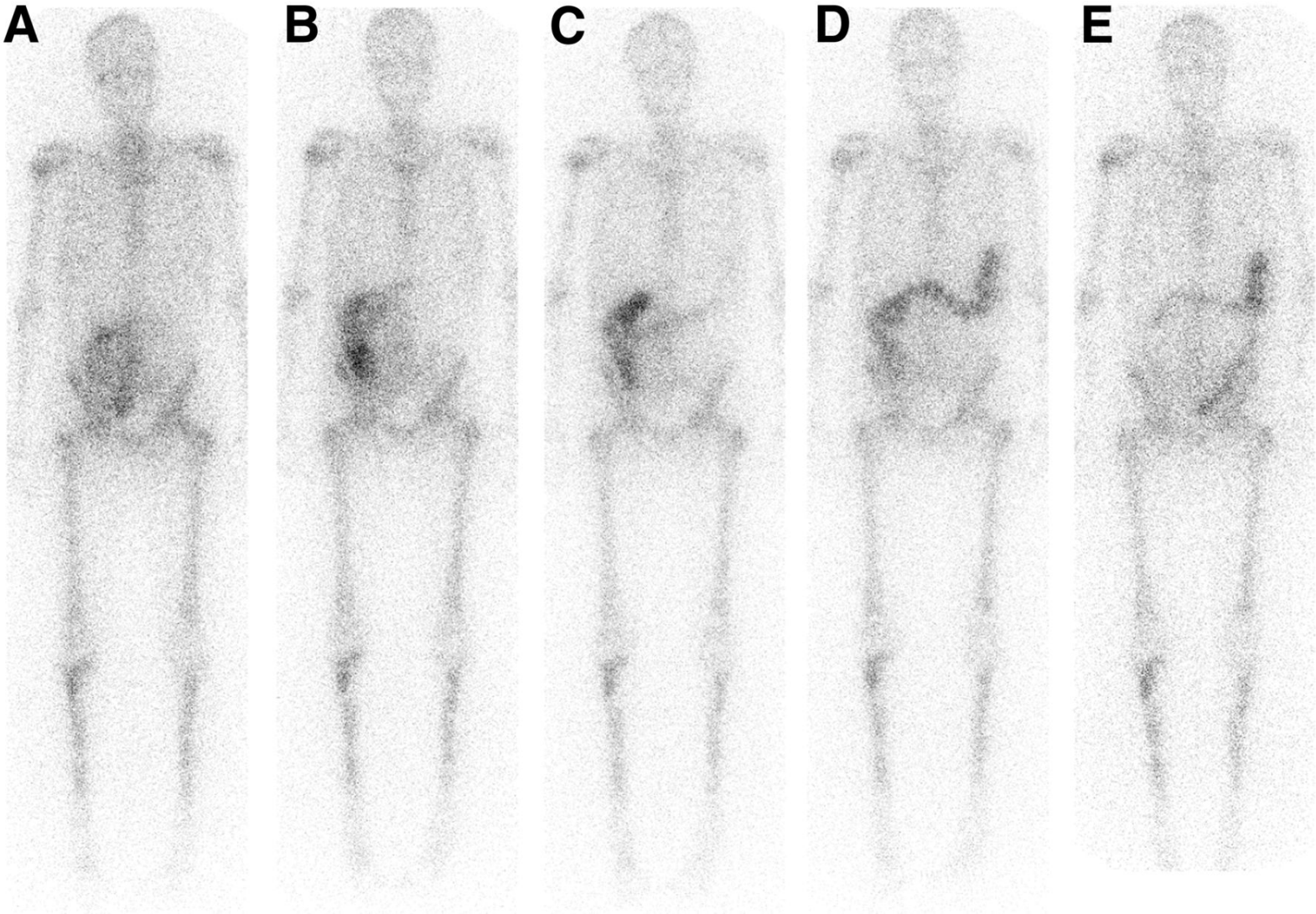
Theranostic approach
Imaging, RNT, and Imaging



RI

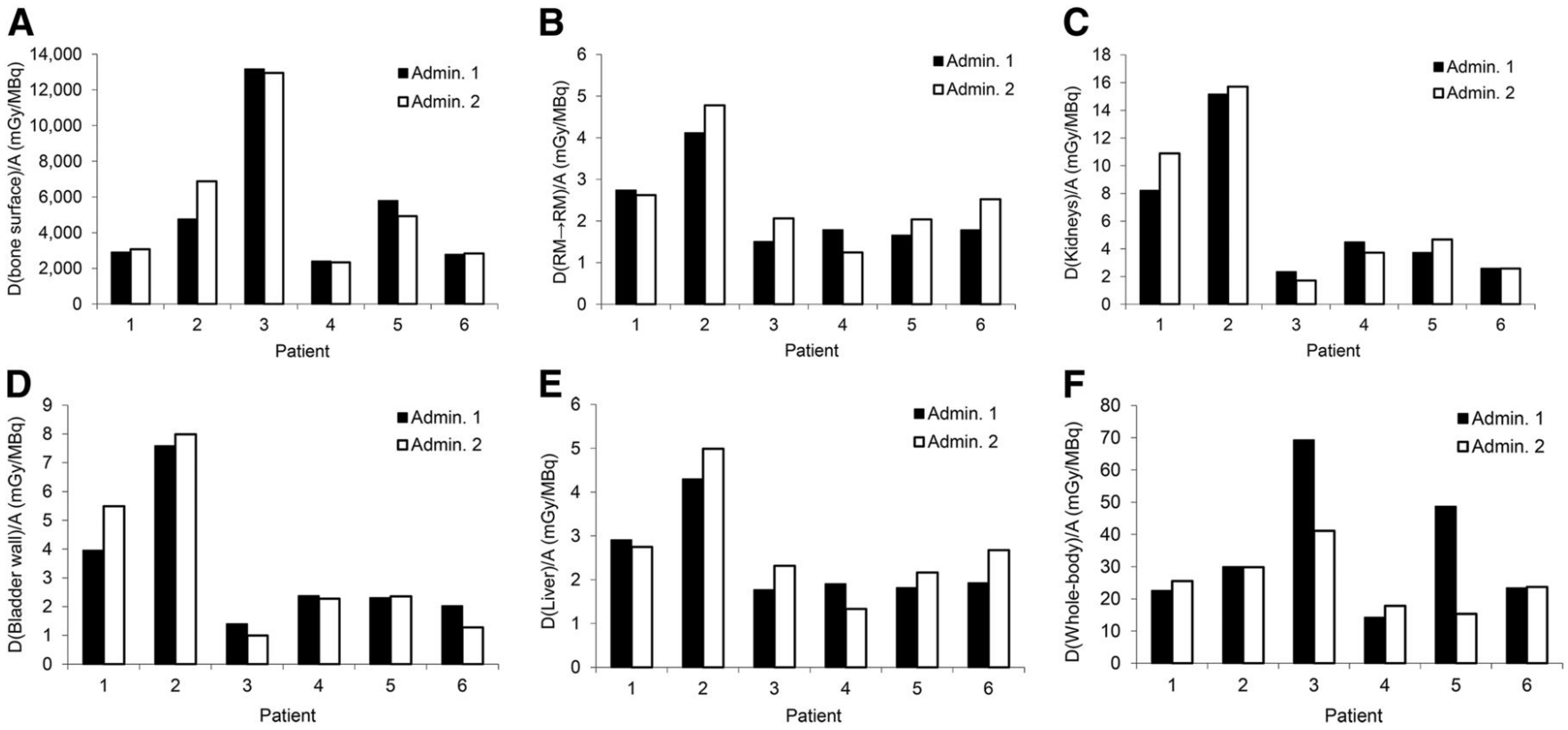
PET/CT

SPECT or SPECT/CT



Whole-body anterior images for patient 3 acquired at 4 (A), 24 (B), 48 (C), 72 (D), and 144 h (E) after administration. Sarah J. Chittenden et al. J Nucl Med 2015;56:1304-1309

JNM The Journal of NUCLEAR MEDICINE



Now: Standard 55kBq/kg x 6 injections (every 4 weeks)
Future: Individualized protocol based on dosimetry

Absorbed dose (in mGy/MBq) for bone surfaces (A), red marrow from blood (B), kidneys (C), bladder wall (D), liver (E), and whole body (F). Sarah J. Chittenden et al. J Nucl Med 2015;56:1304-1309

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Somatostatin Analogs for Treatment of Neuroendocrine Tumors

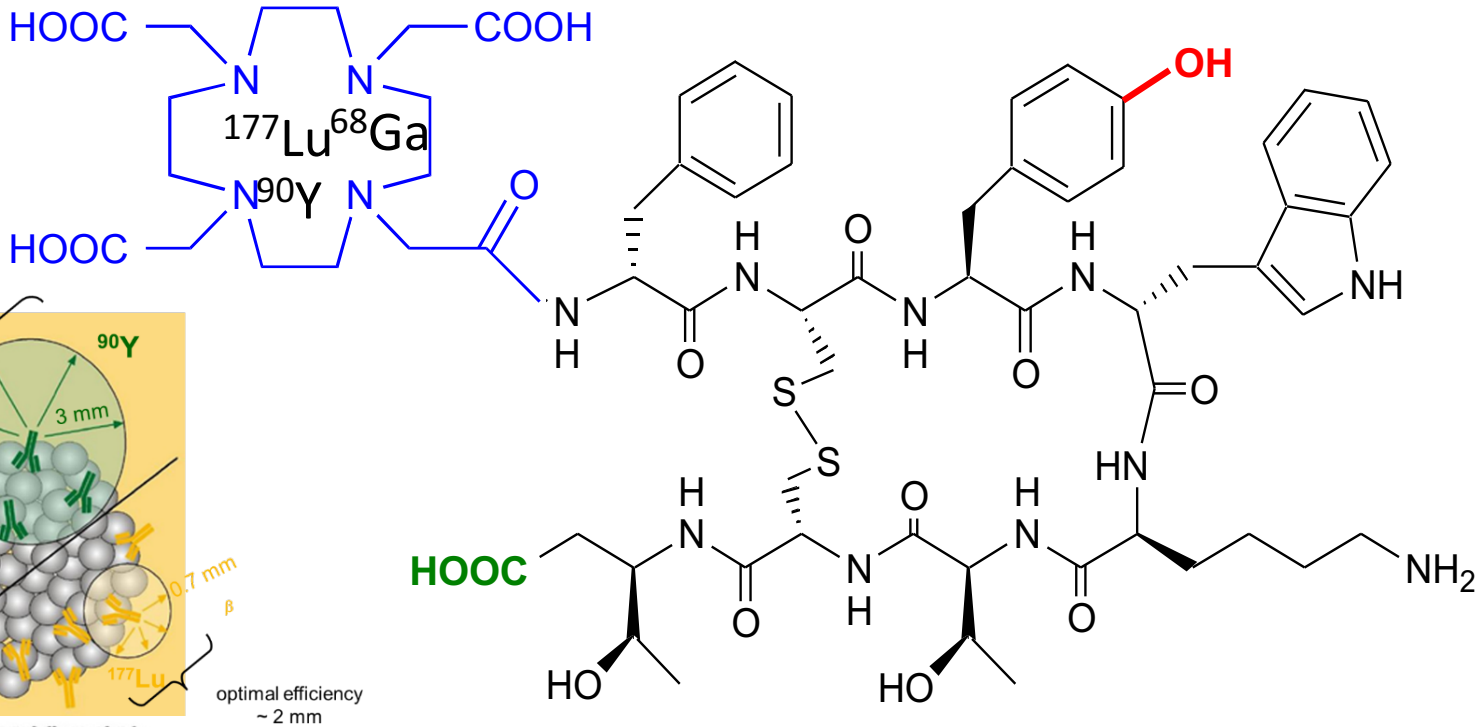
DOTA-OC

DOTA-TOC

DOTA-TATE

P. Powell and H.R. Mäcke

^{111}In-DTPA-octreotide: FDA approval in 1994



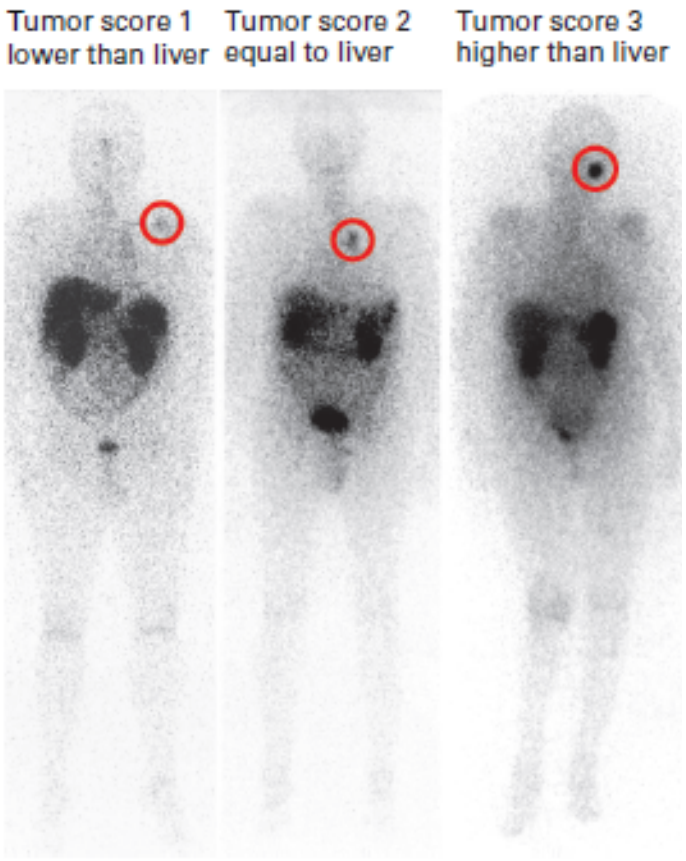
Universitätsspital Basel

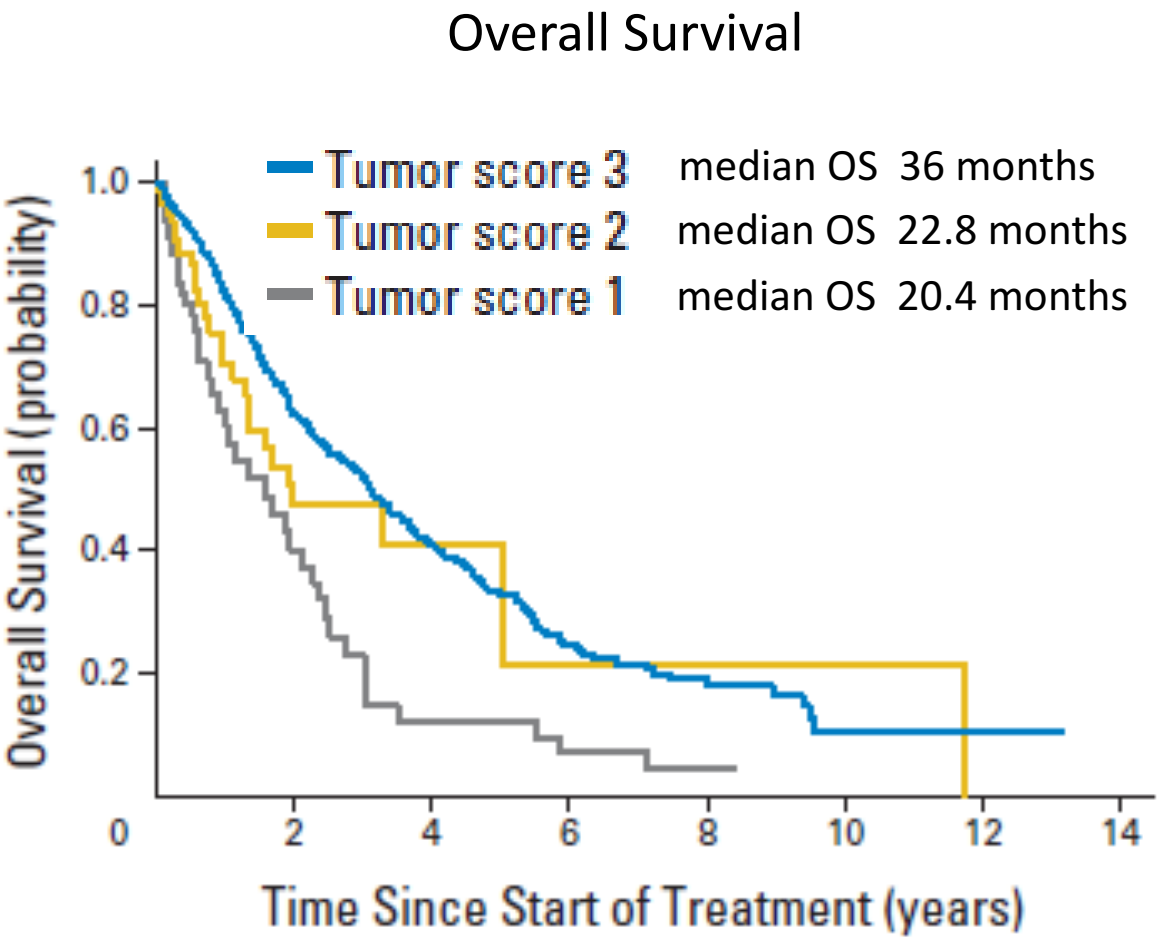
- Imaging: ^{99m}Tc, ^{111}In, ^{68}Ga etc.
- Therapy: ^{177}Lu, ^{90}Y, ^{213}Bi etc.

Theranostic Approach

2 x ^{90}Y-DOTATOC in NETs (Theranostic approach)

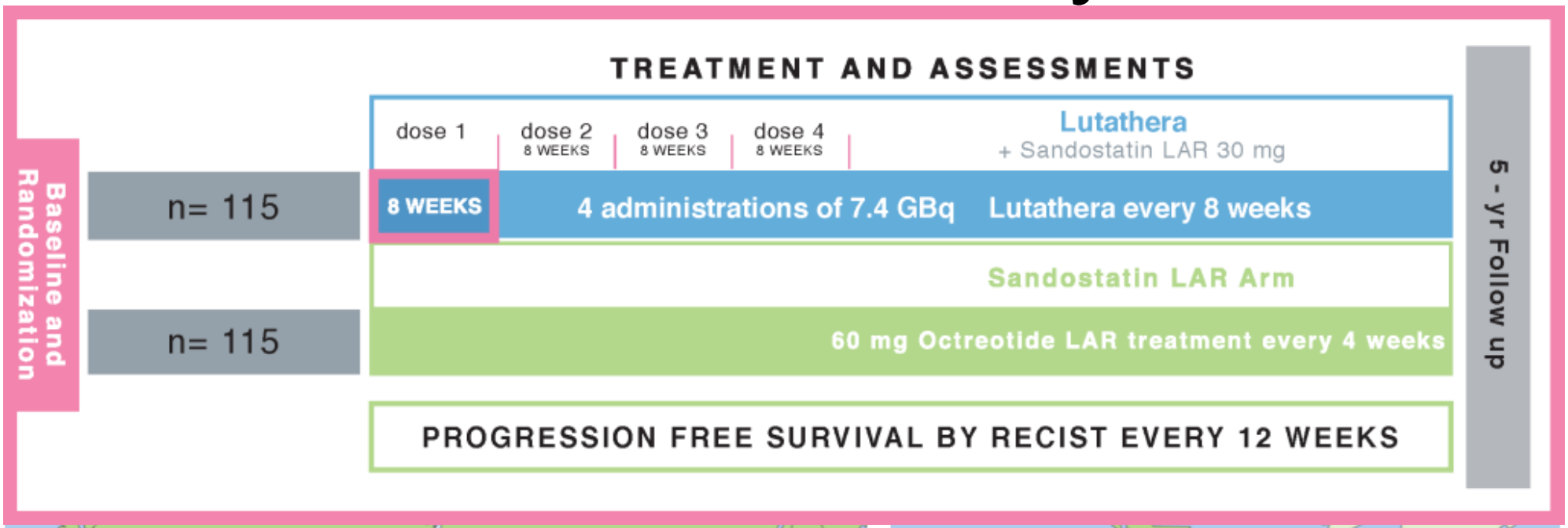
Large open label phase II study, N = 1109





Imhof A et al. J Clin Oncol. 2011;29:2416-2423.

NETTER-1 study



Progression-Free Survival

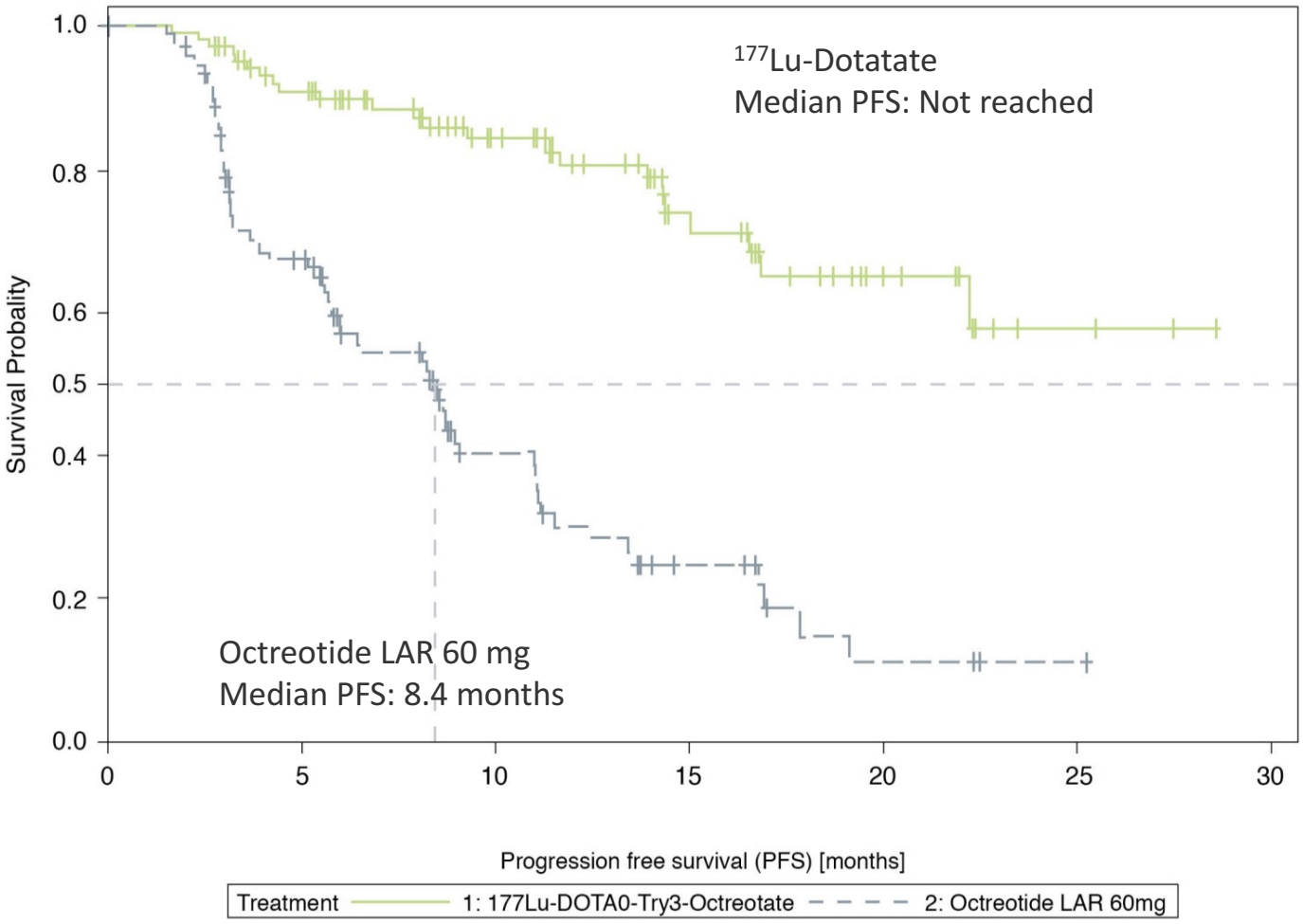
N = 229 (ITT)
Number of events: 90

- ^{177}Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21** [0.129 – 0.338] **p < 0.0001**

79% reduction in the risk of disease progression/death

Estimated Median PFS in the ^{177}Lu-Dotatate arm **≈ 40 months**



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Prostate cancer

- Antitumour activity of ^{177}Lu-PSMA617 in metastatic hormone-refractory prostate cancer by Kratochwil and coworkers from the University of Heidelberg.
- A total of 30 patients have undergone three treatment cycles in intervals of 2 months each. After a third treatment cycle, reduction in PSA levels was >50 % in more than 70 % of patients, indicating highly effective tumour cell kill.

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PSMA Ligands

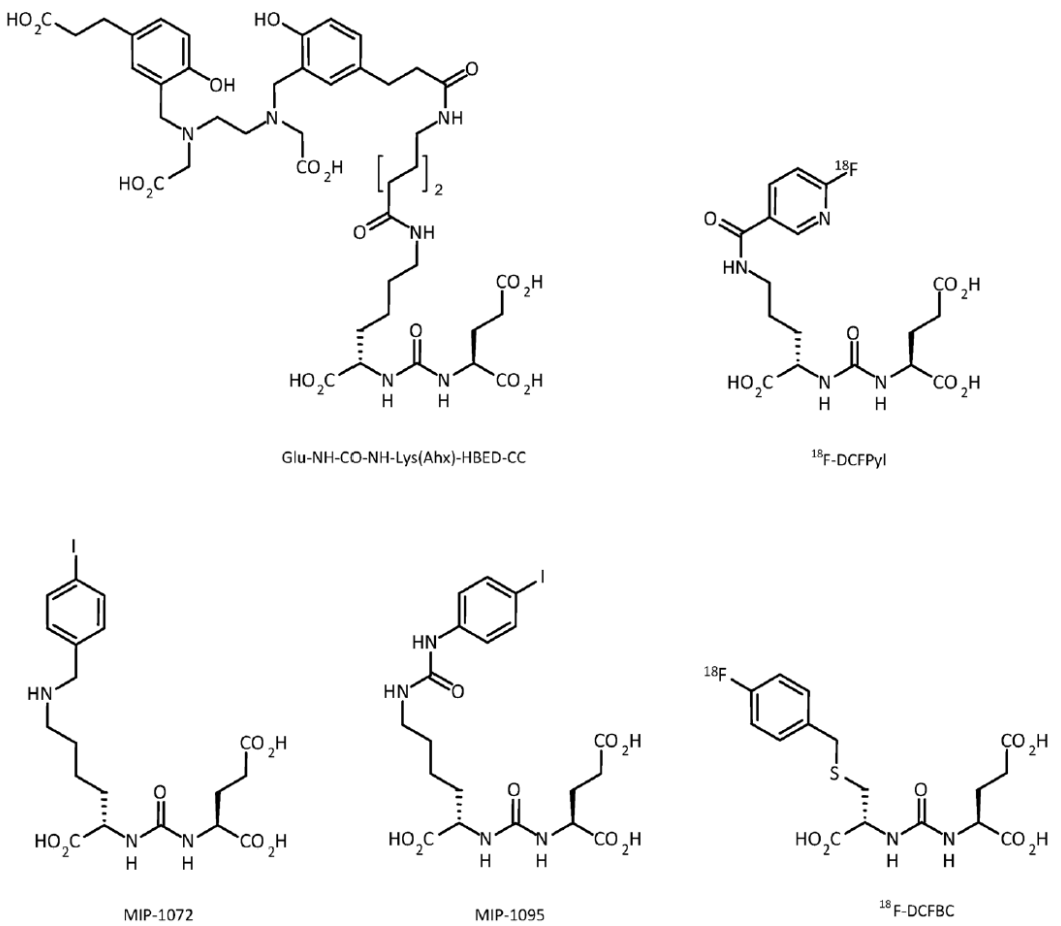
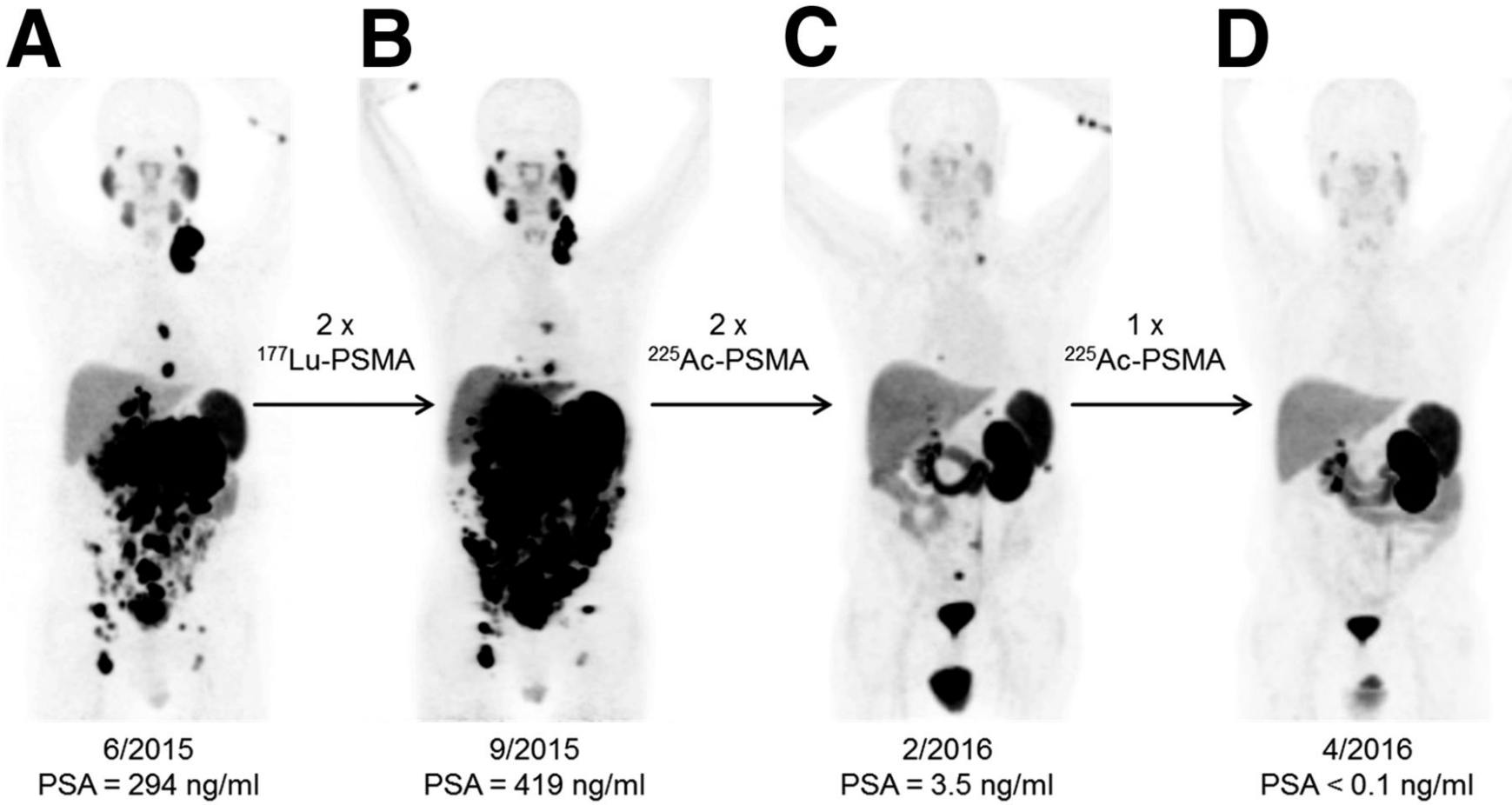


Figure 2: Small-molecule PSMA ligands currently being investigated for PCa imaging in clinical settings. All possess the characteristic glu-urea-lys core.

Lütje et al. Theranostic 2015:5:12

^{225}Ac-PSMA-617 Therapy for Prostate Cancer (^{68}Ga-PSMA-11 PET)



68Ga-PSMA-11 PET/CT scans of patient B. In comparison to initial tumor spread (A), restaging after 2 cycles of β-emitting 177Lu-PSMA-617 presented progression (B). Clemens Kratochwil et al. J Nucl Med 2016;57:1941-1944

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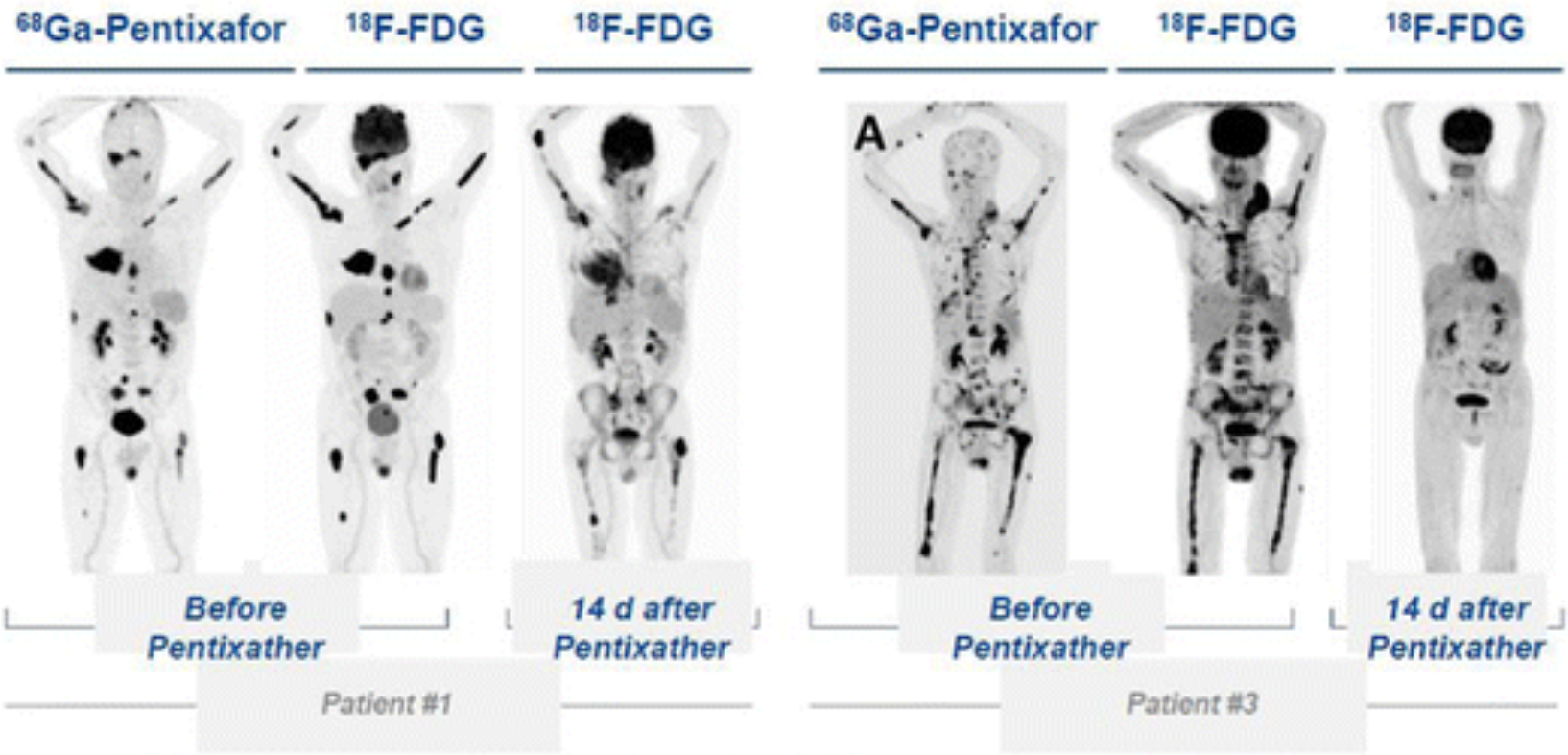
Multiple Myeloma
^{177}Lu- or ^{90}Y-labelled CXCR4-specific ligands (Pentixather®)

- > **50% decrease** in ratio involved/uninvolved serum FLC as **response to Pentixather**



- PET/CT: **PR** (ΔSUVmax >35%, #1) and **CR** (#3)
- OS: 6 months (#1) and 3 months (#3)

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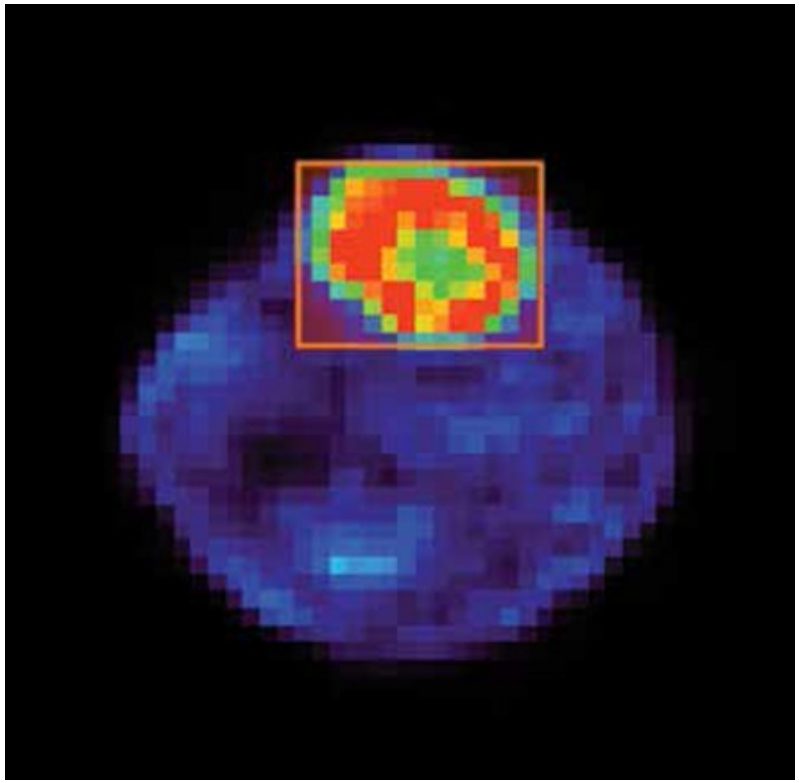
Cu-64 ATSM

Cu-diacetyl-bis(N 4-methylthiosemicarbazone)

Hypoxia Targeting

β+ particles: PET imaging & Therapy



Sanghera et al. Mol Imaging Radionucl Ther. 2016 Feb; 25(1): 19–25.

Targeted Alpha-Particle Immunotherapy for Acute Myeloid Leukemia

Isotope	Particle(s) Emitted	Half-Life	Particulate Energy (KeV)	Mean Range of Emission (mm)
Beta-emitters				
Iodine-131	Beta, gamma	8.1 d	610	0.8
Yttrium-90	Beta	2.5 d	2,280	2.7
Rhenium-188	Beta, gamma	17 h	2,100	2.4
Alpha-emitters				
Bismuth-213	1 Alpha, 2 beta, 1 gamma	46 min	8,400	0.05-0.08
Actinium-225	4 Alpha, 2 beta, 2 gamma	10 d	6,000-8,400	0.04-0.08
Astatine-211	1 Alpha, 1 gamma	7.2 d	6,800	0.04-0.10

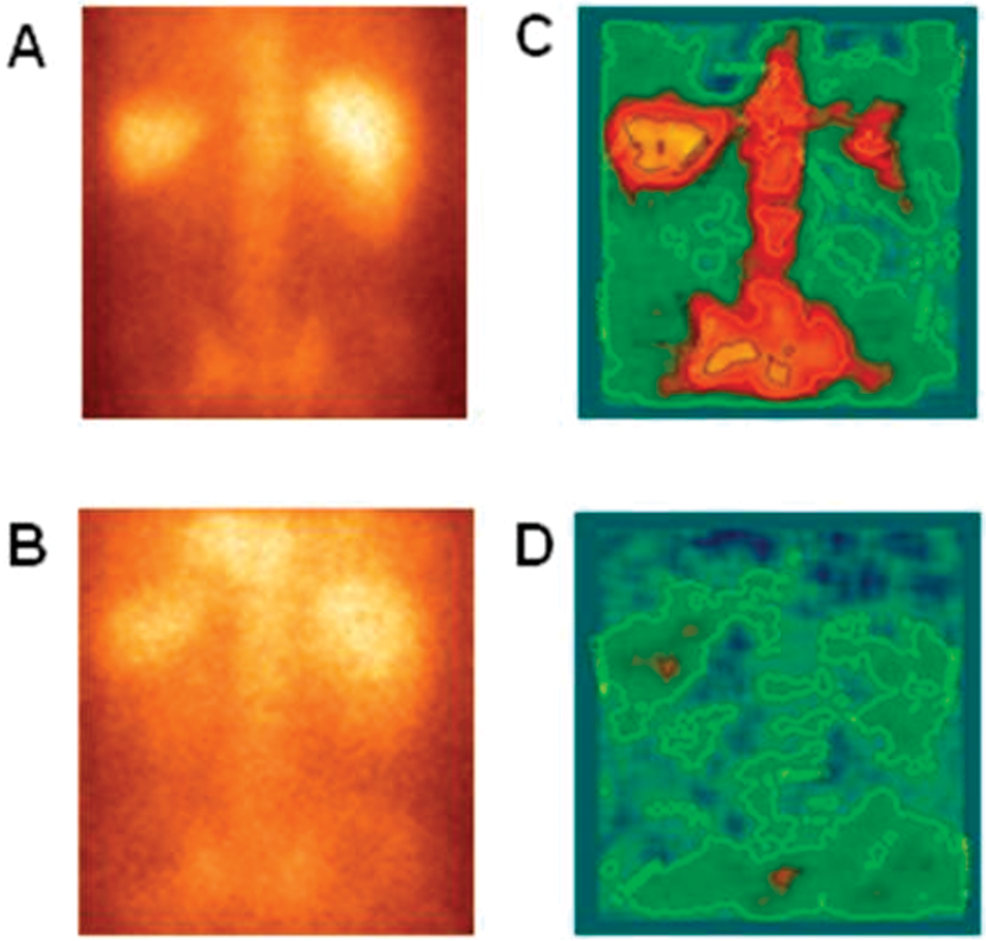
Abbreviations: d, days; h, hours; min, minutes.

Author	Year	Phase of Study	Agent	Dose	Additional Therapy	Disease Status	No. of Patients	Outcomes
Jurcic[15]	2002	I	^{213}Bi-lintuzumab	0.28-1 mCi/kg	None	Relapsed/refractory	18	14 patients with reductions in marrow blasts
Rosenblat[16]	2010	I/II	^{213}Bi-lintuzumab	0.5-1.25 mCi/kg	Cytarabine	Untreated $>$ 60 yrs, relapsed/refractory	31	2 CRs, 2 CRp, 2 PRs
Jurcic[20]	2011	I	^{225}Ac-lintuzumab	0.5-4 μCi/kg	None	Relapsed/refractory	18	10 patients with reductions in marrow blasts; 3 with $\leq$ 5%
Jurcic[21]	2013	I/II	^{225}Ac-lintuzumab	1-2 μCi/kg (in 2 fractions)	LDAC	Untreated $\geq$ 60 yrs	7	4 patients with reductions in marrow blasts (mean, 58%) after cycle 1

Abbreviations: LDAC, low-dose cytarabine; CR, complete remission; CRp, CR with incomplete platelet recovery; PR, partial remission.

Jurcic and Rosenblat, Am Soc Clin Oncol Educ Book. 2014:e126-31. doi: 10.14694/EdBook_AM.2014.34.e126.

Targeted Alpha-Particle Immunotherapy for Acute Myeloid Leukemia



- **FIG 1. Gamma camera images after partial cytoreduction of leukemic burden with cytarabine show targeting of 213Bi to marrow, liver, and spleen after the first injection (A) and blood pooling after the last (B). Rate images show uptake of 213Bi by bone marrow, liver, and spleen over 1 hour after the first injection (C) and clearance after the last (D), indicating saturation of CD33 sites within target organs. Originally published by the American Association for Cancer Research (Rosenblat TL et al. Clin Cancer Res. 2010;16:5303-5311.).**

Jurcic and Rosenblat, Am Soc Clin Oncol Educ Book. 2014:e126-31. doi: 10.14694/EdBook_AM.2014.34.e126.

Bi-213&Ac-225 Abs for Acute Myeloid Leukemia

Actinium Pharmaceuticals, Inc.

CONTACT SITEMAP

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Business Description

Actinium Pharmaceuticals, Inc. (www.actiniumpharma.com) is a New York-based biopharmaceutical company developing innovative targeted payload immunotherapeutics for the treatment of advanced cancers. Actinium's targeted radiotherapy products are based on its proprietary delivery platform for the therapeutic utilization of alpha-emitting actinium-225 and bismuth-213 and certain beta emitting radiopharmaceuticals in conjunction with monoclonal antibodies. The Company's lead radiopharmaceutical product candidate Iomab-B is designed to be used, upon approval, in preparing patients for hematopoietic stem cell transplant, commonly referred to as bone marrow transplant. The Company plans to conduct a single, pivotal, multicenter Phase 3 clinical study of Iomab-B in refractory and relapsed AML patients over the age of 55 with a primary endpoint of durable complete remission. The Company's second product candidate, Actimab-A, is continuing its clinical development in a Phase 1/2 trial for newly diagnosed AML patients over the age of 60 in a single-arm multicenter trial.

Company Info

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Industry Classifications

Sector:
Healthcare

Industry:
Biotechnology

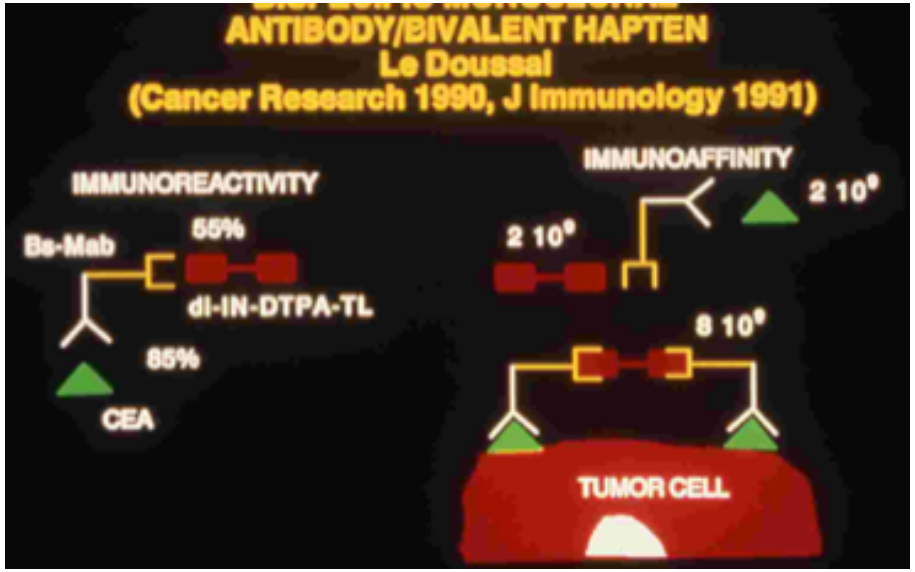
NAICS:
Pharmaceutical Preparation Manufacturing (325412)

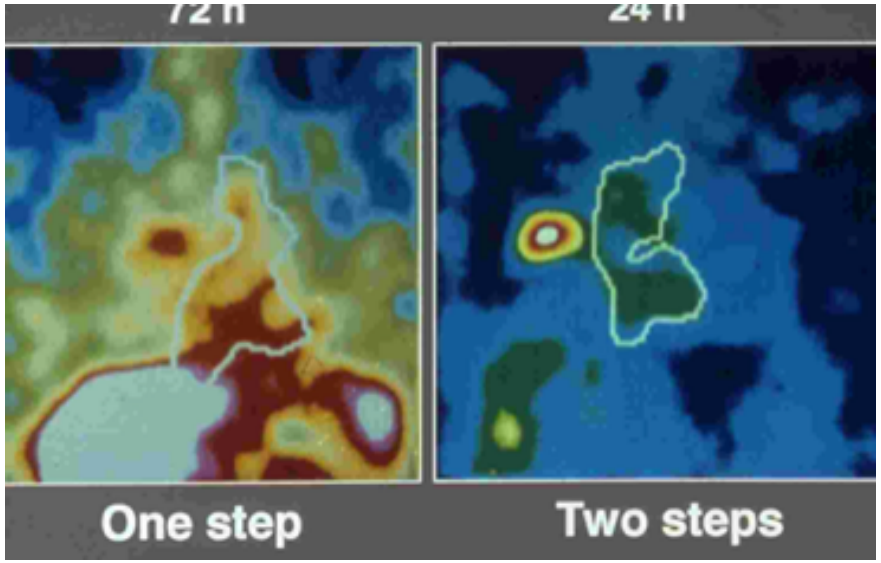
SIC:
Pharmaceutical Preparations (2834)

Pretargeting

Bispecific antibody+radiolabeled hapten

Higher tumor-to-normal





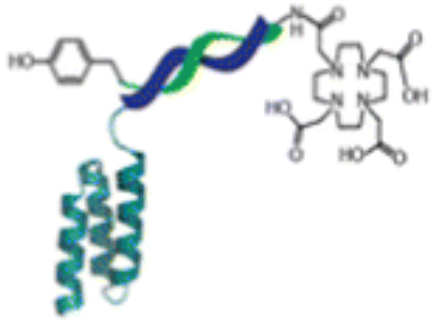
Le Doussal et al. Cancer Research 1990
Hosono, Chatal et al. JNM 1997, 1998

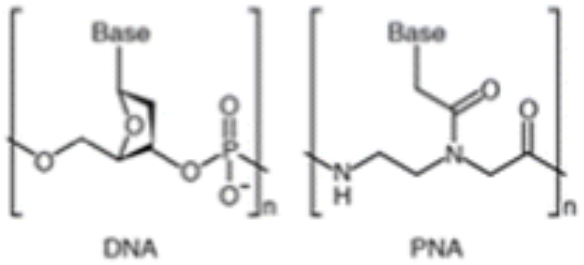
Pretargeting

UPPSALA UNIVERSITET

Feasibility of Affibody molecule-based PNA-mediated pre-targeting

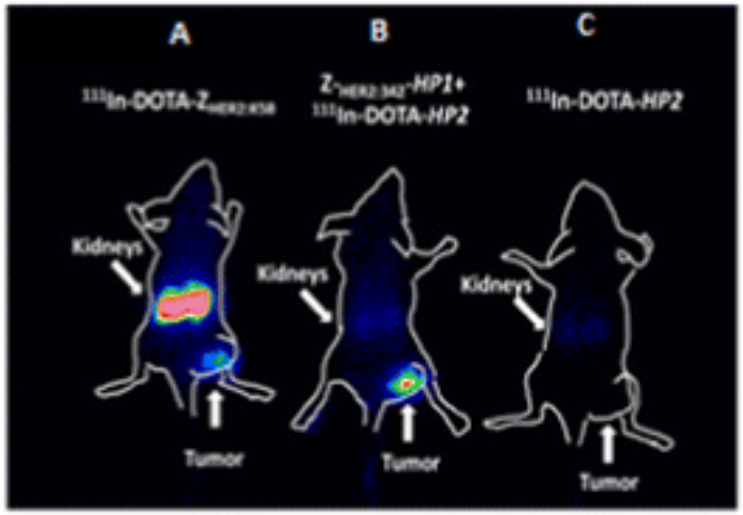
KTH VETENSKAP OCH KONST





Hadis Honarvar[1], Kristina Westerlund[2], Mohamed Altai[1], Matties Sandström[1], Anne Orlova[1], Vladimir Tolmachev[1], Amelie Eriksson Karlström[2]

Gamma-camera imaging of nude mice bearing HER2-expessing SKOV-3 xenografts at 1 h after injection of ^{111}In-labelled agents



A. Conventional Affibody molecule ^{111}In-DOTA-Z$_{HER2:S1}$;
B. ^{111}In-DOTA-*HP2* injected 4 h after pre-injection of Z$_{HER2:342}$-*HP1*;
C. ^{111}In-DOTA-*HP2* injected without pre-injection of Z$_{HER2:342}$-*HP1*.

EANM2015

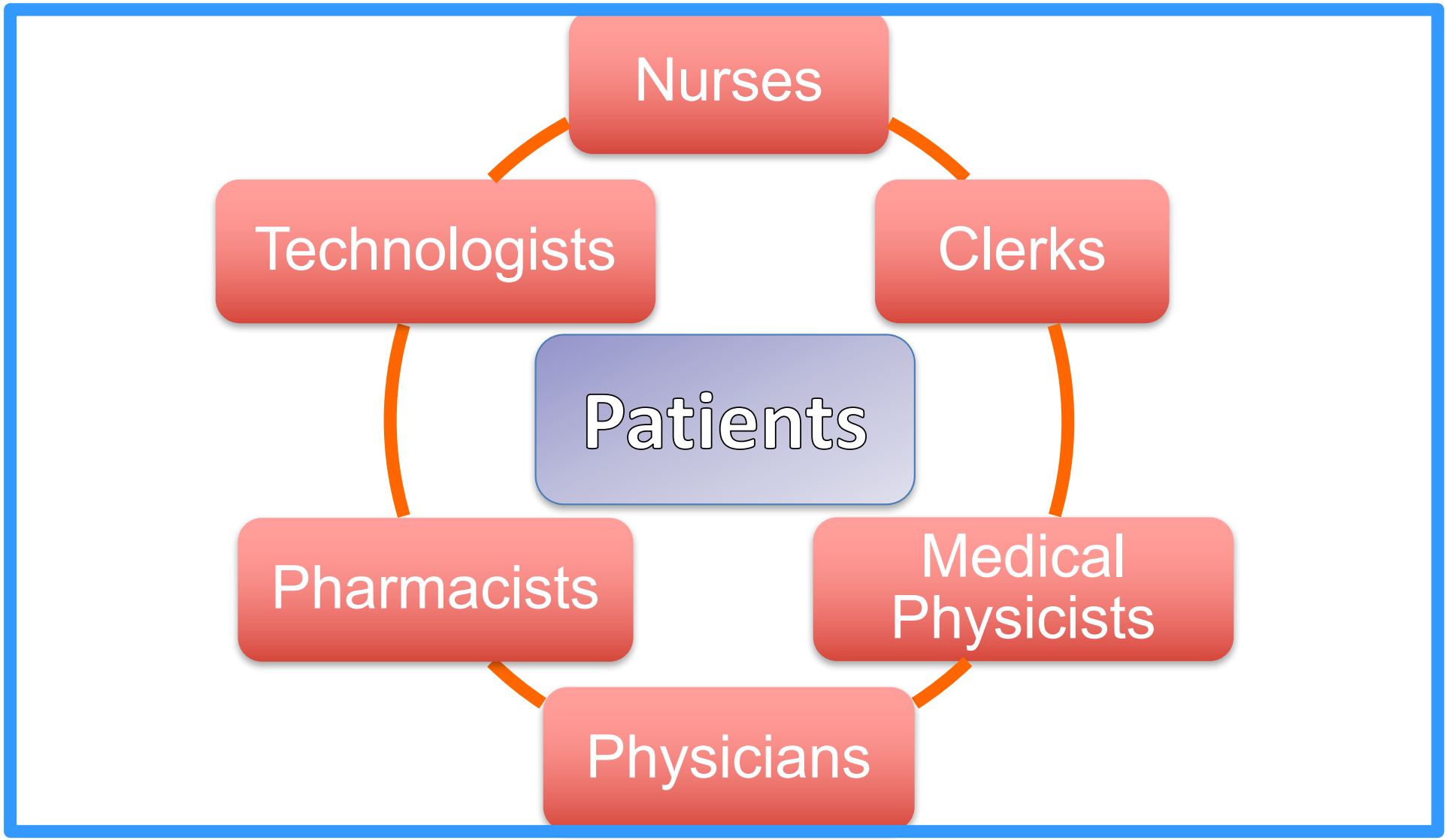
Fukushima Medical University
Fukushima Global Medical Science Center
Targeted Alpha Therapy

FMU website

Global Trends for Targeted Alpha Therapy
TAT-10

May 30-June 1, 2017, Kanawaza, Japan

RNT practices as a multidisciplinary team



Summary

- RNT procedures with alpha-emitting or beta emitting nuclides are making remarkable progress across the globe.
- We should present radiological protection guidelines to disseminate and facilitate new technologies of RNT.

Thank you very much