بسم الله الرحمن الرحیم

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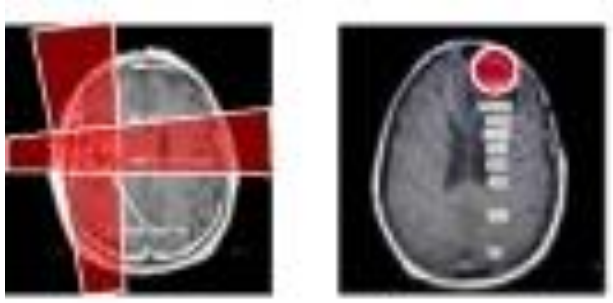
Alpha emitter radionuclide therapy
Current Status and Future Perspectives

By

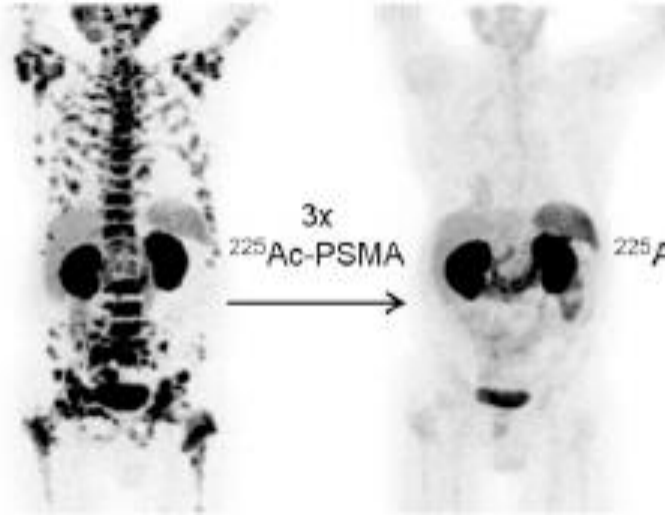
Faraj Tabeie, Ph.D.

Nuclear medicine radionuclide therapy

- Radionuclide therapy for curative therapy, disease control, or palliation therapy constitute a major tasks in nuclear medicine activities.



- TRT has opened a rapidly growing interests for making steps forward to more efficient radiotherapy options.



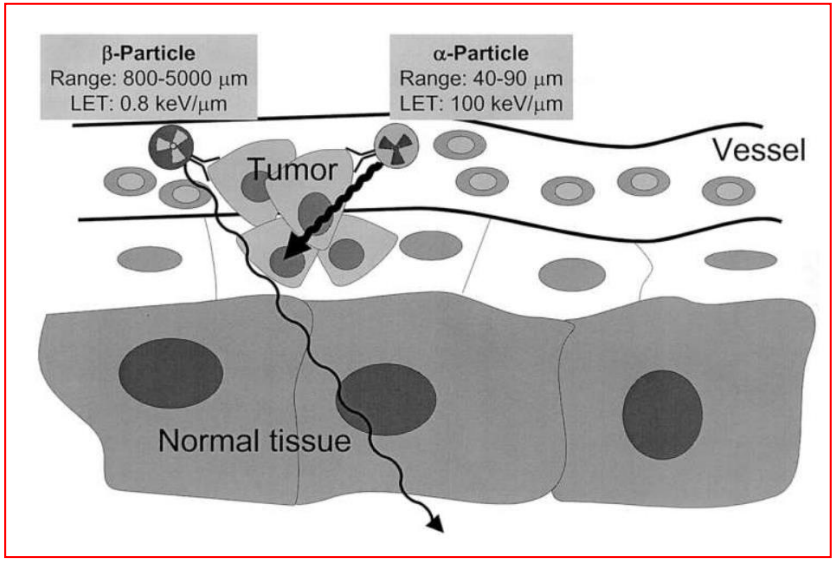
- In comparison with external irradiation therapy, approaches to *treating single cells*.
- One distinct TRT option is use of alpha emitting radionuclides.

Targeted radionuclide therapy, TRT

- Betta emitter radionuclides
- Alpha emitter radionuclides

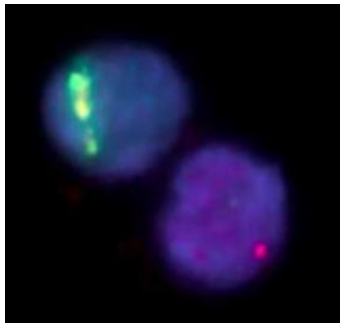
Physics and radiobiology Beta-emitters

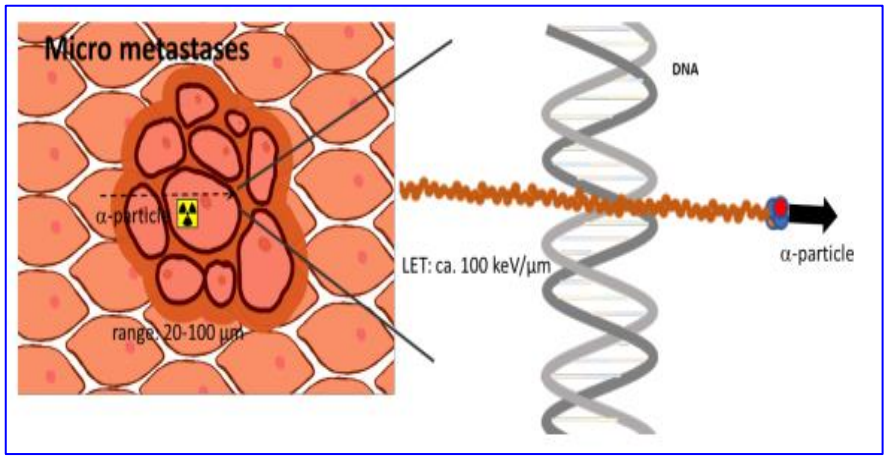
- Beta-emitting radioisotopes have:
  - Largest particle path length (up to 12 mm)
  - Lowest linear energy transfer (LET) (~0.2 keV/µm)
  - More efficient in medium to large tumors
  - Mostly SSB breaks in target DNA cells
  - Advantageous in evenly distributing radiation dose in heterogeneous tumors
  - More irradiation of healthy
  - tissue surrounding tumor site

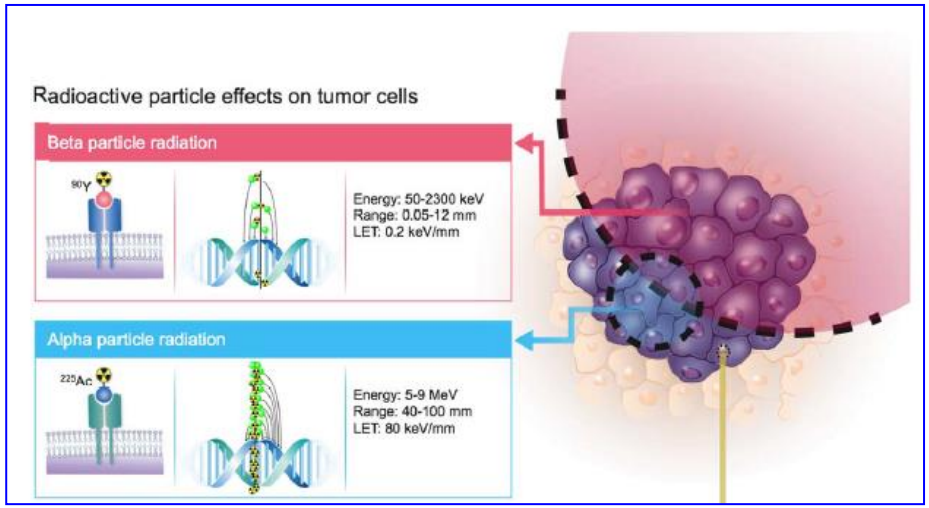


Physics and radiobiology of alpha emitters

- **High LET**
  - (80–100 keV/µm) and up to 10-fold higher RBE in comparison with β
- **Short range**
  - Alpha range(50–80 µm) in comparison with β(1-10mm)
- **Higher DSBs** or higher cytotoxicity in tumoral target tissue
  - More direct actions and efficient in hypoxic tumoral cells
- **Higher direct effects**
  - More direct effects and minor indirect effects have also been observed.







Targeted radionuclide therapy, TRT

TRT with betta emitter TRT

- Betta emitter radionuclides have been used in nuclear medicine therapy for a long time.
- These radionuclides undergone into main categories:
- Betta and gamma emitters(theranostics):
  - I-131, Lu-177, Sm-153, Re-188, Re-186
- Pure Betta emitters
  - P-32, Y-90, Sr-89-Sr-90

Why do TRT with alpha emitters?

- The beta-emitting ^{177}Lu-PSMA-617 approved for treatment of metastatic castration-resistant prostate cancer (mCRPC) expressing PSMA.
- ^{177}Lu-DOTATATE (Lutathera), approved for therapy of somatostatin receptor-positive neuroendocrine tumors ,NETs
- A major limitation of these theranostic agents is that 26-55% of patients only showed stable disease and 18-32% showed refractory or progressive disease after treatment.
- So, there is an increasing attention to improve the efficacy of TRT by labeling the peptides with alpha-particle emitters.

Targeted alpha therapy, TAT

- A fundamental aspect of using alpha emitters is their selective delivery to a cancer cell target.
- Alpha-emitting radionuclides have been successfully conjugated to a wide range of biomolecules, antibodies and peptides.
- Numerous α-conjugates showing promising preclinical outcomes are now being evaluated in clinical trials studies.

Choice of alpha-particle-emitting radionuclides

- The key criteria for the choice of alpha-particle-emitting radionuclides are:
  - Half-life,
  - **Stable binding to a chelating agent?? , Radiolysis**
  - Particle energy
  - Decay chain properties
  - Kinetics of the daughters
  - Cost and availability
- These features result in a small number of radionuclides that are suitable, including:
  - Actinium-225
  - Radium-223
  - Bismuth-213
  - Astatine-211
  - Thorium-227
  - Lead-212

Characteristics of therapeutic alpha emitting radionuclides

Isotope	Half-life	Decays per atom	Production method
^{223}Ra	11.43 days	4α,2β$^-$	^{227}Ac generator
^{211}At	7.21 h	1α, 1EC	α-particles cyclotron
^{225}Ac	9.92 days	4α,2β$^-$	^{229}Th generator
^{213}Bi	45.61 min	1α,2β$^-$	^{225}Ac generator
^{212}Pb	10.64 h	1α,2β$^-$	^{224}Ra generator
^{227}Th	18.70 days	5α,2β$^-$	^{227}Ac generator

Mostly generator produced

Carriers for α-particles to target tumors

Carriers for α-particles to target tumors

- Because of high cytotoxicity, α-particles need carriers for delivery to tumors.

- **Some carriers of α-particles includes:**
- Peptides
- Monoclonal antibodies
- Nanoparticles

Radiolabeled peptides

- **Benefits of radiolabeled peptides include:**
  - Accessible radiolabeling
  - Relatively straightforward chemical synthesis
  - Quick clearance from circulation
  - Quick penetration
  - Even target tissue distribution
  - Reduced immunogenicity

Radiolabeled antibodies

- TAT based on antibodies is being explored in preclinical and clinical studies.
- Single-domain antibodies (nanobodies), with a molecular weight of about 15 kDa, have several advantages compared with conventional monoclonal antibodies, including:
  - High affinity
  - Enhanced stability
  - Good water solubility
  - Powerful tumor penetration

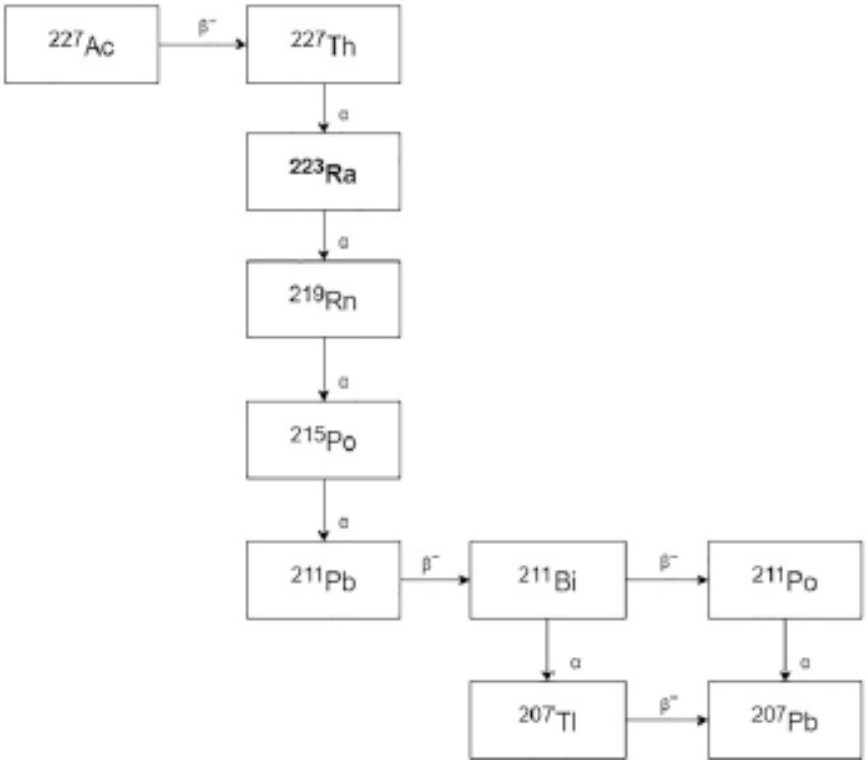
Alpha emitter radionuclides used in preclinical and clinical studies

Alpha emitter radionuclides used in preclinical and clinical studies

- The targeted alpha therapy (TAT) is attracted attentions following several preclinical studies and a few early clinical studies.
- In these studies radionuclides used such as:
- ^{223}Ra
- ^{225}Ac
- ^{213}Bi
- ^{211}At
- ^{227}Th
- ^{212}Pb

Radium-223 chloride

- $^{223}RaCl_2$ (Xofigo) is approved for the treatment of castration-resistant prostate cancer (CRPC) with symptomatic bone metastases and no visceral metastatic disease (mCRPC).
- Radium-223 is selectively accumulated in the bone, specifically in areas of high bone turnover.
- Radium-223 is produced from an actinium-227 (Ac-227) generator.
- In this generator, actinium-227 decays via its daughter radionuclide thorium-227 to radium-223



^{223}Ra, Xofigo clinical trial

- Results showed a significant benefit in terms of overall survival compared to placebo, leading to the approval of radium-223(^{223}Ra,Xofigo) in this indication.
- The approved activity is 55kBq/kg, administered for six cycles every 4 weeks.
- However, Radium-223 has not been successfully used in other indications.
- The side effects is low and its combination with targeted beta-emitting therapy is possible.

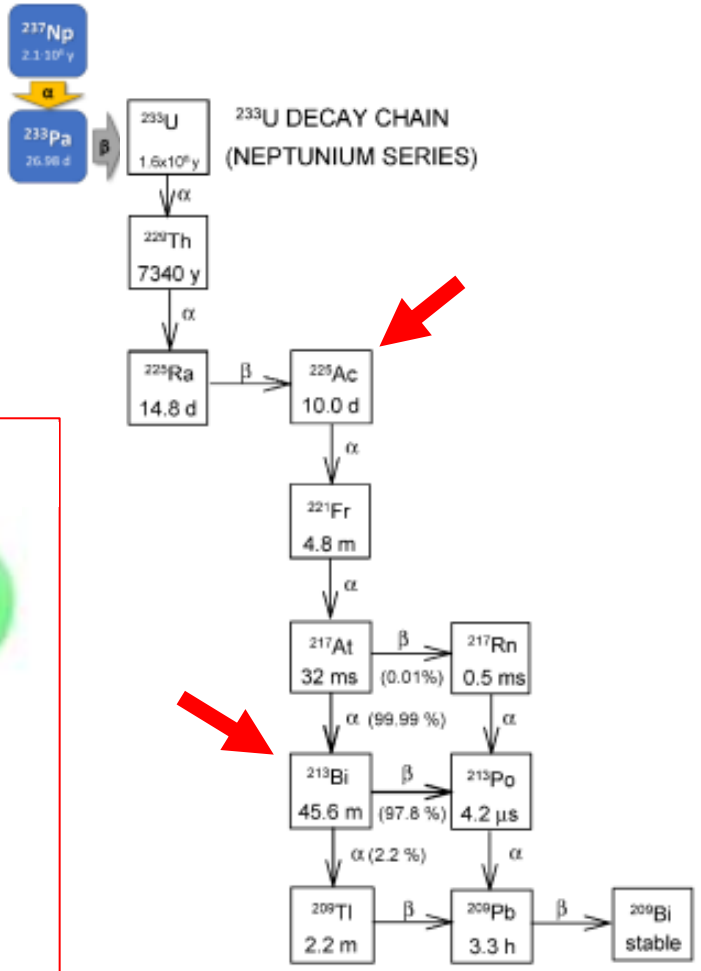
Preclinical studies with ^{225}Ac and ^{213}Bi

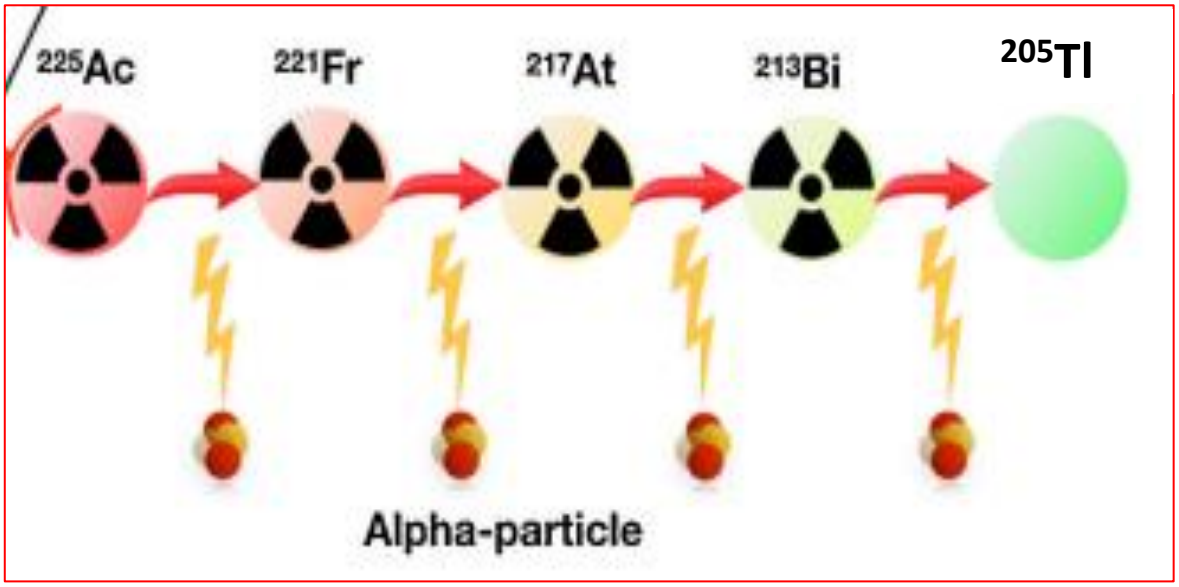
- Some clinical trials used Actinium-225 (^{225}Ac) and its daughter ^{213}Bi.
- Clinical trials using ^{225}Ac because of it`s potential for SPECT imaging and theranostic applications has more clinical trials.
- However, the ^{225}Ac has limitations such as accessibility and production techniques

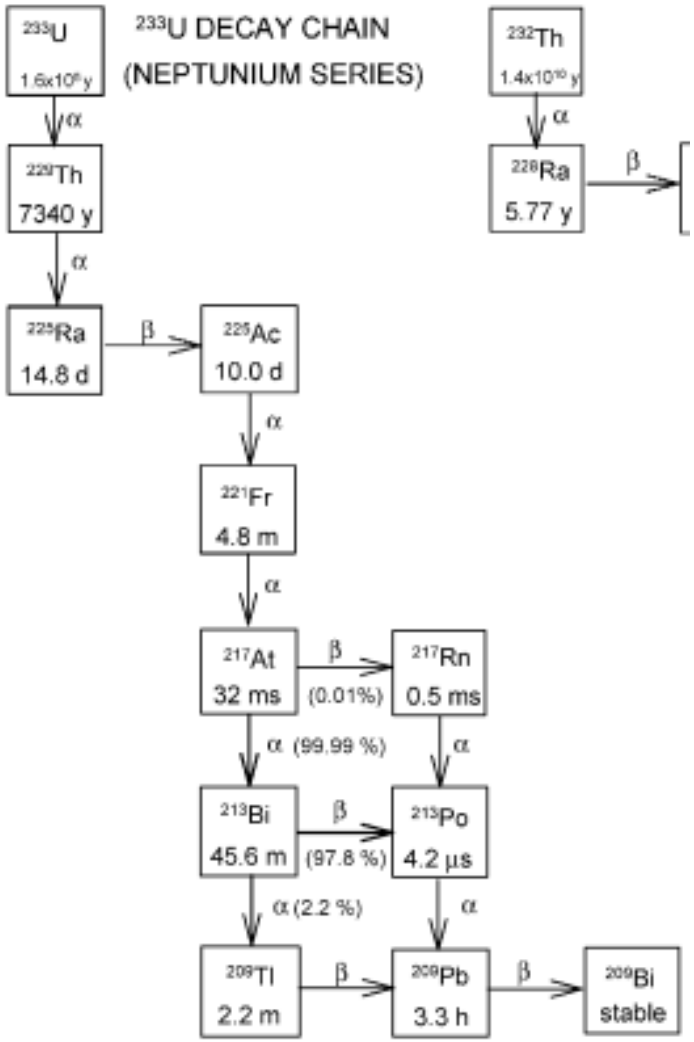
Decay chain of ^{225}Ac and ^{213}Bi

- ^{225}Ac has long half-life of 9.9 days and as a part of the "neptunium decay series" and emissions of α , β and γ radiation ending with ^{209}Pb.
- The cascade includes emissions of

α particles, β− particles, and γ radiation.






233U DECAY CHAIN
(NEPTUNIUM SERIES)
233U
1.6x10^5 y
α
229Th
7340 y
α
225Ra
14.8 d
β
225Ac
10.0 d
α
221Fr
4.8 m
α
217At
32 ms
β
(0.01%)
217Rn
0.5 ms
α (99.99 %)
α
213Bi
45.6 m
β
(97.8 %)
213Po
4.2 µs
α (2.2 %)
α
209Tl
2.2 m
β
209Pb
3.3 h
β
209Bi
stable
232Th
1.4x10^10 y
α
228Ra
5.77 y
β

Summary of the preclinical and clinical trials

Clinical trials

Targeted alpha therapy	Target	Cancer type
^{211}At-OKT10-B10	CD38	Multiple myeloma
^{211}At-OKT10-B10	CD38	Multiple myeloma
^{211}At-BC8-B10	CD45	Hematopoietic cell transplant for non-malignant disease
^{211}At-BC8-B10	CD45	High-risk acute leukemia
^{211}At-BC8-B10	CD45	High-risk AML, acute lymphocytic leukemia
^{211}At-MABG	Norepinephrine transporter	Ovarian cancer
^{211}At[NaAt]	-	Differentiated thyroid cancer
^{225}Ac-DOTA-TOC	SSTR2	Neuroendocrine tumors
^{225}Ac-DOTATATE	SSTR2	Paragangliomas
^{225}Ac-PSMA-617	PSMA	Acute myeloid leukemia
^{225}Ac-lintuzumab	CD33	Prostatic neoplasms, castration-resistant
^{213}Bi-HuM195	CD33	Acute myeloid leukemia
^{213}Bi-DOTA-SP	NK-1R	Glioblastoma
^{213}Bi-PSMA-617	PSMA	Metastatic castration-resistant prostate cancer
^{212}Pb-TCMC-trastuzumab	HER2	Ovarian cancer colon cancers

Published clinical trials on TRT

Eur J Nucl Med Mol Imaging (2014) 41:2106–2119
DOI 10.1007/s00259-014-2857-9

ORIGINAL ARTICLE

^{213}Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience

C. Kratochwil · F. L. Giesel · F. Bruchertseifer · W. Mier ·

First Clinical Results for PSMA-Targeted α-Therapy Using ^{225}Ac-PSMA-I&T in Advanced-mCRPC Patients

J Nucl Med 2021; 62:669–674
DOI: 10.2967/jnumed.120.251017

Mathias Johannes Zacherl[1], Franz Josef Gildehaus[1], Lena Mittlmeier[1], Guido Böning[1], Astrid Gosewisch[1], Vera Wenter[1],

^{225}Ac-PSMA-617 for PSMA-Targeted α-Radiation Therapy of Metastatic Castration-Resistant Prostate Cancer

J Nucl Med 2016; 57:1941–1944
DOI: 10.2967/jnumed.116.178673

Clemens Kratochwil*[1], Frank Bruchertseifer*[2], Frederik L. Giesel[1], Mirjam Weis[2], Frederik A. Verburg[3], Felix Mottaghy[3], Klaus Kopka[4], Christos Apostolidis[2], Uwe Haberkorn[1], and Alfred Morgenstern[2]

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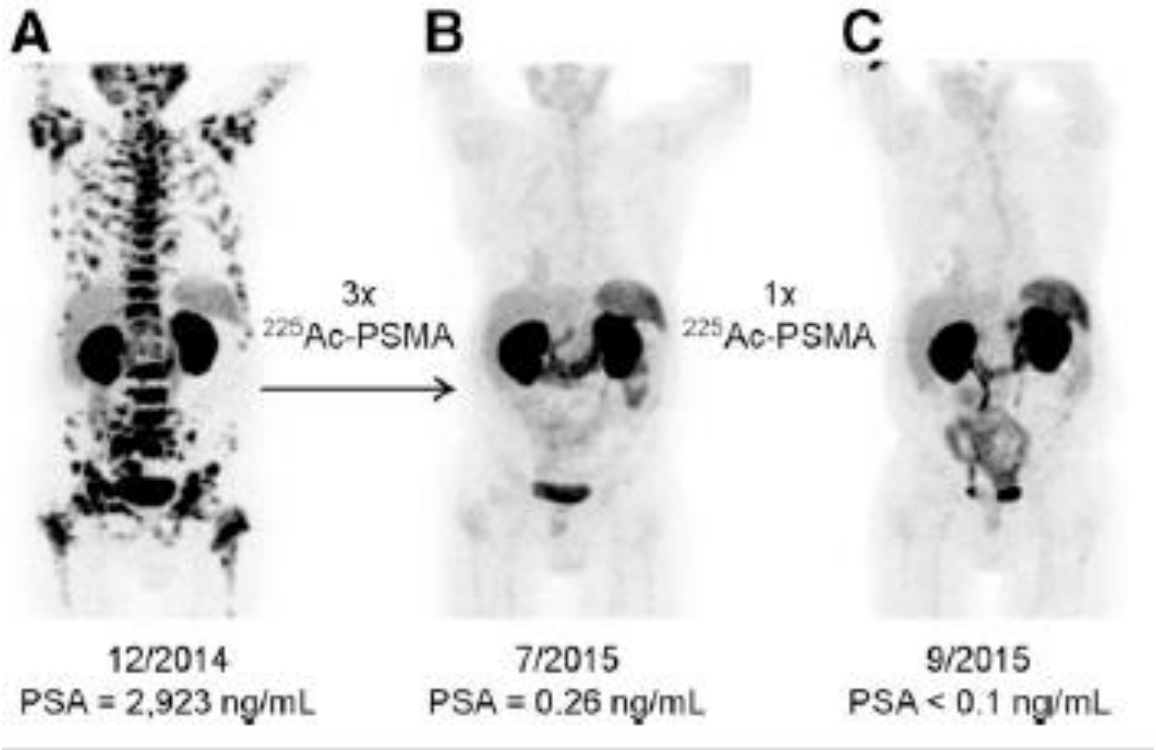
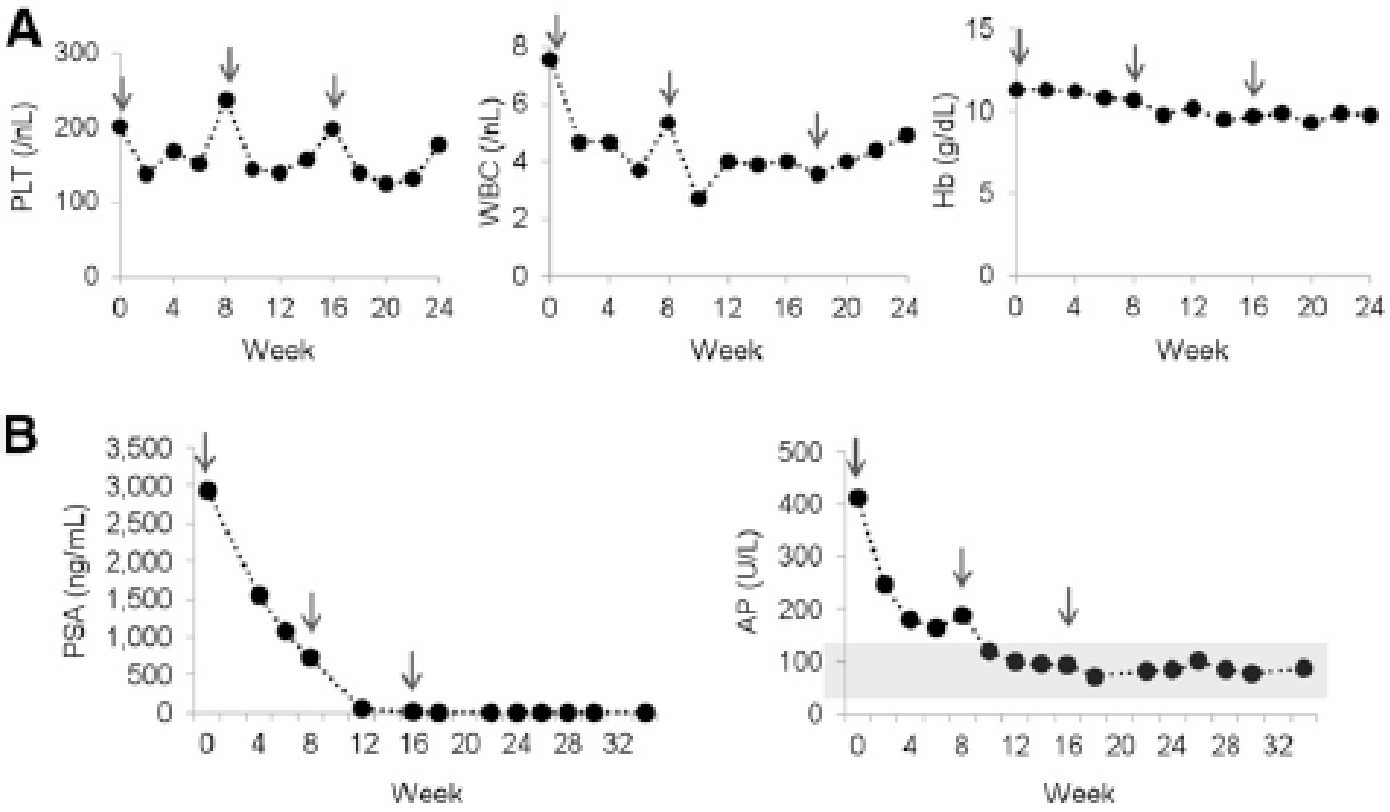
- A) ^{68}Ga-PSMA, PET/CT scans of patient.
- B) Restaging 2 months after third cycle of ^{225}Ac-PSMA-617, 100-kBq(2.7uci)per kg
- C) Restaging 2 months after one additional consolidation therapy.



Laboratory test follow-up of patient A

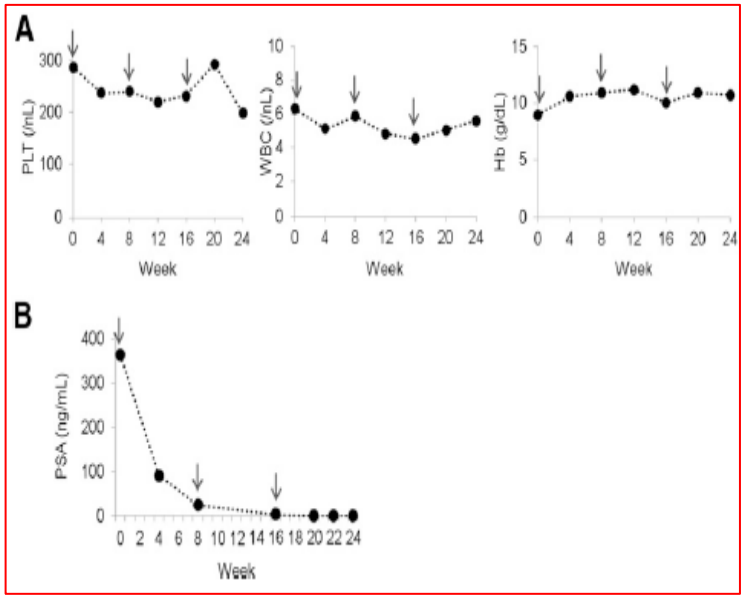
- (A) Blood cell count shows moderate hematologic toxicity.
- (B) Decline of tumor markers to none measurable or reference range correlates with imaging response.

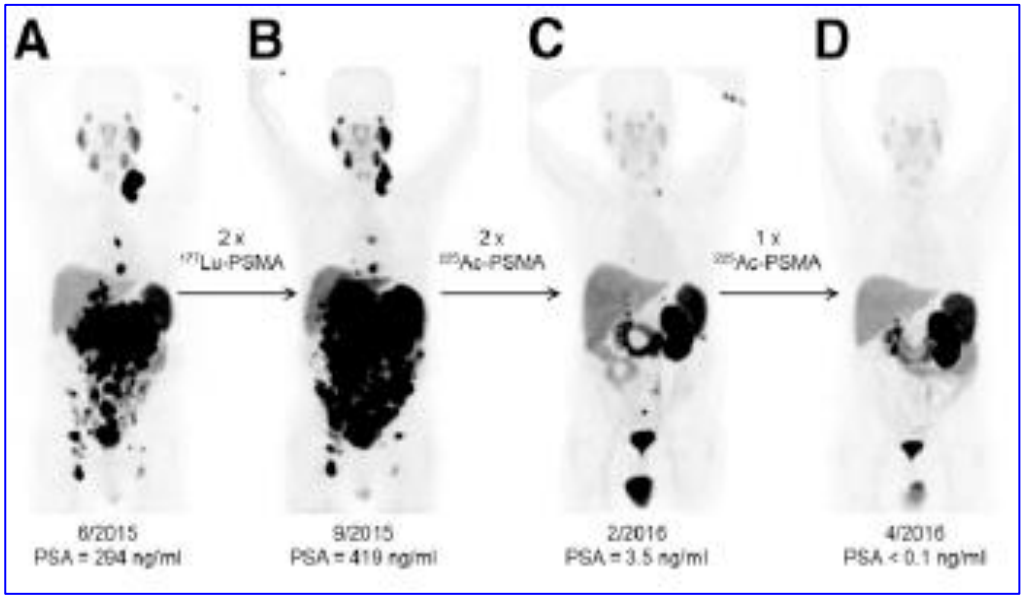


Arrows indicate administration of treatment cyces

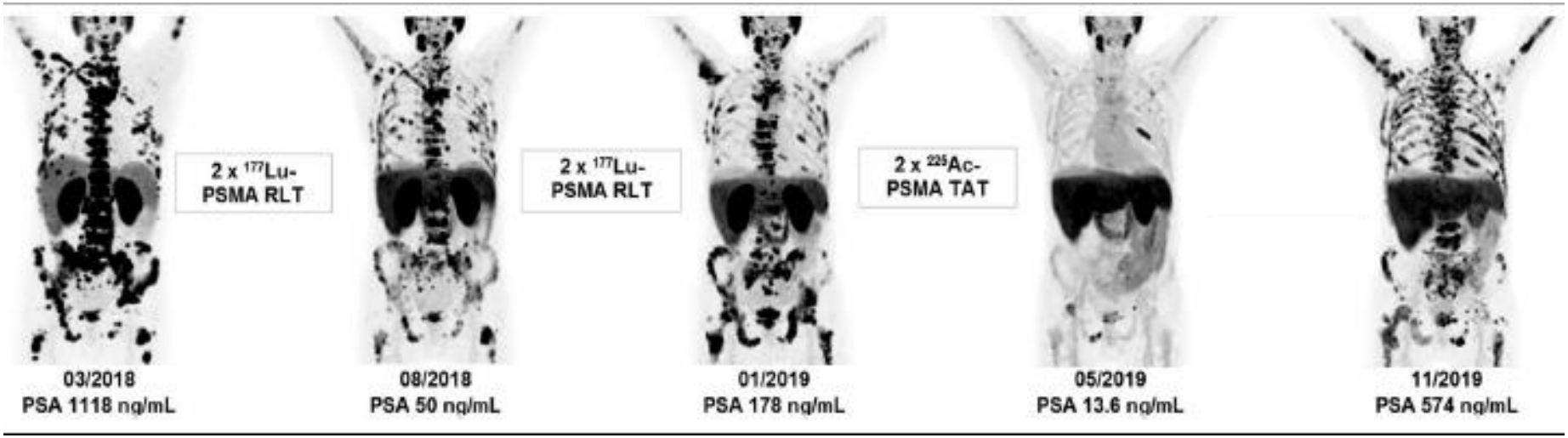
^{68}Ga-PSMA, PET/CT scan and laboratory tests of patient B

- B) In comparison to initial tumor spread , restaging after 2 cycles of β-emitting ^{177}Lu-PSMA-617 presented progression
- C) Restaging after second (C) and third (D) cycles of α-emitting ^{225}Ac-PSMA-617 presented impressive response.
- **Laboratory test follow-up of patient B.**
- Arrows indicate administration of treatment cycles.
- A) Blood cell count always stayed in reference range
- B) Tumor marker PSA finally declined to none measurable.





- A 79-y-old mCRPC patient with lymphatic and bone metastases.
- Patient received 2 cycles of ^{177}Lu-PSMA RLT (10.5 GBq) after failure of docetaxel and showed initial response.
- However, disease progression was observed in January 2019 after 2 additional ^{177}Lu-PSMA RLT cycles (12 GBq), and patient was admitted for 225Ac-PSMA-I&T TAT.
- PSA follow-up and PSMA PET showed response after 2 cycles (13.4 MBq).
- Unfortunately, patient developed grade 3 leukocytopenia, and TAT could not be continued.
- Disease progression was observed in November 2019.



Theranostic approaches using radiolabeled ligands for imaging and therapy (I&T)

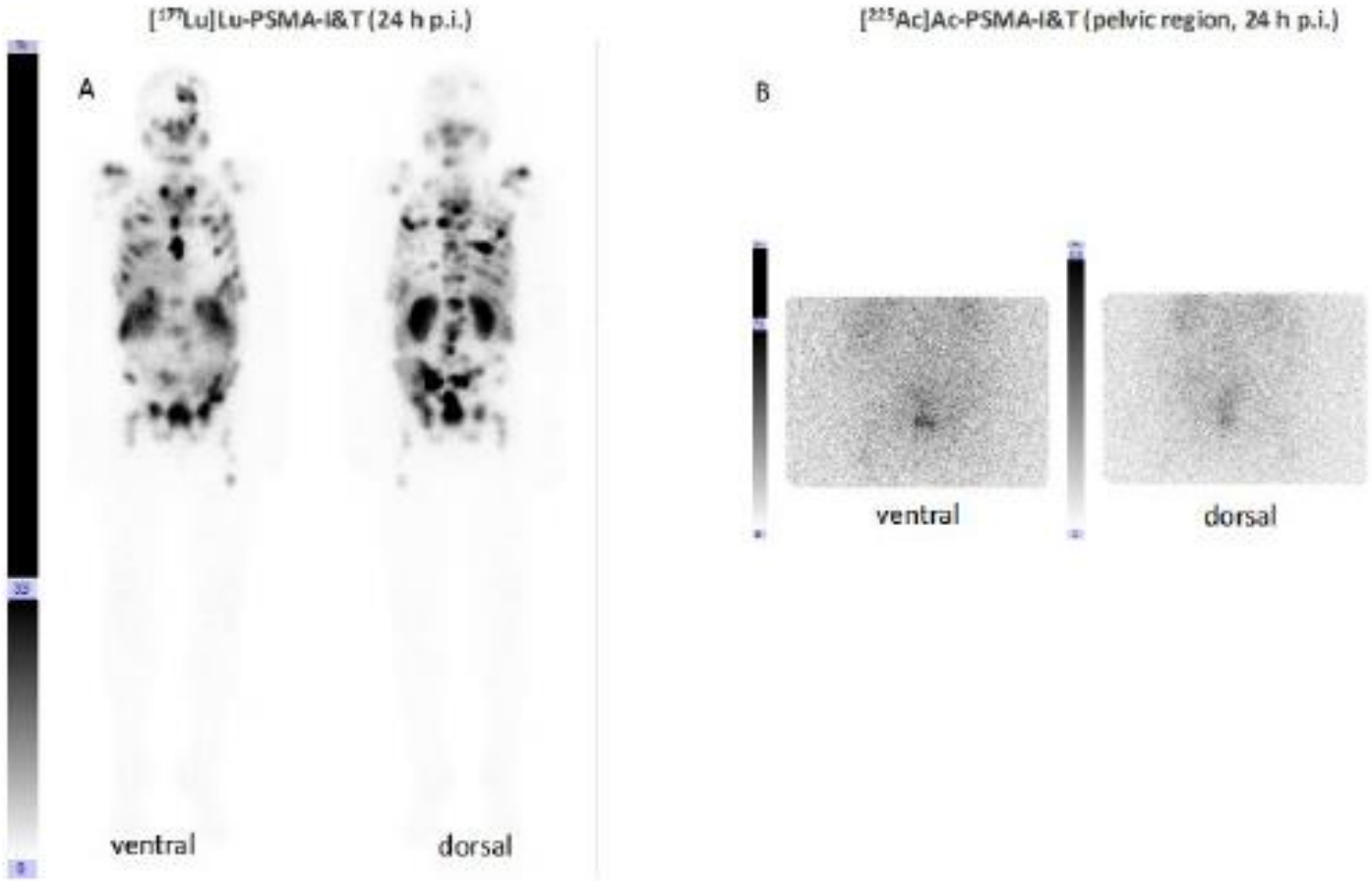


Figure 8. Anterior and posterior scintigraphic imaging of a patient treated with 5 GBq [^{177}Lu]Lu–PSMA–I&T (**A**) and subsequently—due to rising PSA levels combined with reduced bone marrow reserve—with 8 MBq [^{225}Ac]Ac–PSMA–I&T 6 months afterwards (**B**).

Clinical outcomes and treatment patterns in REASSURE: planned interim analysis of a real-world observational study of radium-223 in metastatic castration-resistant prostate cancer

Celestia S. Higano,[a,*] Daniel J. George,[b] Neal D. Shore,[c] Oliver Sartor,[d] Kurt Miller,[e] Peter S. Conti,[f] Cora N. Sternberg,[g] Fred Saad,[h] Juan Pablo Sade,[i] Joaquim Bellmunt,[j] Matthew R. Smith,[k] Kumari Chandrawansa,[l] Per Sandström,[l] Frank Verholen,[m] and Bertrand Tombal[n]

[a]Departments of Medicine and Urology, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[b]Departments of Medicine and Surgery, Duke Cancer Institute, Duke University, Durham, NC, USA
[c]Carolina Urologic Research Center, Myrtle Beach, SC, USA

- A survey on long-term safety and treatment patterns in patients who received radium-223 in real-world clinical practice.
- Global, prospective, observational study of radium-223 in men with mCRPC.
- **Primary outcomes :**
- Adverse events (AEs), including treatment-emergent serious AEs (SAEs) and drug related AEs during and ≤30 days after radium-223 completion
- Grade 3/4 haematological toxicities ≤6 months after last Ra-223 dose
- Drug-related SAEs after Ra-223 therapy completion, and second primary malignancies

Results

- A survey on long-term safety and treatment patterns in patients who received radium-223 in real-world clinical practice.
- Total of 1465 patients were evaluated
- For second primary malignancies, 1470 patients were evaluable, 21 (1%) of whom had a total of 23 events.
- During therapy, 311 (21%) of 1465 patients had treatment-emergent SAEs, and 510 (35%) had drug-related AEs.
- In the 6 months after therapy, 214 (15%) patients had grade 3/4 haematological toxicities.
- Eighty patients (5%) had post-treatment drug-related SAEs.
- Median overall survival was 15.6 months (95% confidence) from radium-223 initiation.
- Patient-reported pain scores declined or stabilized.
- Seventy (5%) patients had fractures.

Clinical trial. Lancet oncology. 2014 Nov;15(12):1397-406.

Efficacy and safety of radium-223 dichloride in patients with castration-resistant prostate cancer and symptomatic bone metastases, with or without previous docetaxel use: a prespecified subgroup analysis from the randomised, double-blind, phase 3 ALSYMPCA trial

Peter Hoskin [1], Oliver Sartor [2], Joe M O'Sullivan [3], Dag Clement Johannessen [4], Svein I Helle [5], John Logue [6], David Bottomley [7], et al

- [1]Mount Vernon Cancer Centre, Northwood, Middlesex, UK.
- [2]Tulane Cancer Center, New Orleans, LA, USA.
- [4]Ullevål University Hospital, Oslo, Norway.[5]Haukeland University Hospital, Bergen, Norway.

- Phase 3 RCT of 921 patients during 2008-2011.
- Ra-223, improved overall survival compared with placebo and was well tolerated in CRPC and mCRPC patients.
- Risk for the first skeletal events was reduced with radium-223 versus placebo.
- The incidences of anemia and neutropenia were similar between the radium-223 and placebo groups.

TRT Guidelines, radiation safety and dosimetry

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-017-3900-4 2017

GUIDELINES

EANM guideline for radionuclide therapy with radium-223 of metastatic castration-resistant prostate cancer

Thorsten D. Poeppel[1] · Daria Handkiewicz-Junak[2] · Michael Andreeff[3] · Alexander Becherer[4] · Andreas Bockisch[1] · Eva Fricke[5] · Lilli Geworski[6] · Alexander Heinzel[7] · Bernd J. Krause[8] · Thomas Krause[9] · Markus Mitterhauser[10,11] · Wilfried Sonnenschein[1] · Lisa Bodei[12] · Roberto C. Delgado-Bolton[13] · Michael Gabriel[14,15]

- Facility and personnel requirements
- Adverse reactions
- Indication and Contraindication
- Interruption of therapy, delay of treatment cycles
- Dosimetry
- Handling and preparation of the radiopharmaceutical
- Storage, quality control

Radiation safety precautions and regulatory requirements

Radiation Safety Considerations and Clinical Advantages of α-Emitting Therapy Radionuclides

J Nucl Med Technol 2022; 50:10–16
DOI: 10.2967/jnmt.121.262294

Brian Serencsits[1], Bae P. Chu[1], Neeta Pandit-Taskar[2], Michael R. McDevitt[2], and Lawrence T. Dauer[1]

[1]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York; and [2]Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York

- In working with alpha emitting radionuclides we have to consider:
  - Preparation
  - Administrative procedures
  - Radiation safety precautions and regulatory requirements
- In addition, proper selection of radiation detection equipment is required for monitoring and dosimetry

Reported administration protocols

- All radionuclides were administered according to protocol recommendations.
- $^{223}RaCl_2$ was administered as a slow bolus intravenous injection over 3–5 min
- ^{225}Ac- and ^{227}Th-labeled antibodies were administered over a 15- to 30-min infusion.
- All 3 protocols have completed, or plan to complete, based on dose-limiting patient toxicity levels.
- $^{223}RaCl2$ and ^{225}Ac treatment activities were based on patient weight
- Whereas planned ^{227}Th doses were based strictly on fixed activity levels

Reported α-emitting radionuclide protocols in clinical trials

Radionuclide	Activity administered (kBq kg^{-1})	Total treatment cycles	Period between cycles (wk)
^{223}Ra			
Phase 1.1	50	1	NA
Phase 1.2	100	1	NA
Phase 1.3	200	1	NA
Phase 2	50	6	4
Phase 3	50	6	4
NIST-adjusted Xofigo	55	6	4
^{225}Ac			
Phase 1.1	18.5	1	NA
Phase 1.2	37	1	NA
Phase 1.3	74	1	NA
Phase 1.4	148*	1	NA
Phase 1.5	111	1	NA

Committed effective dose equivalent

- The committed effective dose equivalent, added to any external occupational exposure, is called the total effective dose equivalent.
- For an individual a limit of 5,000 mrem annually in the US.
- The annual limit on intake values is the amount of radioactive material that would need to be inhaled or ingested to reach the annual occupational

Restrictive Annual Limit on Intake Values for Select α-Emitting Radionuclides and Radionuclides in Common Medical Use

Radionuclide	Decay mode	Restrictive annual limit on intake (MBq)
^{18}F	β	1,850
^{99m}Tc	IT	2,960
^{131}I	β	1.11
^{223}Ra	α	0.026
^{225}Ac	α	0.011
^{227}Th	α	0.011

Dosimetry and contamination Survey Instrumentation

- Regular surveying practices, proper radiation instrumentation, and methods should always be present during alpha emitting radioactive material administration.
- An alpha probe, such as a ZnS scintillation detector or a similar device, may be preferable to a standard Geiger–Muller (GM) detector for the detection of a-emitting radionuclides.
- Alpha-probes can filter out the measurement of β or photons, allowing them to have lower background levels of radiation and a lower minimal detectable activity (MDA).

Reported Radiation safety considerations for 223Ra

- Exposure rate constant for an unshielded point source of 223Ra is 1.85 µSv h^{-1} mCi^{-1}
- Total dose to others was estimated to be 17, 34, or 69 µSv for the study dose activity levels of 50, 100, or 200 kBq kg^{-1}, respectively, for 70 kg patient.
- Therefore, all patients at all dose levels, were treated as outpatients in accordance with ICRP, NCRP, and NRC (public below 1 mSv).
- The mean shallow dose rate on contact with the syringe was 4.8 µGy min^{-1} MBq^{-1} .
- Shallow dose rates on contact with the shipped glass vial demonstrated lower levels at 0.6 µGy min^{-1} MBq^{-1}

wipe test contamination instrumentation

- As 223Ra dichloride emits alpha, beta, and gamma radiation, a wide range of instrumentation can be used to perform general area surveys.
  - Thin windowed Geiger Mueller (GM) probe
  - Sodium iodide low energy gamma (NaI-LEG) probe
  - Zinc sulfide (ZnS) probe
  - Liquid scintillation counter
  - Gamma counter

			Minimum detectable activity	
Instrument	**Background (cpm)**	**Efficiency (cpm/dpm)**	**(dpm)**	**(Bq)**
Alpha Probe (Zinc Sulfide)[a]	0	0.08	71	1.2
Thin Window Beta/Gamma Probe (GM)[a]	28	0.13	350	5.8
Low Energy Gamma Probe (Sodium Iodide)[a]	94	0.29	1296	21.6
Liquid Scintillation Counter	49	0.97	64	1.1
Gamma Counter	210	0.40	333	5.6

Administration

- The administration of ^{223}Ra dichloride is similar to that for any other ready-to-use radiopharmaceutical, except that external radiation dose rates are considerably lower.
- Radioactivity in the vial was verified in a dose calibrator before dispensing.
- It was estimated that a worker might receive approximately 41 µSv for each administration.
- Therefore, a worker could perform over 1,200 administrations of ^{223}Ra dichloride before reaching the threshold for monitoring of the extremities, which is 50 mSv

Targeted α-Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{225}Ac-PSMA-617: Dosimetry Estimate and Empiric Dose Finding

- Dosimetry estimates for 1 MBq of ^{225}Ac-PSMA-617 revealed mean doses of 2.3 Sv for salivary glands, 0.7 Sv for kidneys, and 0.05 Sv for red marrow that are composed of 99.4% α, 0.5% β, and 0.1% photon radiation, respectively.
- In clinical application, severe xerostomia is the dose-limiting toxicity if treatment activity exceeded 100 kBq/kg per cycle.
- At 100 kBq/kg, the duration of PSA decline was less than 4 mo, but if therapy was repeated every 2 mo patients experienced additive antitumor effects.
- Treatment activities of 50 kBq/kg were without toxicity but induced insufficient antitumor response in these high-tumor-burden patients.
- For advanced-stage patients, an activity of 100 kBq/kg of ^{225}Ac-PSMA-617 per cycle repeated every 8 wk presents a reasonable trade-off between toxicity and biochemical response.