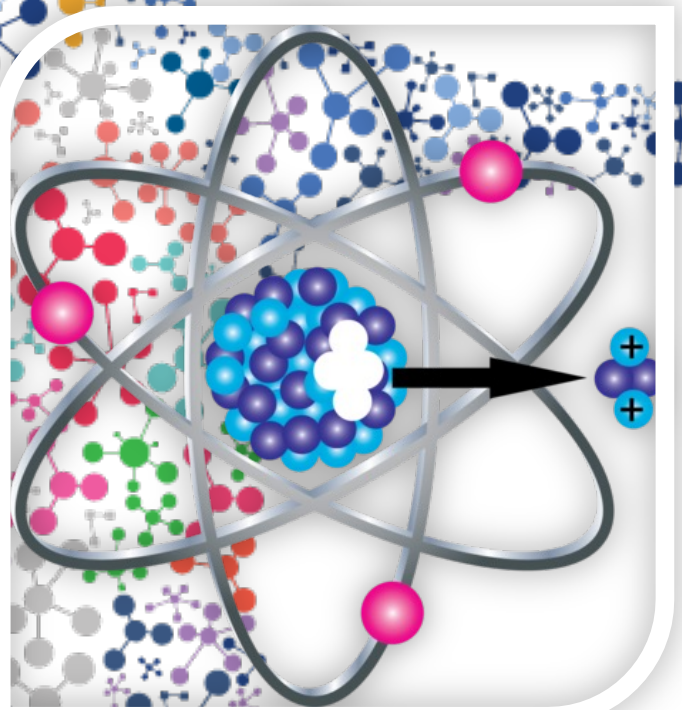
Clinical Applications of Targeted Alpha Therapy (TAT): Present and Future



Prof Mariza Vorster

Head Of Department: Dept of Nuclear Medicine

University of KwaZulu-Natal

President of the Colleges of Nuclear Physicians

MBChB, MMed (NuclMed), MPharmMed (cum laude), FCNP(SA),PhD

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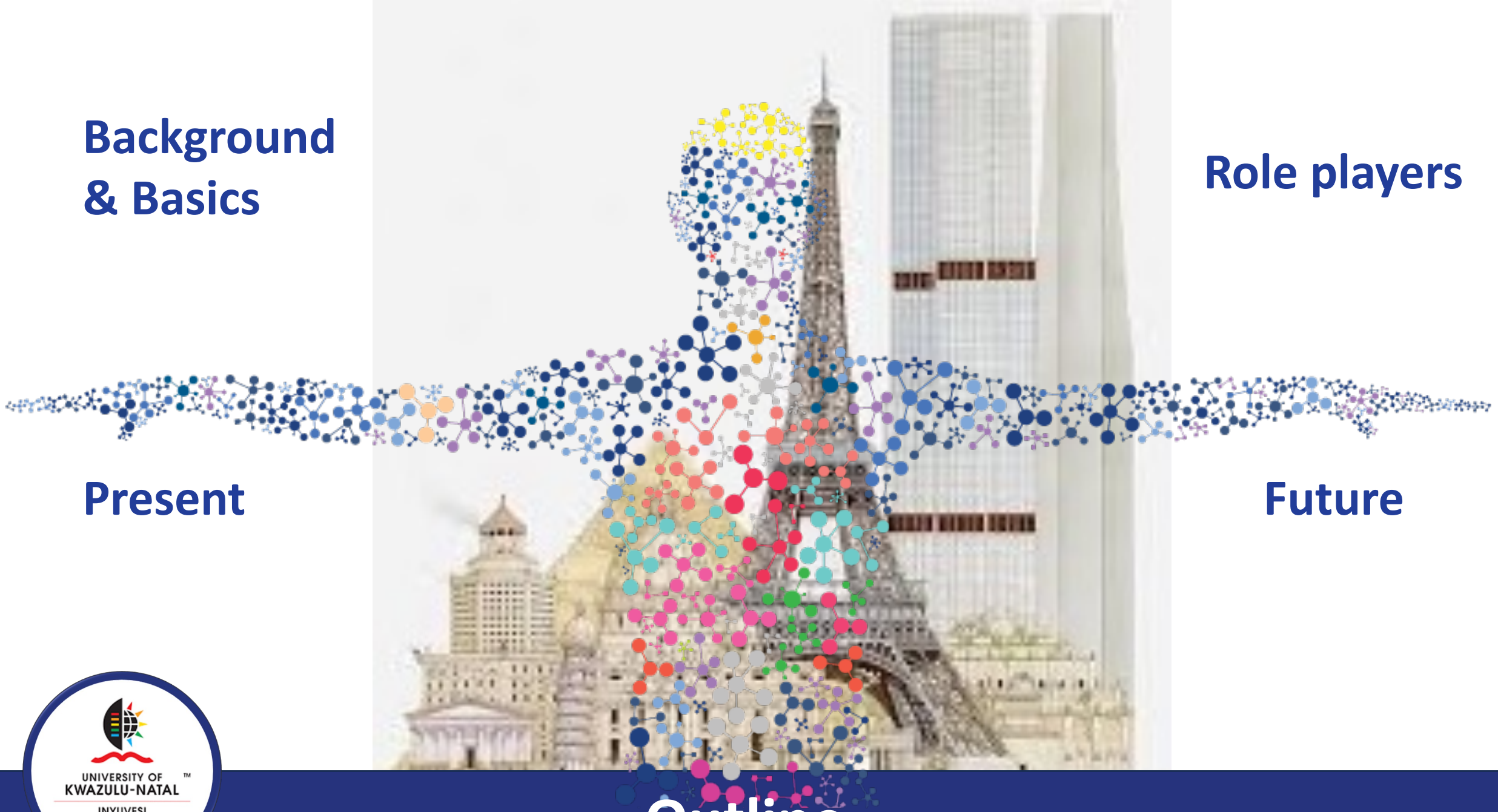
INYUVESI YAKWAZULU-NATALI

February 2024 Paris

Background & Basics

Role players



Present

Future

Outline

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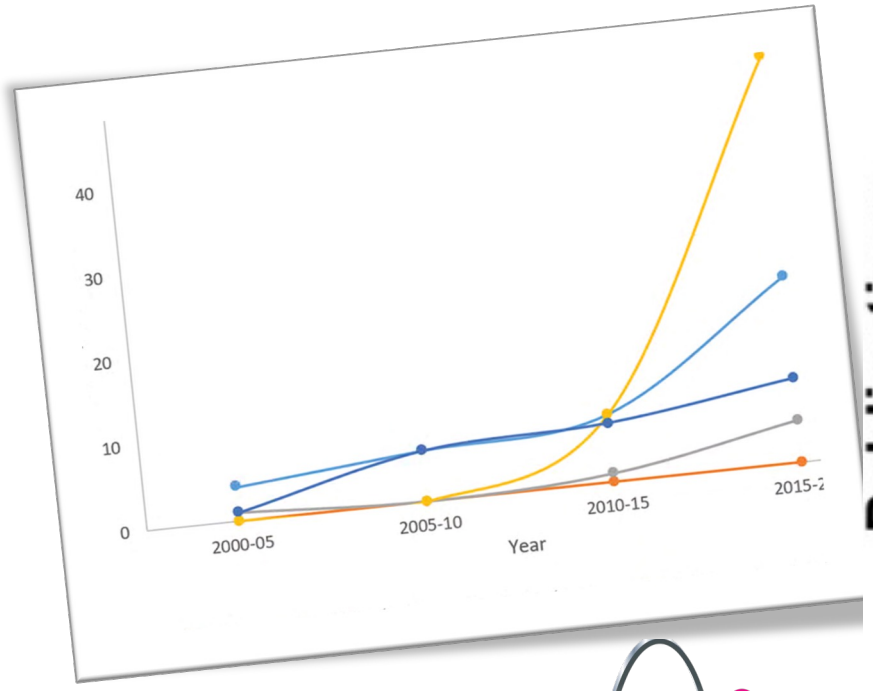
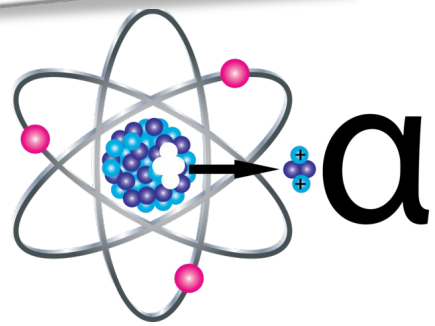
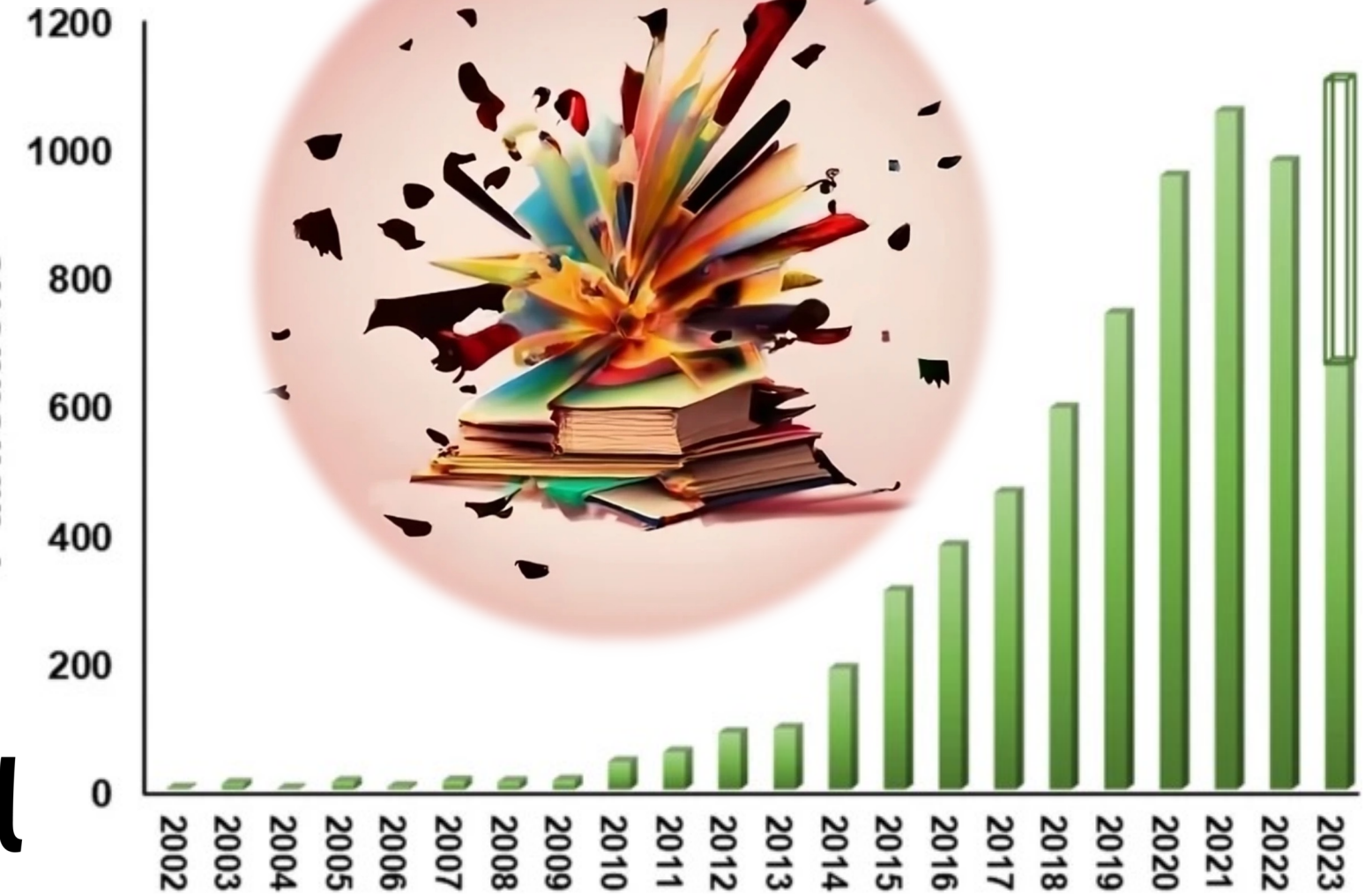
Publications on TAT





α



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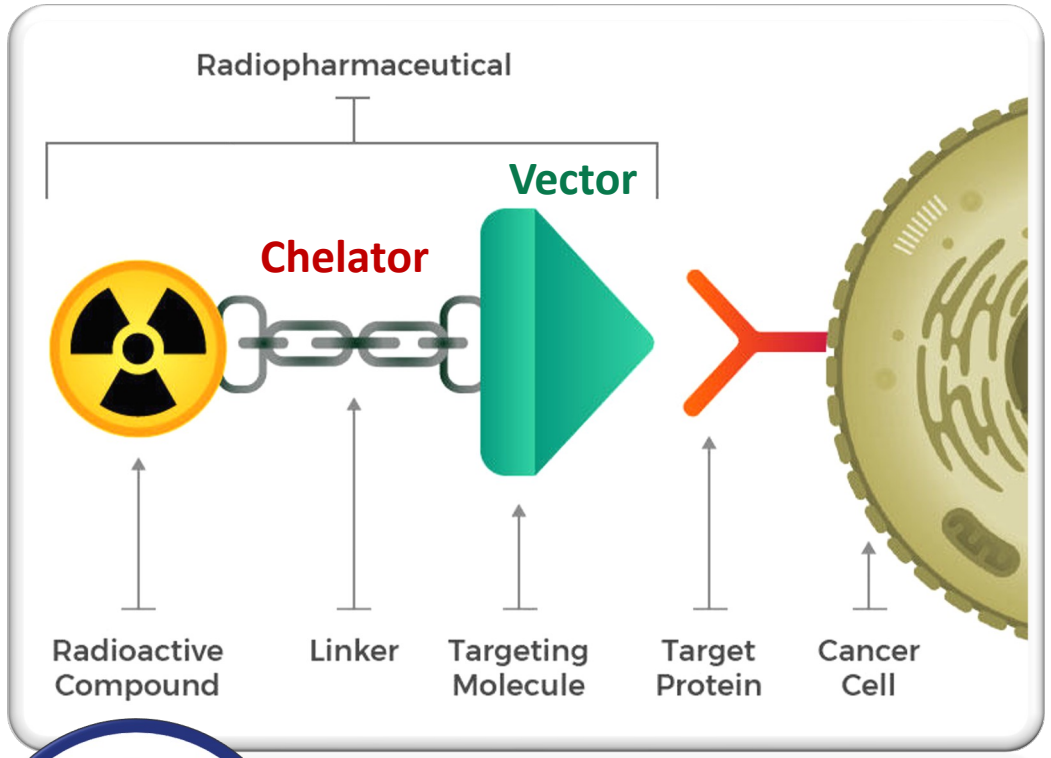
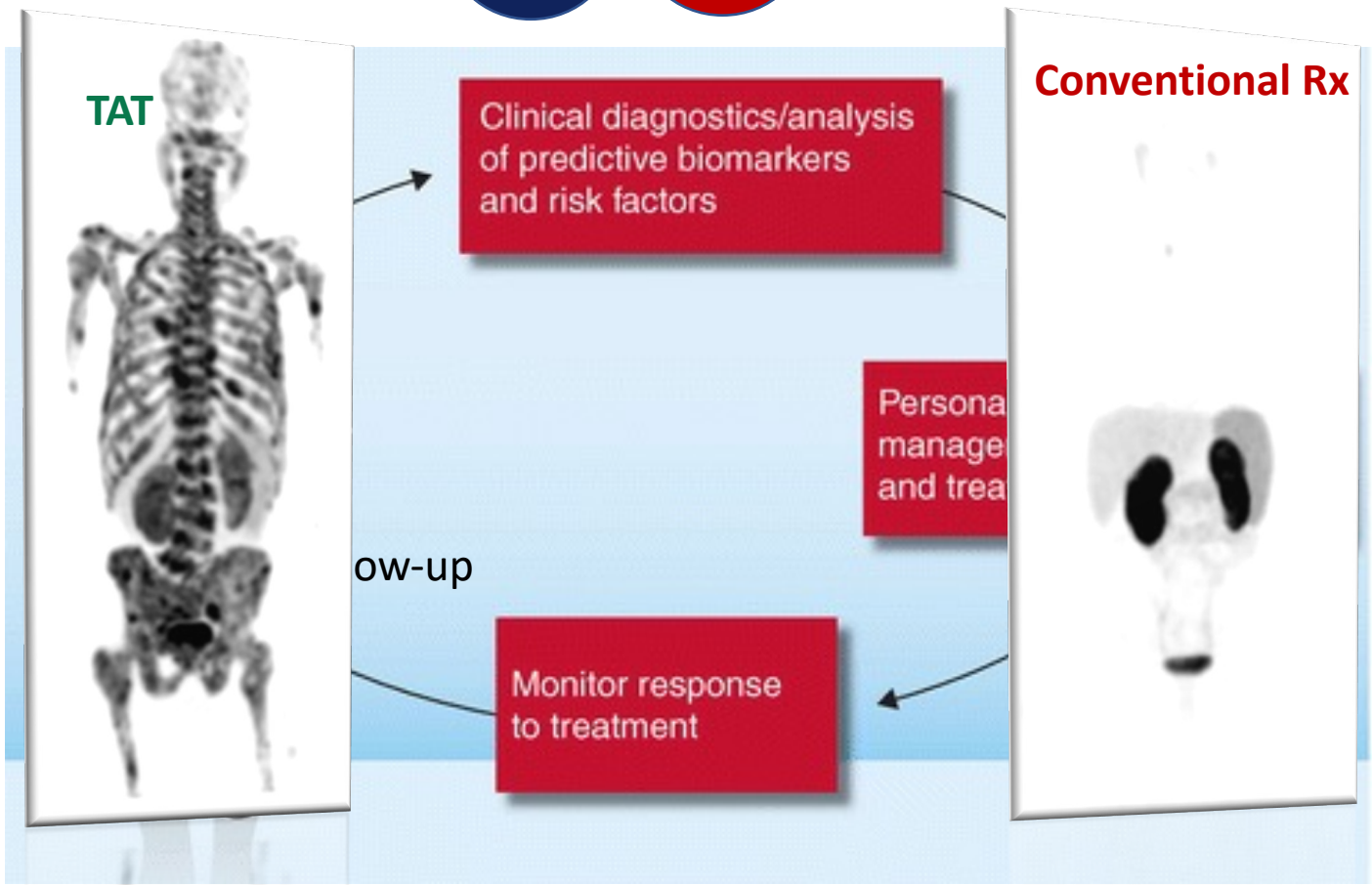
Theranostics



MoAb, Peptides, folic acid

Therapeutics

Diagnostics



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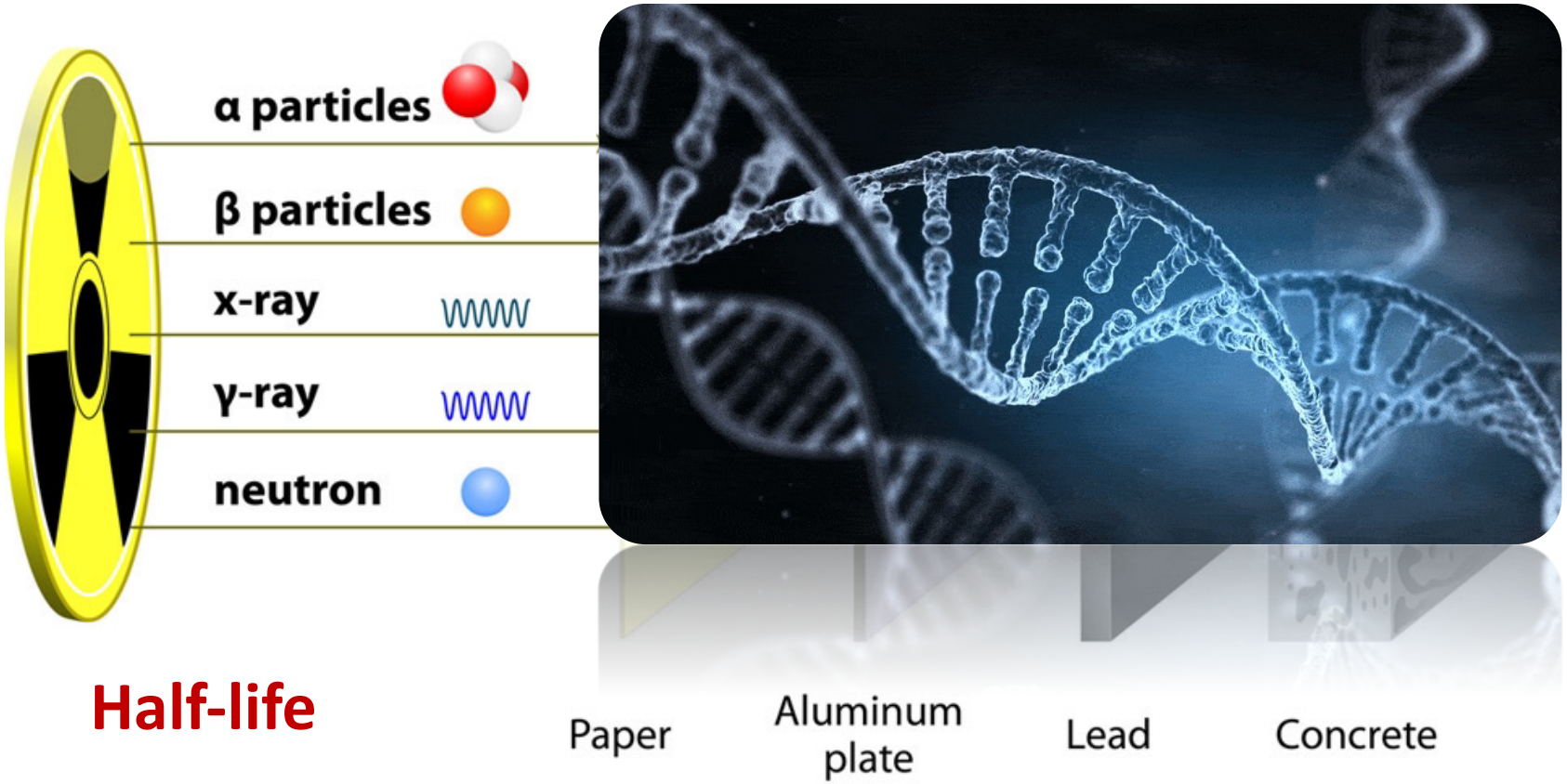
Basic principles

Types of radiation

Single vs Double-stranded DNA breaks

Labeling options

PSMA
DOTATATE
FAPI
& More…!



Recoil of daughters

Half-life

Tumour size

Internalization

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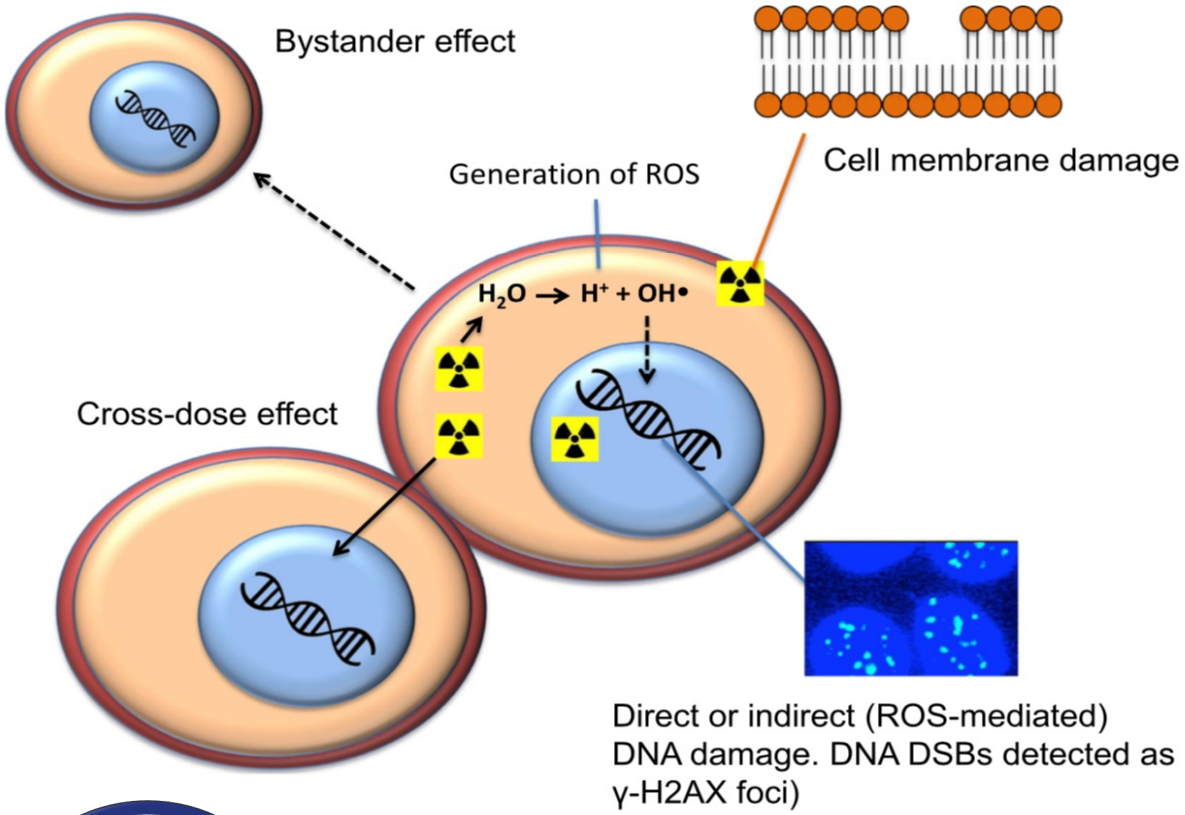
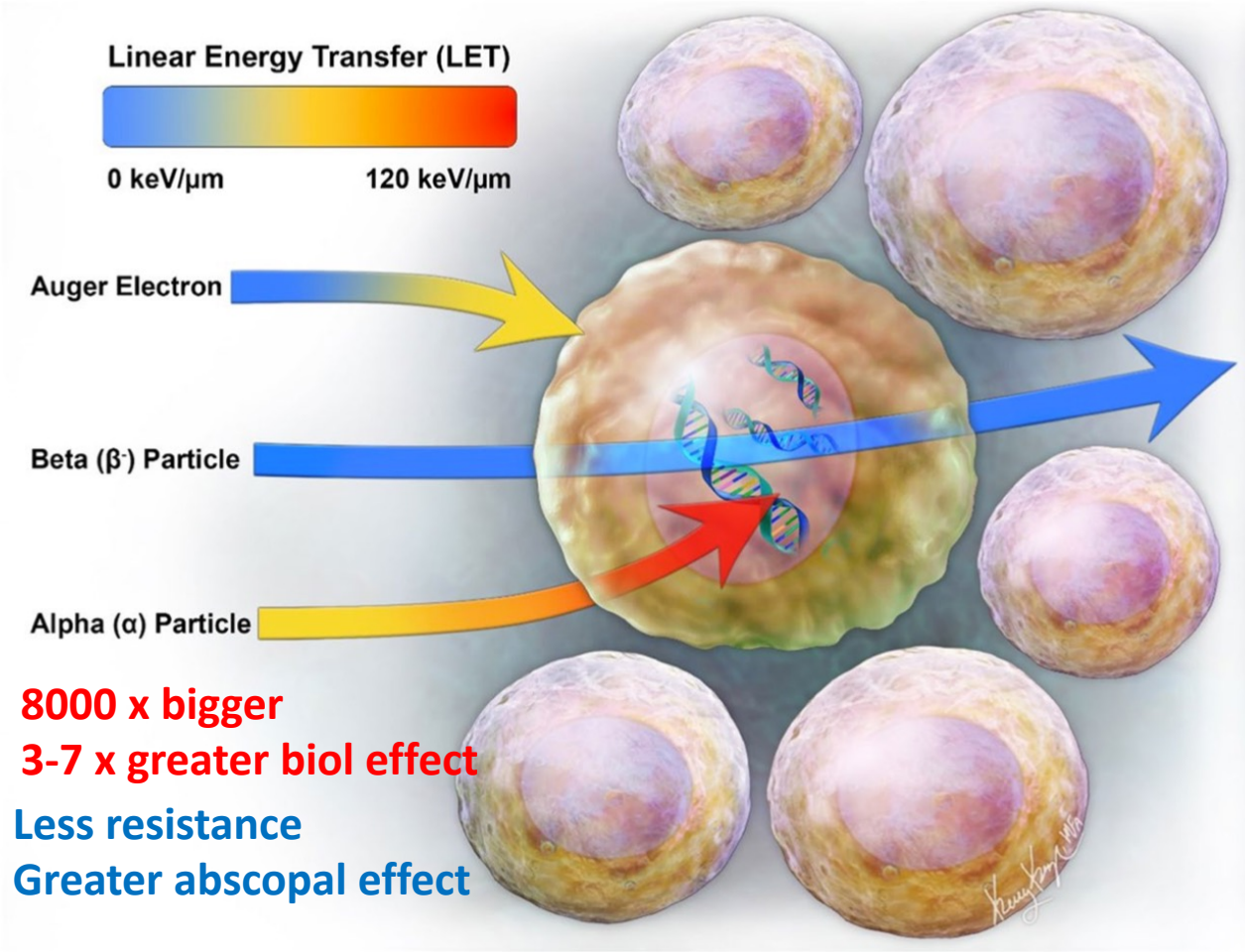
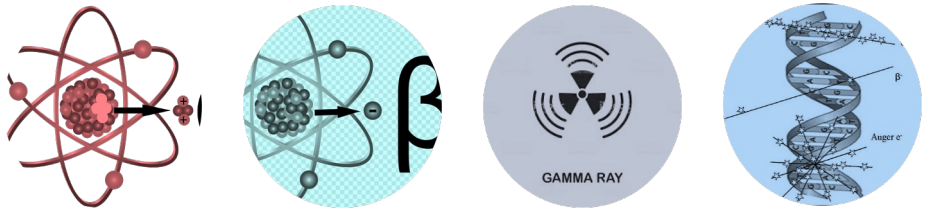
Basic principles





8000 x bigger
3-7 x greater biol effect

Less resistance
Greater abscopal effect



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Molecular Imaging and Biology (2023) 25:991–1019

PET

SPECT

Beta Therapy

Alpha Therapy

Diagnostic Surrogates

$^{132/133}La$			^{209}At		
^{226}Ac					
$^{134}Ce/^{134}La$	^{203}Pb	^{131}Ba	$^{123/124/131}I$	$^{134}Ce/^{134}La$	$^{152/155}Gd$
⇅	⇅	⇅	⇅	⇅	⇅
^{225}Ac	^{212}Pb	$^{223/224}Ra$	^{211}At	^{227}Th	^{149}Tb

Alpha Therapy

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Review

Targeted Alpha-Particle Therapy: A Review of Current Trials

Albert Jang [1], Ayse T. Kendi [2], Geoffrey B. Johnson [2,3], Thorvardur R. Halfdanarson [4] and Oliver Sartor [2,4,5,*]

Table 1. Current active and recruiting clinical trials with commercial sponsors using targeted alpha therapy.

Trial Number	Alpha Particle	Target	Agent(s)	Setting	Primary Outcome Measures
			Cornell		
NCT03276572	^{225}Ac	PSMA	^{225}Ac-J591	mCRPC treated with prior ARPI	DLT, MTD
NCT04506567	^{225}Ac	PSMA	^{225}Ac-J591	mCRPC treated with prior ARPI	DLT, MTD, RP2D
NCT04576871	^{225}Ac	PSMA	^{225}Ac-J591	mCRPC treated with prior ARPI	DLT
NCT04886986	^{225}Ac	PSMA	^{225}Ac-J591 with ^{177}Lu-PSMA-I&T	mCRPC treated with prior ARPI	DLT, MTD, RP2D, PSA decline
NCT04946370	^{225}Ac	PSMA	^{225}Ac-J591 with pembrolizumab and ARPI	mCRPC treated with prior ARPI	DLT, RP2D, response rate
NCT05567770	^{225}Ac	PSMA	^{225}Ac-J591	mHSPC	DLT, MTD
			Fusion Pharmaceuticals		
NCT03746431	^{225}Ac	IGF-1R	^{225}Ac-FPI-1434	IGF-1R-positive solid tumors refractory to standard therapies	AE, DLT, ORR
NCT05605522	^{225}Ac	NTSR1	^{225}Ac-FPI-2059	NTSR1-positive solid tumors refractory to standard therapies	AE, MTD
NCT05219500	^{225}Ac	PSMA	^{225}Ac-FPI-2265 (PSMA-I&T)	mCRPC with prior ARPI	PSA50, safety
			Bayer		
NCT04147819	^{227}Th	HER2	BAY2701439	HER2-positive solid tumors refractory to standard therapies	AE, ORR
			AdvanCell		
	^{212}Pb	PSMA	^{212}Pb-ADVC001	mCRPC with prior ARPI and no prior exposure to ^{177}Lu	RP2D
			Novartis		
	^{225}Ac	PSMA	^{225}Ac-PSMA-617	mCRPC	RP2D

Table 1. *Cont.*

Trial Number	Alpha Particle	Target	Agent(s)	Setting	Primary Outcome Measures
			Radiomedix and Orano Med		
NCT03466216	^{212}Pb	SSTR2	^{212}Pb-DOTAMTATE	SSTR2-positive neuroendocrine tumors refractory to standard therapies	DLT, MTD
NCT05153772	^{212}Pb	SSTR2	^{212}Pb-DOTAMTATE	SSTR2-positive neuroendocrine tumors refractory to standard therapies	ORR, AE
			RayzeBio		
NCT05477576	^{225}Ac	SSTR2	RYZ101	SSTR2-positive gastroenteropancreatic neuroendocrine tumors with prior ^{177}Lu therapy	RP3D, PFS
NCT05595460	^{225}Ac	SSTR2	RYZ101 with carboplatin, etoposide, and atezolizumab	SSTR2-positive extensive-stage small-cell lung cancer	RP2D, safety, tolerability
			Orano Med		
NCT05283330	^{212}Pb	GRPR1	^{212}Pb-DOTAM-GRPR1	GRPR1-positive solid tumors refractory to standard therapies	RP2D
			Actinium Pharmaceuticals		
NCT03441048	^{225}Ac	CD33	^{225}Ac-lintuzumab with cladribine, cytarabine, filgrastim, and mitoxantrone	Relapsed/refractory AML	DLT, MTD, AE, OS
NCT03867682	^{225}Ac	CD33	^{225}Ac-lintuzumab with venetoclax	Relapsed/refractory AML	MTD, overall response

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Clinical trials

Table 2. Current active and recruiting investigator-initiated clinical trials using targeted alpha therapy.

Trial Number	Alpha Particle	Target	Agent(s)	Setting	Primary Outcome Measures
NCT05275946	^{211}At	Thyroid tissue	TAH-1005	Differentiated thyroid cancer refractory to standard therapies	AE, DLT
N/A	^{211}At	Norepinephrine transporter	^{211}At-meta-astatobenzylguanidine	Pheochromocytoma and paraganglioma	Safety, MTD, phase 2 dose
NCT04083183	^{211}At	CD45	^{211}At-BC8-B10	Hematopoietic stem cell transplant regimen for non-malignant hematologic diseases	Graft rejection
NCT03670966	^{211}At	CD45	^{211}At-BC8-B10	Hematopoietic stem cell transplant regimen for malignant hematologic diseases	Toxicity
NCT04579523	^{211}At	CD38	^{211}At-OKT-B10 and fludarabine	Newly diagnosed, recurrent, or refractory high risk multiple myeloma	MTD
NCT04466475	^{211}At	CD38	^{211}At-OKT-B10 and melphalan	Relapsed or refractory multiple myeloma after at least 3 lines of prior therapy	MTD
NCT05363111	^{225}Ac	CD38	^{225}Ac-DOTA-daratumuab and daratumumab	Relapsed or refractory multiple myeloma after at least 2 lines of prior therapy	DLT, MTD
NCT05204147	^{225}Ac	CEA	^{225}Ac-DOTA-M5A	Metastatic solid tumors expressing CEA	AE, MTD

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Clinical trials

Int. J. Mol. Sci. **2023**, *24*, 11626

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Most likely to create a *Big Bang*…?

Ac-225

★★★★★

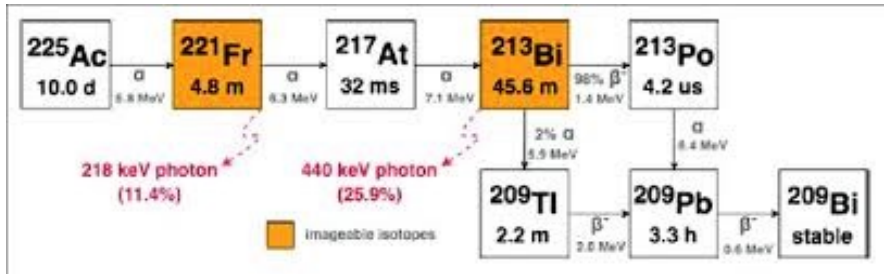
Production & Preparation

Physics: Half-life: 10 days, 4x Alpha emission, recoil

Partner with Gallium-68 PSMA, DOTATATE

Radio-nuclides	α - Recoil Energies
^{225}Ac	104.8 keV
^{221}Fr	116.3 keV
^{217}At	132.8 keV
^{213}Bi	112.0 keV
^{213}Po	160.4 keV

Actinium-225



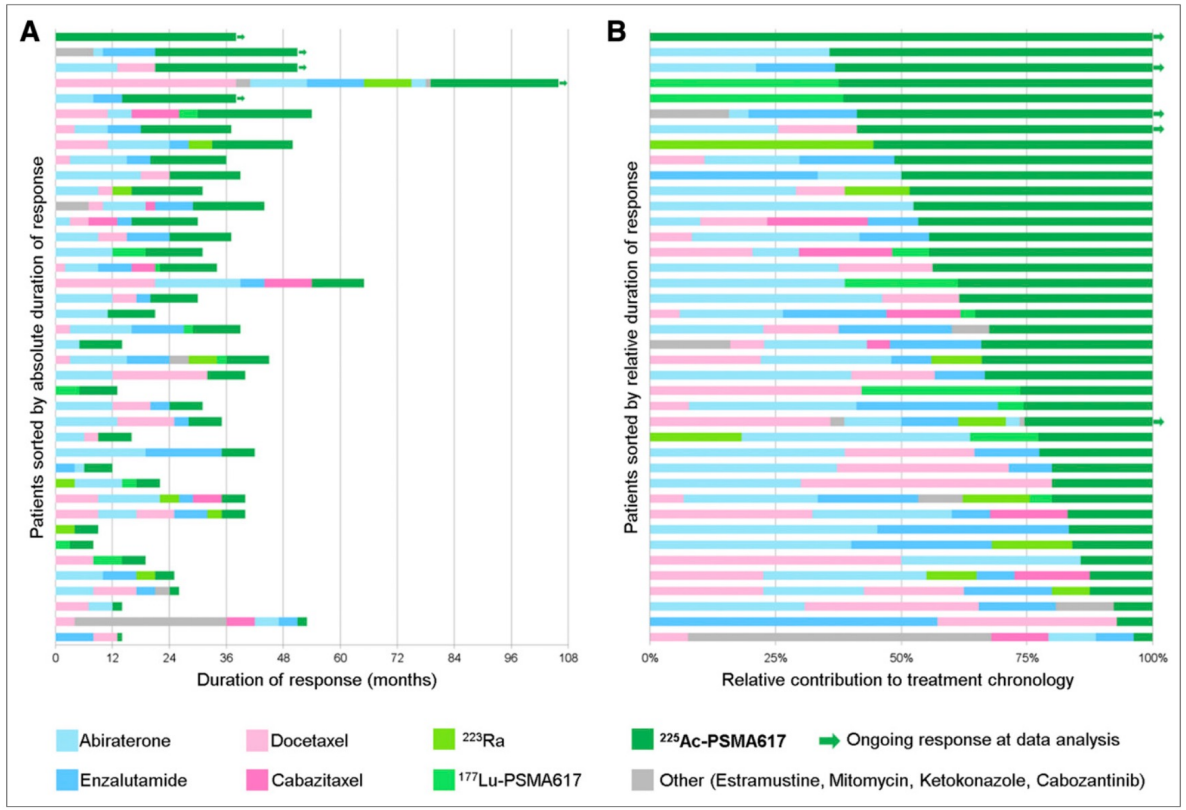


FIGURE 6. Swimmer plots showing duration of tumor control in months (A) and relative to duration of previous treatment lines (B).

J Nucl Med 2018; 59:795–802

89
Ac
Actinium
(225)

Ac-225-PSMA

★★★★★

Various clinical scenarios:

Chemotherapy-naive

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European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:129–138
https://doi.org/10.1007/s00259-018-4167-0

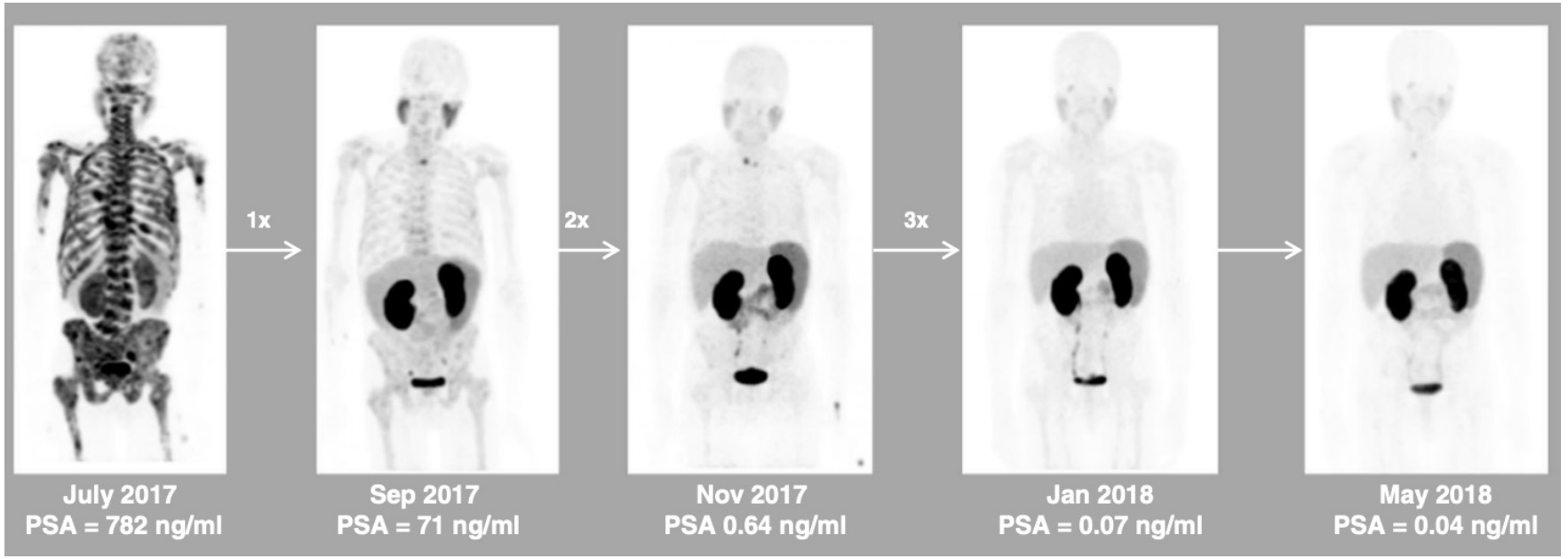
ORIGINAL ARTICLE

CrossMark

^{225}Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study

Mike Sathekge[1] · Frank Bruchertseifer[2] · Otto Knoesen[3] · Florette Reyneke[1] · Ismaheel Lawal[1] · Thabo Lengana[1] · Cindy Davis[1] · Johncy Mahapane[1] · Ceceila Corbett[1] · Mariza Vorster[1] · Alfred Morgenstern[1,2]

Received: 19 August 2018 / Accepted: 12 September 2018 / Published online: 19 September 2018



Group A=Combination of conventional therapy

71 % decrease in tumour markers

Group B: Rx naive

92% decrease in tumour markers

s-PSA response after a single dose (@8w)

Ac-225-PSMA

★★★★★

Various Clinical scenarios:

Post-ADT

FEATURED ARTICLE OF THE MONTH

mCRPC Patients Receiving ^{225}Ac-PSMA-617 Therapy in the Post–Androgen Deprivation Therapy Setting: Response to Treatment and Survival Analysis

Mike Sathekge[1,2], Frank Bruchertseifer[3], Mariza Vorster[1], Ismaheel O. Lawal[1,2], Otto Knoesen[4], Johncy Mahapane[1], Cindy Davis[1], Amanda Mdlophane[2], Alex Maes[1,5], Kgomotso Mokoala[1], Kgomotso Mathabe[6], Christophe Van de Wiele*[1,7], and Alfred Morgenstern*[1,3]

- Any PSA response in 91% of patients
- Undetectable level of serum PSA in 36%.
- A decline in serum PSA by at least 50% was significantly associated with a longer OS.
- A PSA decline of at least 50%, a low pre-treatment platelet level, and radiographic response on ^{68}Ga-PSMA-11 PET/CT were significant predictors of a longer PFS.

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89
Ac
Actinium
(225)

Ac-225-PSMA

★★★★★

Various Clinical scenarios:

Hormone sensitive

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European Journal of Nuclear Medicine and Molecular Imaging (2023) 50:2210–2218
https://doi.org/10.1007/s00259-023-06165-9

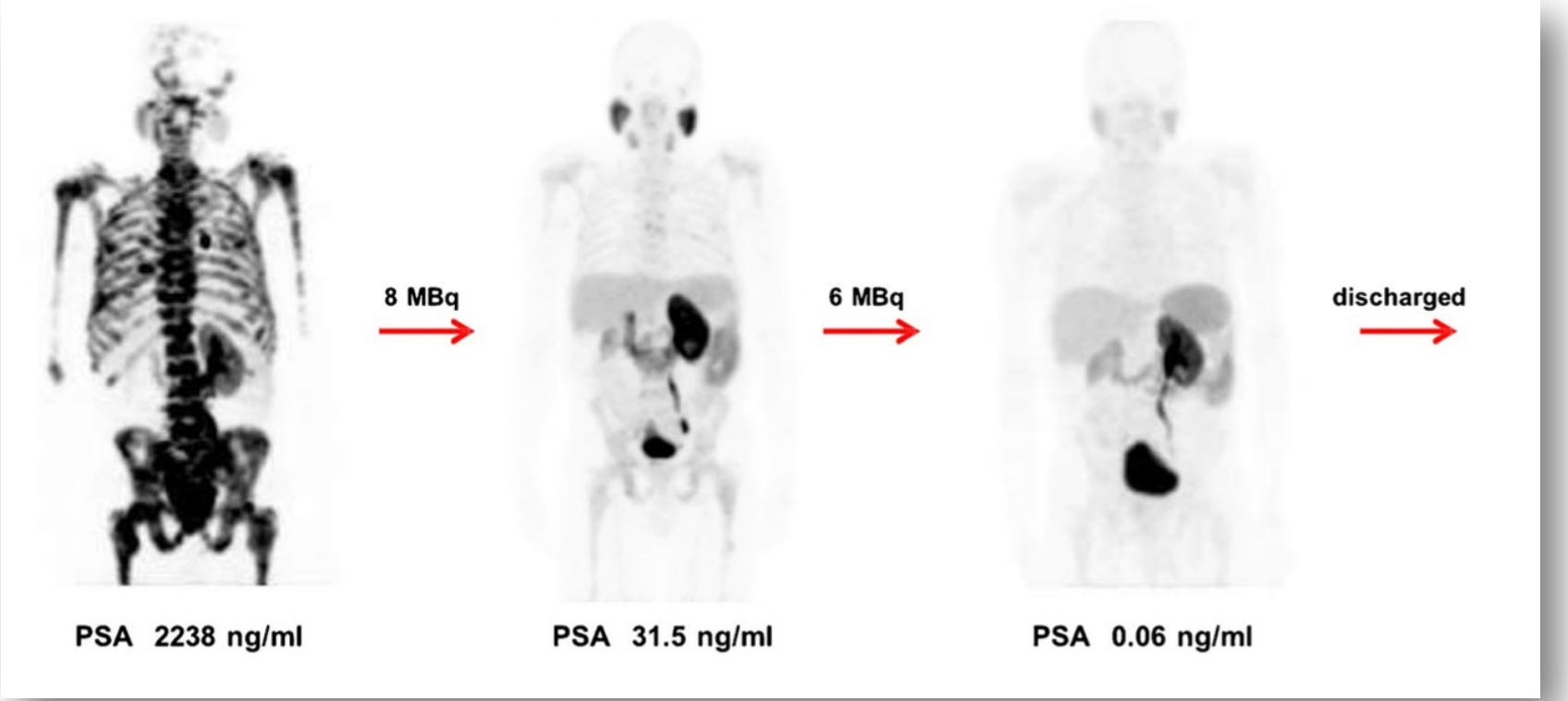
ORIGINAL ARTICLE

Check for updates

^{225}Ac-PSMA-617 radioligand therapy of de novo metastatic hormone-sensitive prostate carcinoma (mHSPC): preliminary clinical findings

Mike Sathekge[1,2] · Frank Bruchertseifer[3] · Mariza Vorster[4] · Ismaheel O. Lawal[1,2] · Kgomotso Mokoala[1,2] · Janet Reed[1,2] · Letjie Maseremule[1,2] · Honest Ndlovu[1,2] · Khanyi Hlongwa[1,2] · Alex Maes[1,5] · Alfred Morgenstern[1,3] · Christophe Van de Wiele[1,6]

n=21 (68 cycles)
95% ANY decline in PSA
86% Decline of ≥ 50%
Undetectable PSA in 4
Median PFS 9 months
50% alive at 34 months



EJNMMI (2023) 50:2210–2218

89
Ac
Actinium
(225)

Ac-225-PSMA

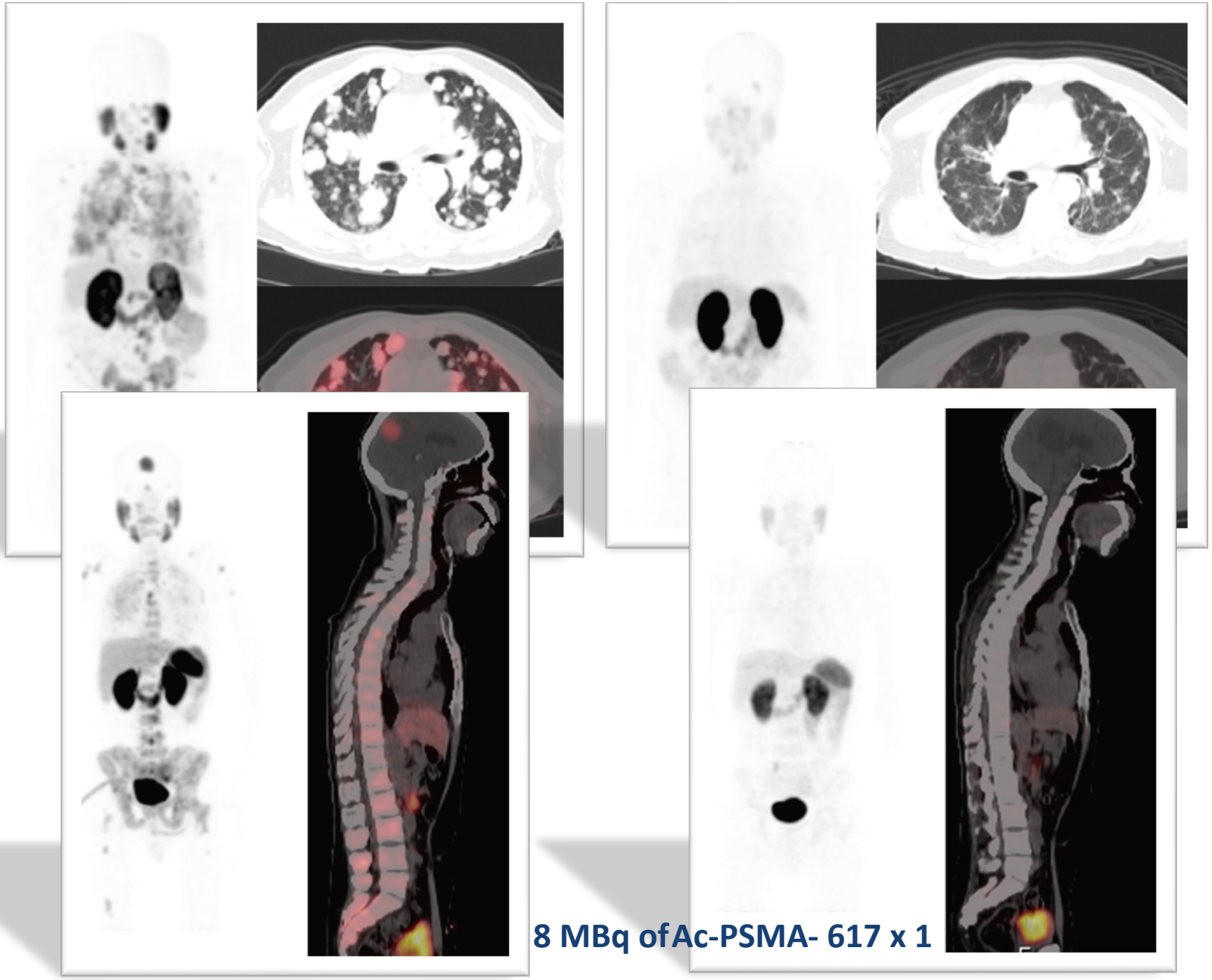
★★★★★

Various Clinical scenarios:

?Hopeless

s-PSA=1897.91 µg/L

s-PSA=17.21 µg/L



8 MBq of Ac-PSMA- 617 x 1

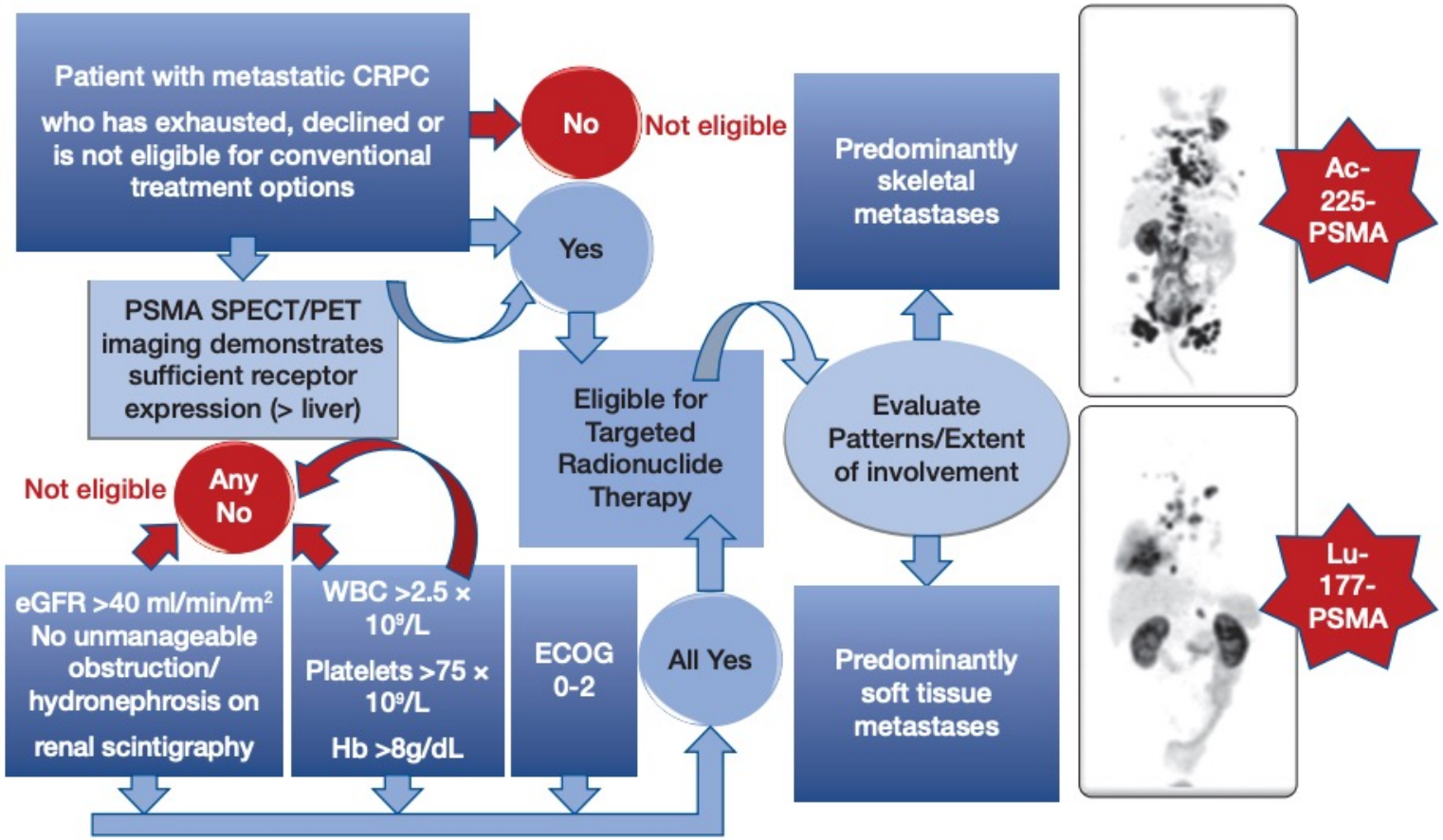
Sathekge et al

89
Ac
Actinium
(225)

Ac-225-PSMA

★★★★★

Actinium-225: Practical aspects



Vorster M & Sathekge MM. Theranostics in Metastatic Castrate Resistant Prostate Cancer 2021 May 27:81-96.

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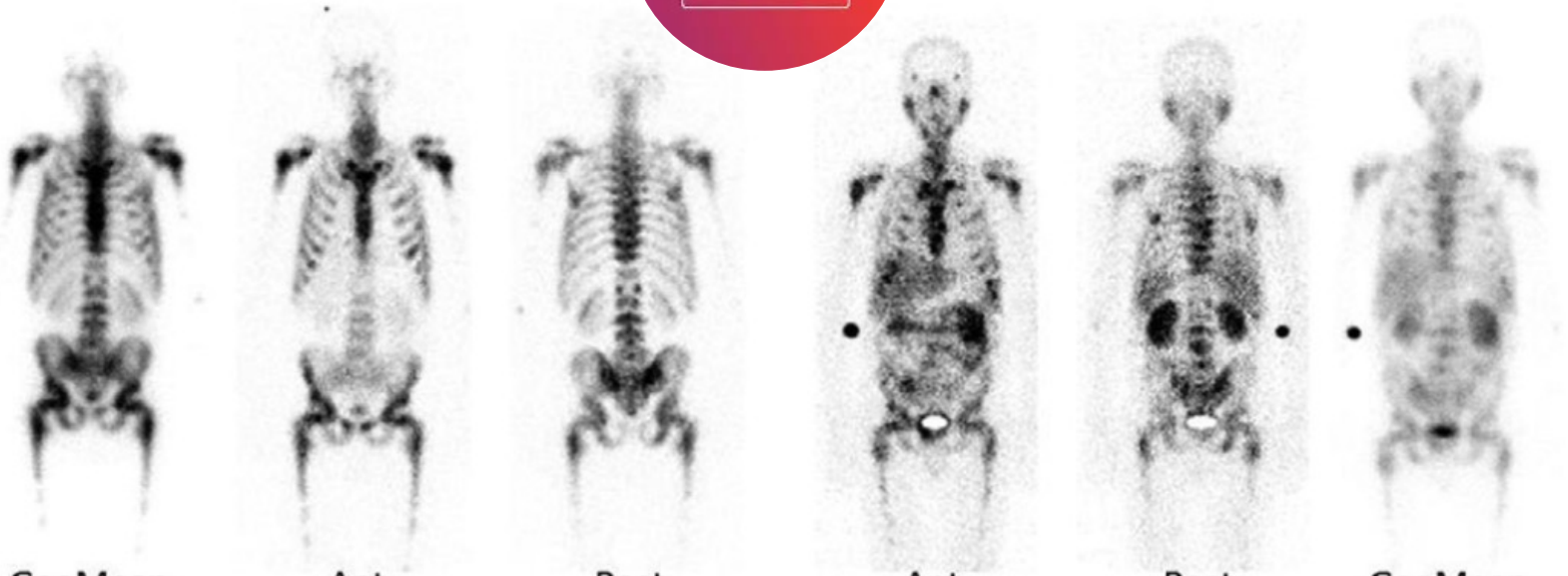
Tandem approaches

ELSEVIER
Seminars in NUCLEAR MEDICINE

^{225}Ac-PSMA-617 for Therapy of Prostate Cancer

PSA=722.5



1. cycle
[1.5 GBq ^{177}Lu-PSMA + 8 MBq ^{225}Ac-PSMA]

2. cycle
[2 GBq ^{177}Lu-PSMA + 6 MBq ^{225}Ac-PSMA]

PSA=0.4

Semin Nucl Med 50:133-140, 2020

Kreish et al.Eur J Nucl Med Mol I. 2020;47(3):721–8.
Kulkarni et al. J Nucl Med. 2016;57(Supplement_3):97S-104S.

^{225}Ac-PSMA Meta-analyses: mounting evidence of efficacy!

Efficacy and Safety of ^{225}Ac-PSMA-617-Targeted Alpha Therapy in Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

*Jiao Ma[1], Lanying Li[1], Taiping Liao[1], Weidong Gong[1] and Chunyin Zhang[1,2,3]**

[1] Department of Nuclear Medicine, The Affiliated Hospital of Southwest Medical University, Luzhou, China, [2] Nuclear Medicine and Molecular Imaging Key Laboratory of Sichuan Province, Luzhou, China, [3] Academician (expert) Workstation of Sichuan Province, Luzhou, China

Journal of Nuclear Medicine, published on September 9, 2021 as doi:10.2967/jnumed.121.262017

Effects of ^{225}Ac-labeled prostate-specific membrane antigen radioligand therapy in metastatic castration-resistant prostate cancer: A meta-analysis

Running title: ^{225}Ac-PSMA RLT effects in mCRPC patients

Dong Yun Lee, MD, PhD,[1] Yong-il Kim, MD, PhD[1]

[1]*Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*

Excellent s-PSA responses, xerostomia

REVIEW ARTICLE

The Prostate WILEY

Article | Published: 21 March 2021

^{225}Ac-PSMA-617-targ
metastatic castration
review and meta-ana

nd therapy in
ate cancer—a

Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study

Sanjana Ballal PhD[1] | Madha
Tripathi MD[1] | Sad

agwant Rai Mittal

his article

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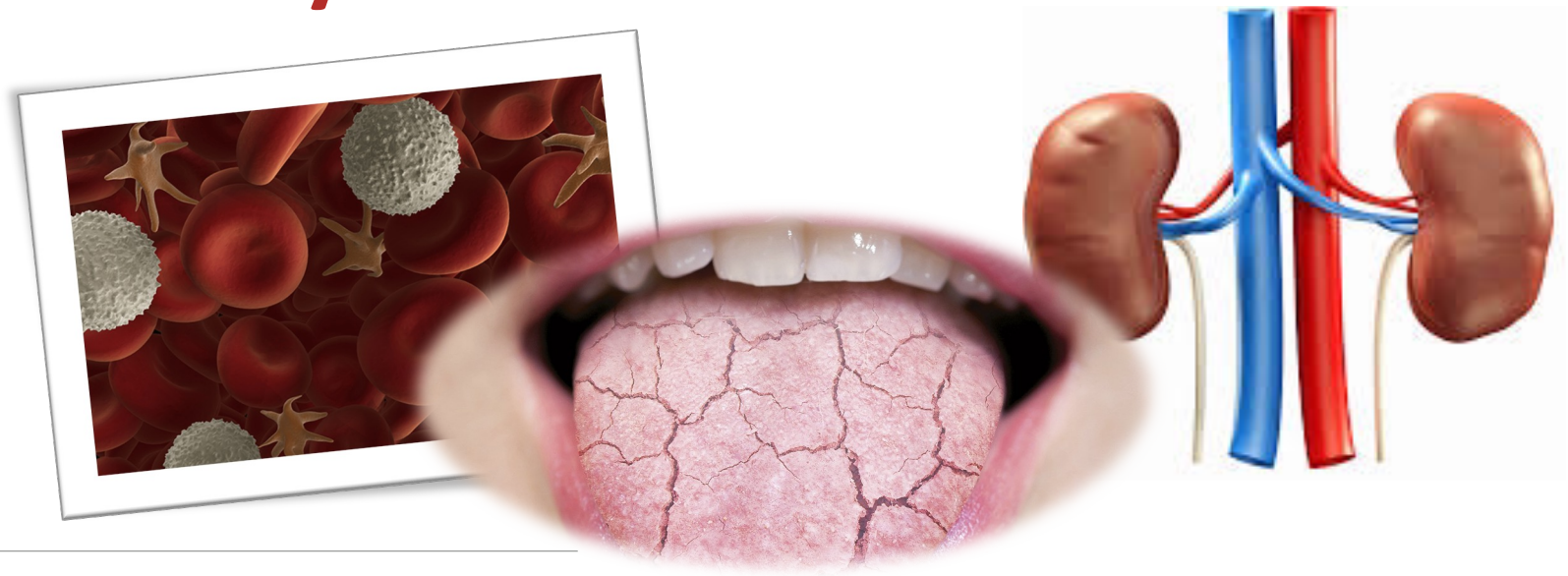
Sathekge 2024 Lancet Oncol

Side effects/ toxicity of Ac-225-PSMA?

Efficacy and Safety of ^{225}Ac-PSMA-617-Targeted Alpha Therapy in Metastatic Castration-Resistant Prostate Cancer: A Systematic Review and Meta-Analysis

*Jiao Ma[1], Lanying Li[1], Taiping Liao[1], Weidong Gong[1] and Chunyin Zhang[1,2,3]**



6 studies
201 pts

TABLE 1 | Quality assessment of the included studies based on the Newcastle–Ottawa Scale.

NO.	Author and year	Selection	Comparability	Outcome	Score
1	Kratochwil et al. (12)	3	1	3	7
2	Sathekge et al. (13)	3	1	3	7
3	van der Doelen et al. (14)	3	1	3	7
4	Satapathy et al. (15)	3	1	2	6
5	Feuerecker et al. (16)	2	1	3	6
6	Sen et al. (17)	3	1	3	7

Xerostomia most common
77.1% (any degree)
Grade III 3.0%.
Anemia 30.3% (any degree)
Grade III 7.5%.
Grade III leukopenia 4.5%
Thrombocytopenia 5.5%
Grade III nephrotoxicity in 3%.

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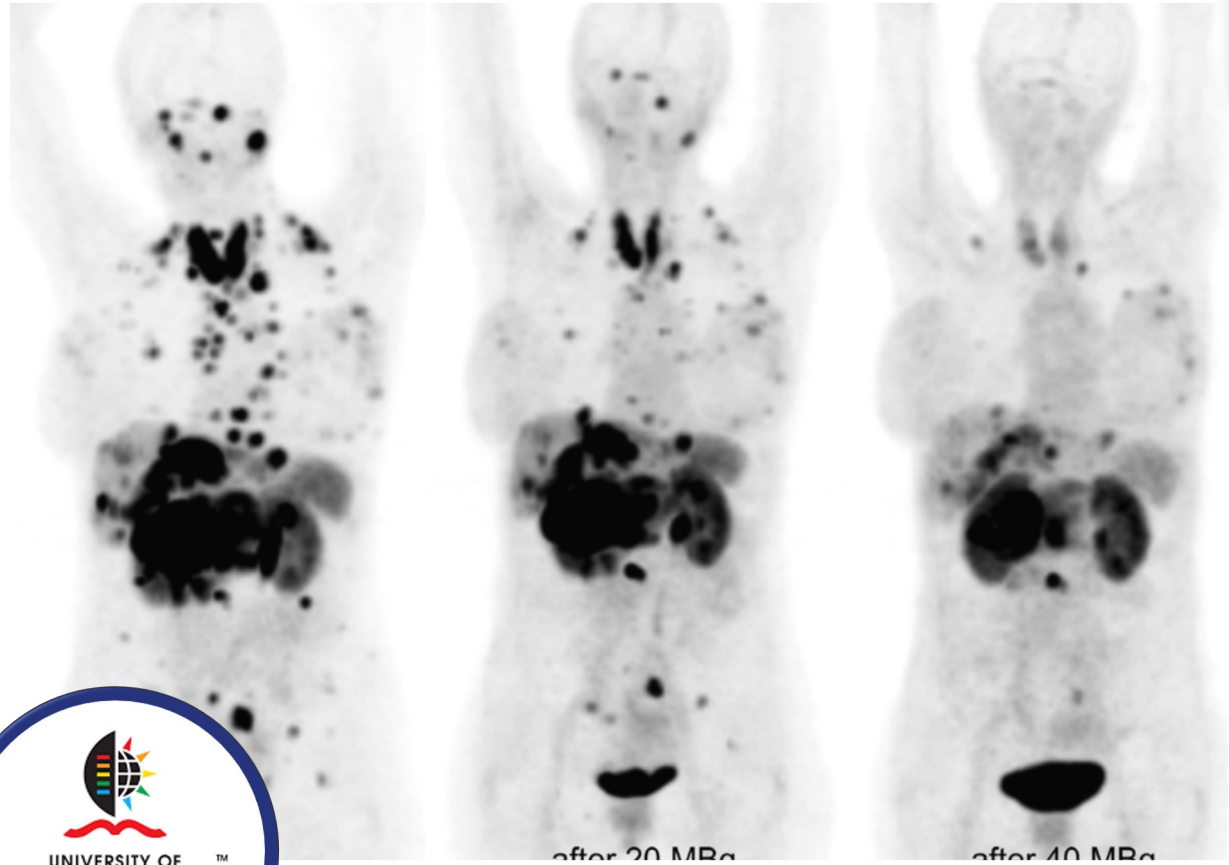
Ma J et al. Frontiers in Oncology. 2022;12.

LSEVIER

Seminars in
NUCLEAR
MEDICINE

'argeted α-Emitter Therapy of Neuroendocrine 'umors

olanta Kunikowska, MD, PhD and Leszek Królicki, MD, PhD



European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-023-06494-9

ORIGINAL ARTICLE

Structural modifications toward improved lead-203/lead-212 peptide-based image-guided alpha-particle radiopharmaceutical therapies for neuroendocrine tumors

Dongyoul Lee[1] · Mengshi Li[2] · Dijie Liu[2] · Nicholas J. Baumhover[2] · Edwin A. Sagastume[2] · Brenna M. Marks[2] · Prerna Rastogi[3] · F. Christopher Pigge[4] · Yusuf Menda[5] · Frances L. Johnson[2] · Michael K. Schultz[2,4,5,6]

"Preclinical studies described here suggest that PSC-PEG2- TOC has the potential to improve the efficacy of Pb-based a-particle therapy for SSTR2-expressing tumors with a **significantly lower toxicity profile** than previous SSTR2- targeted peptide."

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NET: Ac-225-DOTATATE, Pb-212

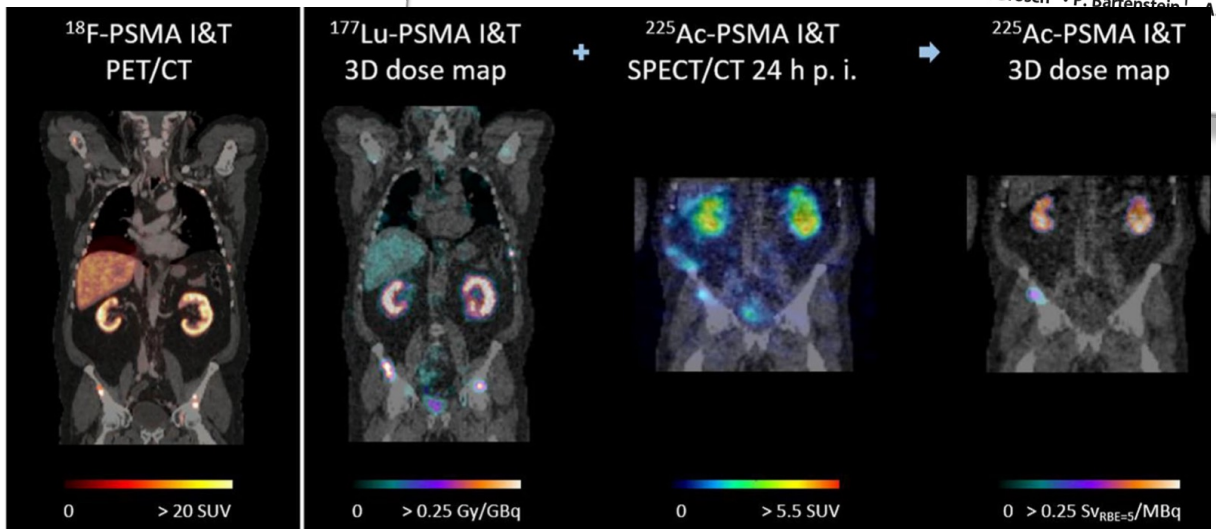
^{225}Ac-PSMA Dose & Dosimetry

https://doi.org/10.1007/s00259-020-05024-1

IMAGE OF THE MONTH

Image-based dosimetry for ^{225}Ac-PSMA-I&T therapy using quantitative SPECT

A. Gosewisch [1] · M. Schleske [1] · F. J. Gildehaus [1] · I. Berg [1] · L. Kaiser [1] · J. Brosch [1] · P. Bartenstein [1] · A. Todic
H. Ilhan [1] · G. Böning [1]



Phys. Med. Biol. **65** (2020) 235012 https://doi.org/10.1088/1361-6560/abbc81

Physics in Medicine & Biology

IPEM Institute of Physics and Engineering in Medicine

PAPER

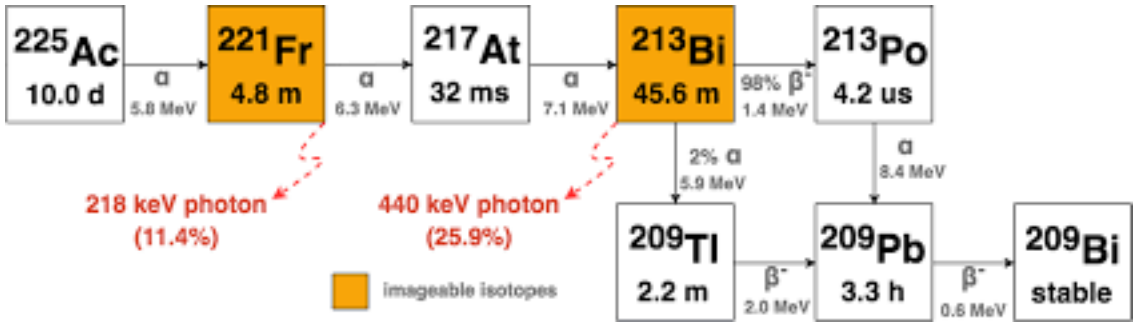
Microdosimetry-based determination of tumour control probability curves for treatments with ^{225}Ac-PSMA of metastatic castration resistant prostate cancer

Pablo Mínguez Gabiña[1,2], John C Roeske[3], Ricardo Mínguez[4], Emilia Rodeño[5,6] and Alfonso Gómez de Iturriaga[6,7]

Some lesions may not be treated sufficiently at 100kBq/kg

Monte Carlo simulations

Tumour control probability curves



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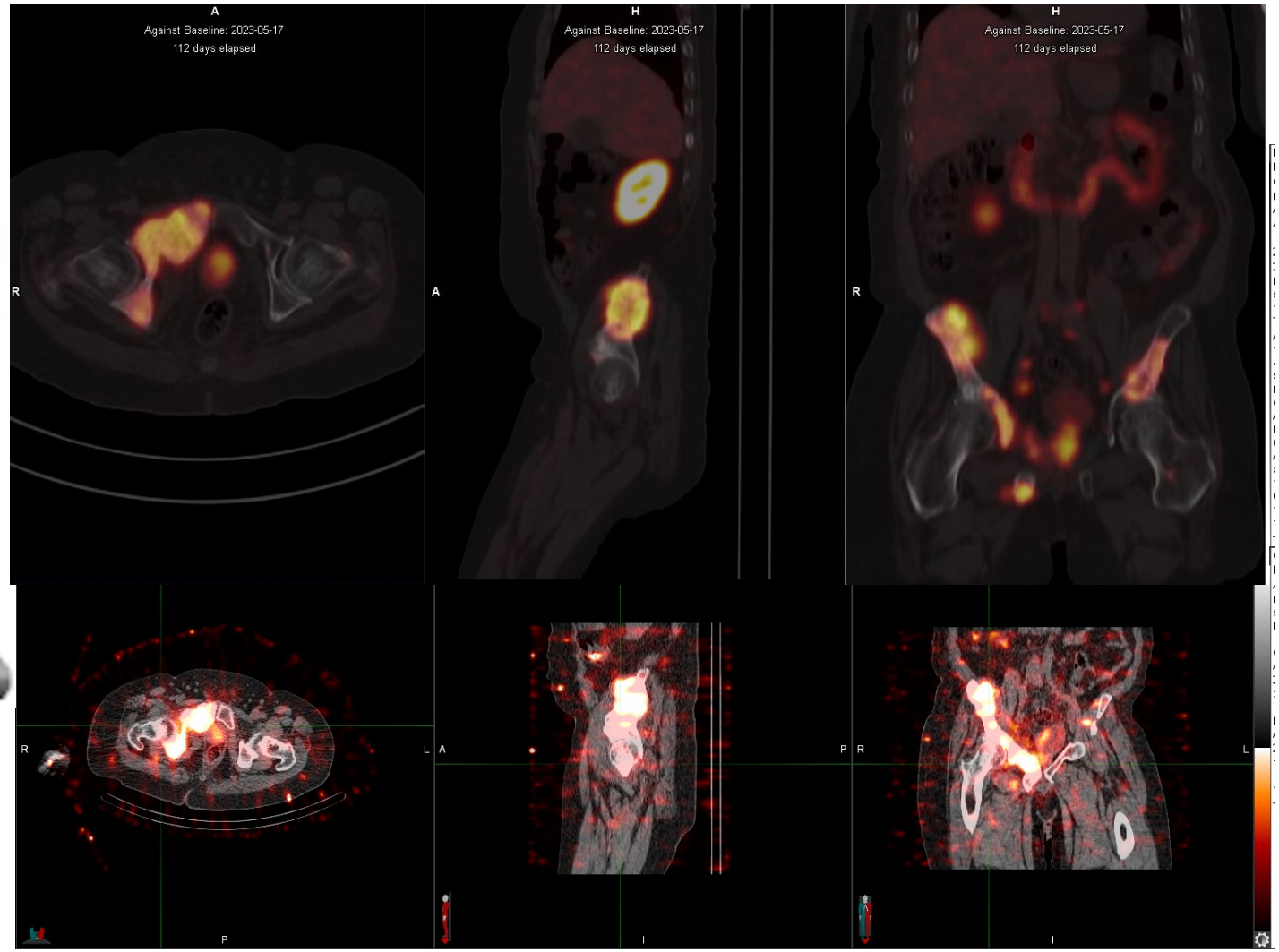
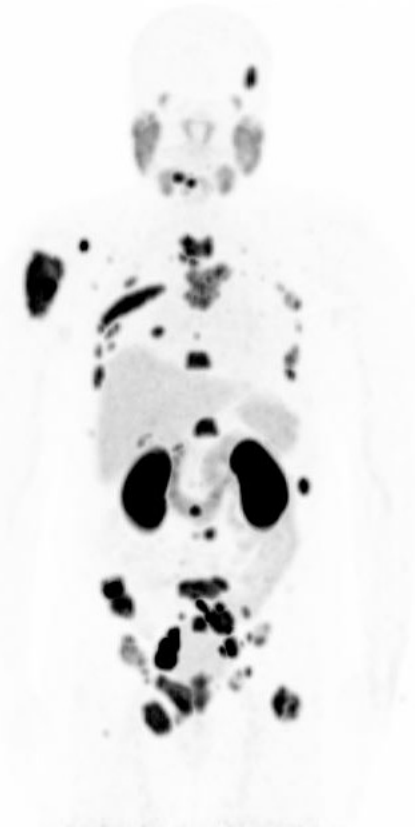
EJNMMI Aug 2020

Phys Med Biol 2020

^{225}Ac-PSMA Dose & Dosimetry

128 x128 matrix
60s per projection
60 projections
(30 per head)
1 bed position
OSEM 5 mm filter
HEGP Collimator





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TARGETED RADIONUCLIDE THERAPY

Bismuth-213

★★★★

Half-life: 45.6 minutes

1x Alpha emission, no recoil

FAPI labeling possibilities

NETA/DEPA over DOTA

Regional (intravesical, intracerebral, intralesional)

& systemic approaches

Renal toxicity

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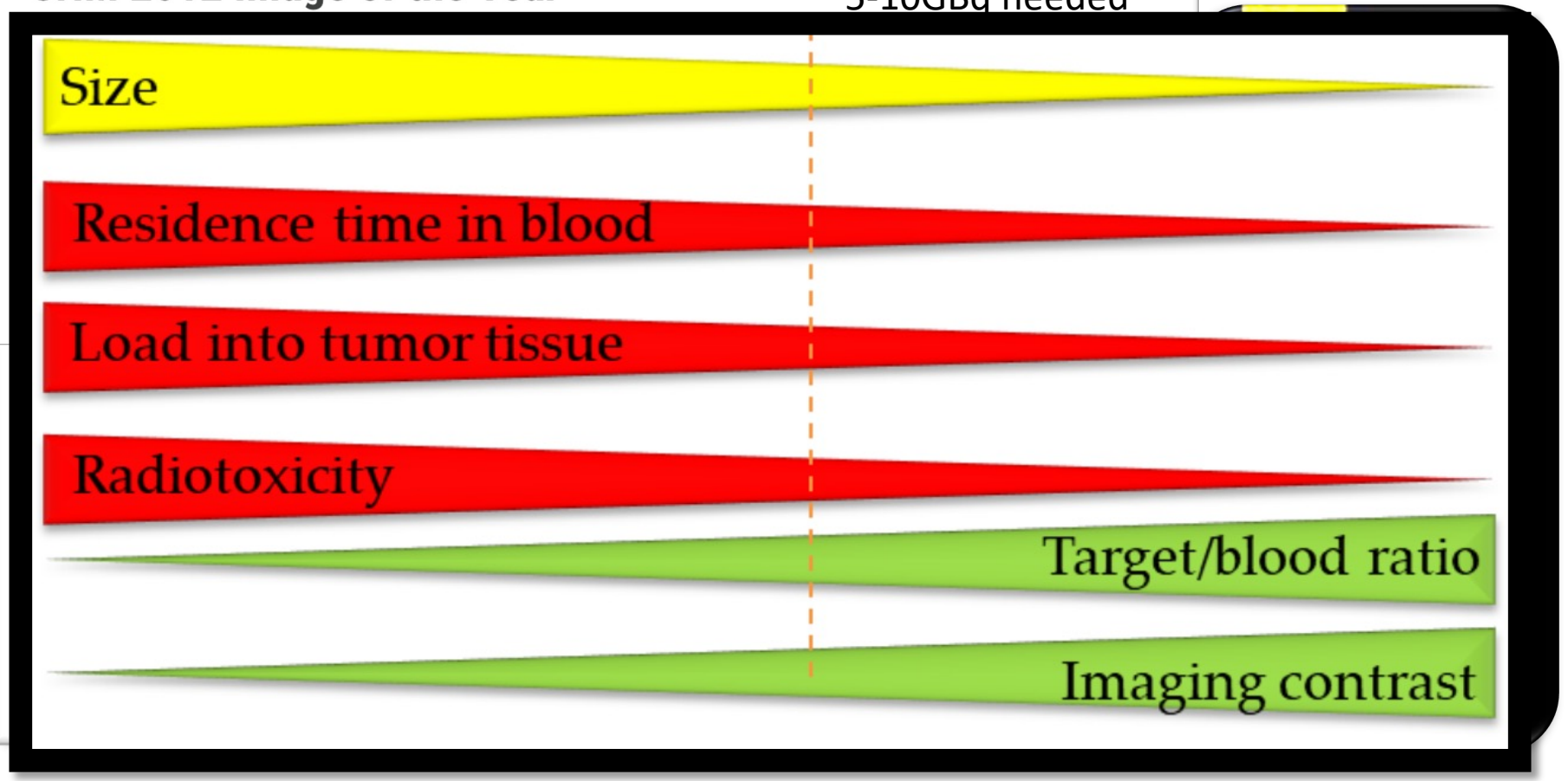
83
Bi
Bismuth
208.980

Bismuth-213

>200 patients with leukemia, lymphoma, melanoma, bladder CA, glioma and NETs treated

SNM 2012 Image of the Year

5-10GBq needed



Pharmaceutics 2021, 13, 599 S Ahenkorah et al

Radium-223

Xofigo (FDA approved)

★★★★

Half-life: 11.4 days

GIT and BM Side effects

Combination Therapies

Sr-89, Sm-153…

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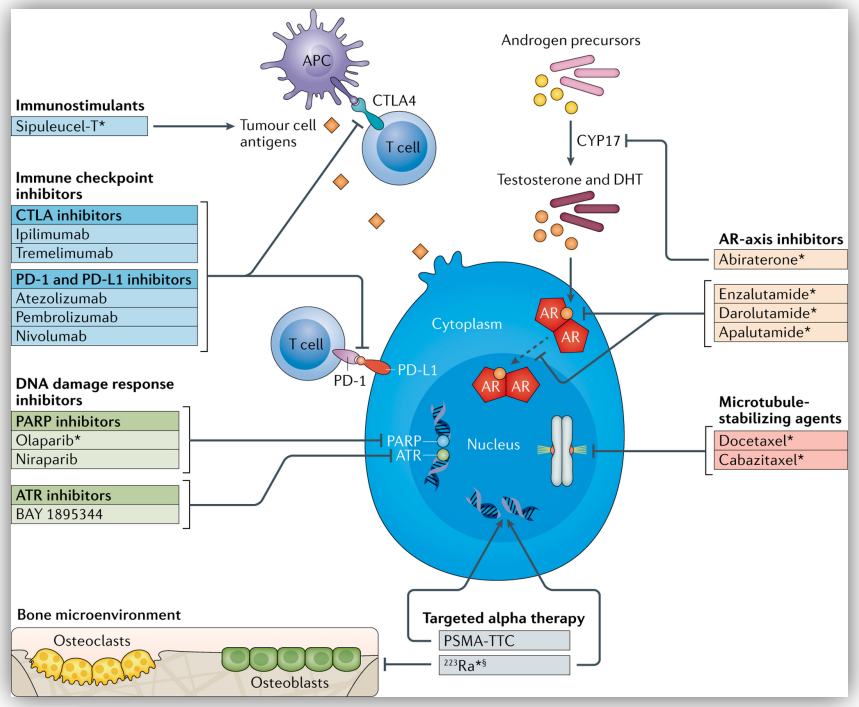
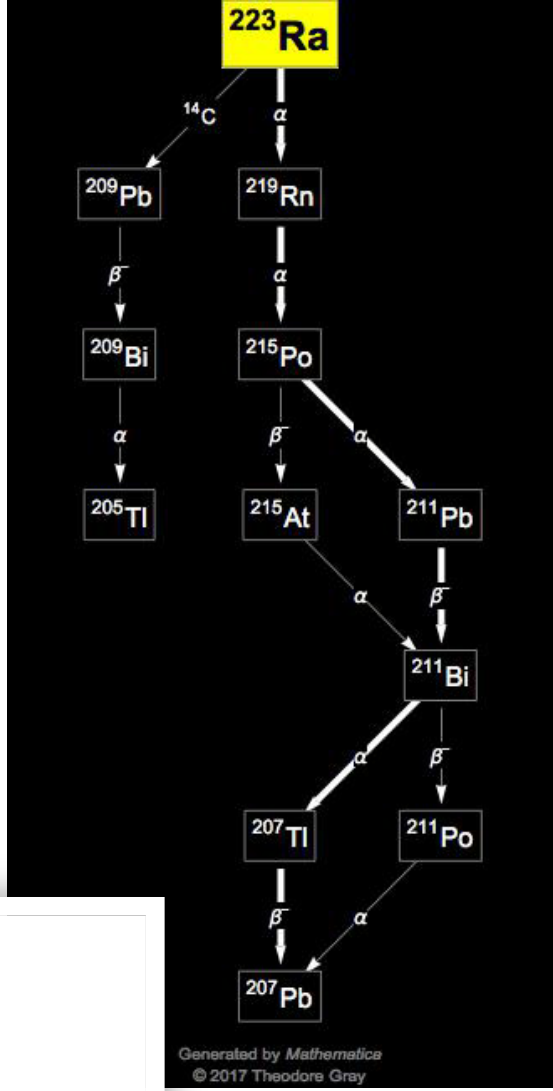
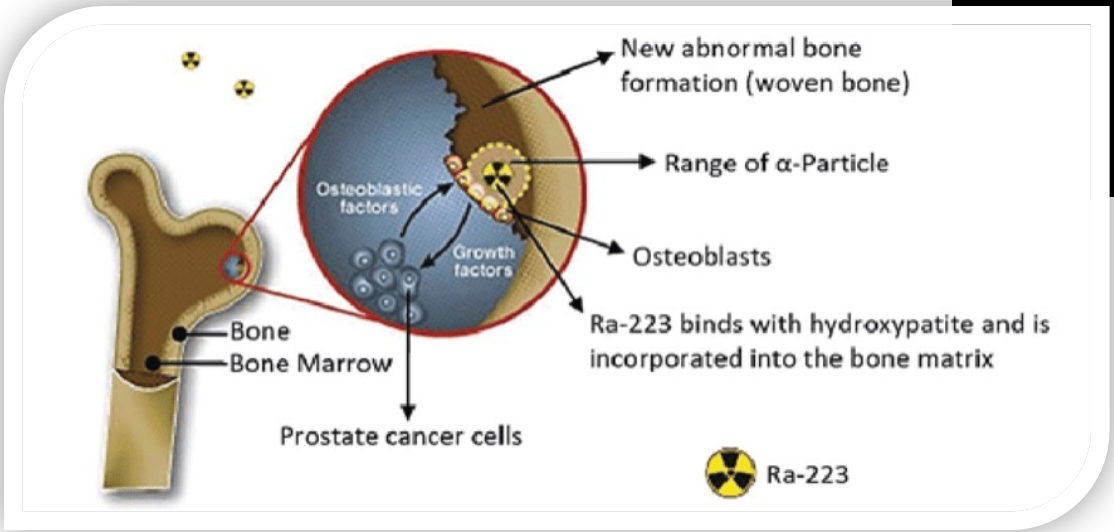
Radium-223







Increased OS
and
Time to first skeletal event

Radium-223

★★★★

Combination Therapies in cancers that spread to bone/

Osteosarcoma

Ass with bone fractures in combination with Abi/pred-ERA 223 trial

Final results due in 2024…

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

Table 28. Clinical applications of ^{223}Ra in combination with other therapies.

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:824–845
https://doi.org/10.1007/s00259-017-3900-4

GUIDELINES

Included in NCCN guidelines: mCRPC, sx fractures, no visceral mets

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]

[^{223}Ra]Ra-dichloride + Leuprolide acetate,	GnRH-receptor agonist	NCT03361735 (Phase II; ongoing)	Prostate cancer [345]
[^{223}Ra]Ra-dichloride + Pembrolizumab	PDL-1	NCT03093428 (Phase II; ongoing)	Prostate cancer [346]
[^{223}Ra]Ra-dichloride + Atezolizumab	PDL-1	NCT02814669 (Phase I; completed)	Castration-resistant prostate cancer [347]
Alpha-DaRT seeds (^{224}Ra containing 316LVM tubes)	Implantation sites	NCT04002479 (Phase not applicable) NCT03970967 (Phase not applicable)	Metastatic pancreatic cancer [348] Metastatic breast cancer [349]

Thorium-227

★★★

Half-life: 18.7 days

5x Alpha emission

Recoil, Daughters, Ra-223

Preclinical potential in lymphoma, breast CA, ovarian CA, AML, renal cell CA, mesothelioma, osteosarcoma, mCRPC

TTC=Targeted Thorium-227 conjugates

Can form highly stable chelator complexes-Rx of several hematological- and solid malignancies

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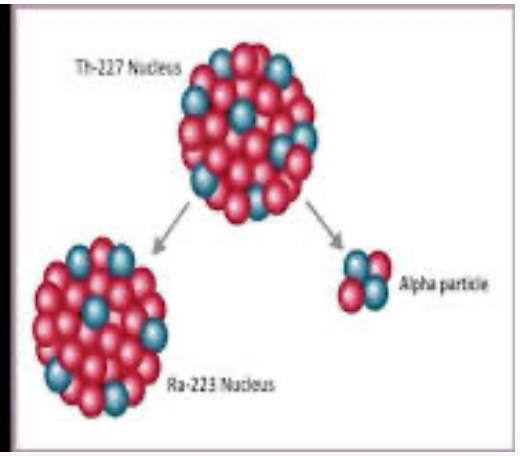
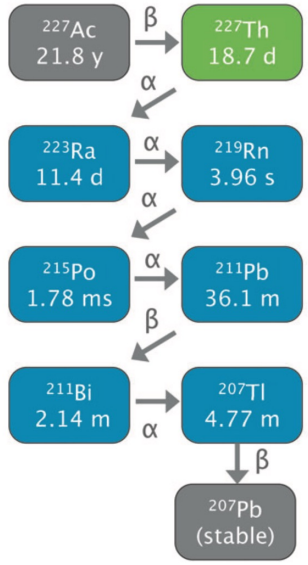
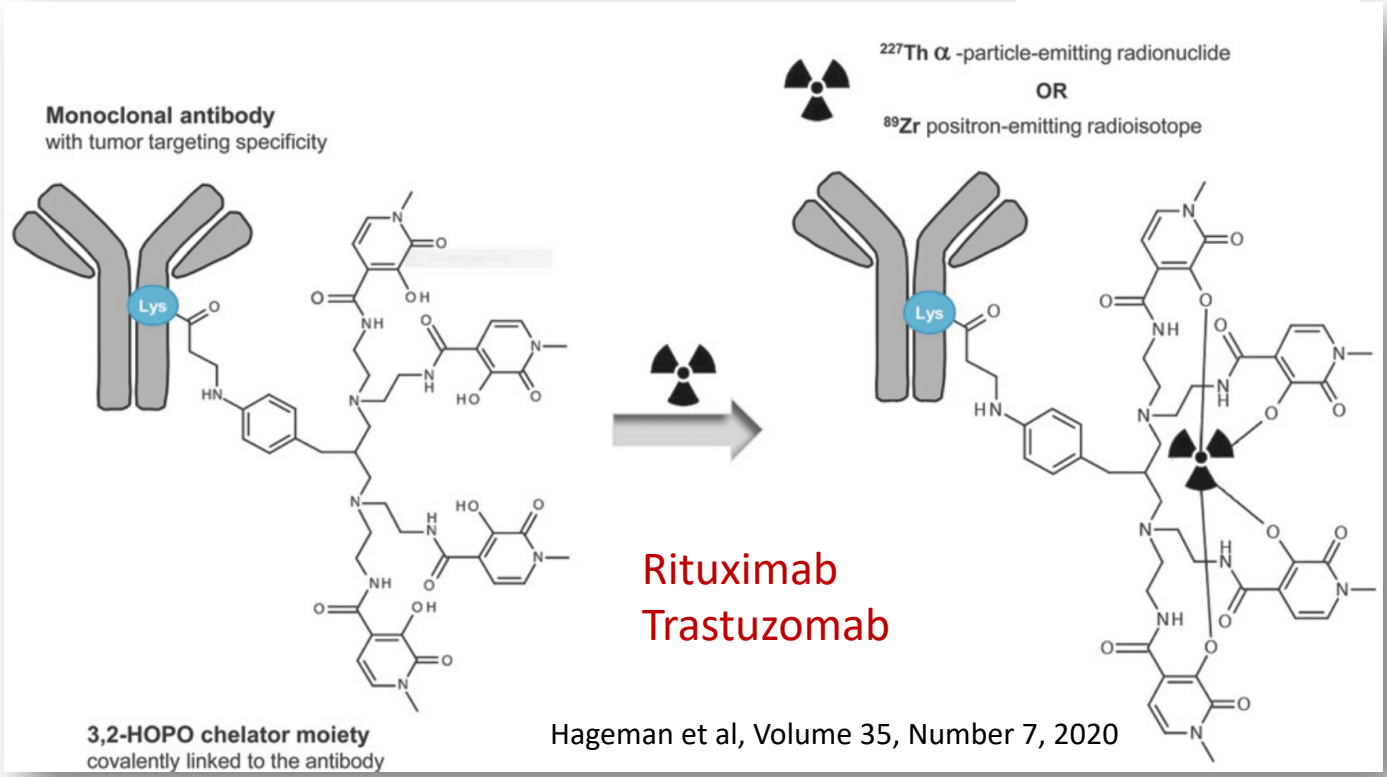
^{227}Th

Thorium-227







Hageman et al, Volume 35, Number 7, 2020

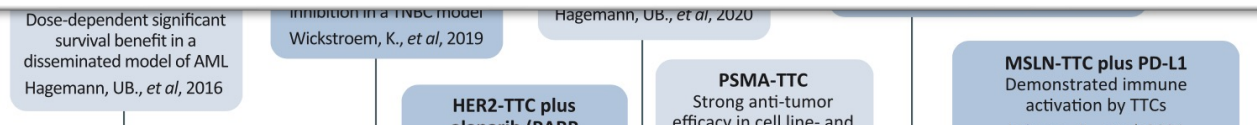
Thorium-227

Thorium-227

★★★

Table 30. Clinical applications of ^{227}Th-labeled radiopharmaceuticals.

Radiopharmaceuticals	Targets	NCT Number ^	Disease
[^{227}Th]Th-anti PSMA (BAY2315497)	PSMA	NCT03724747 (Phase I; ongoing)	Metastatic castration-resistant prostate cancer [355]
[^{227}Th]Th-anti Mesothelin (BAY2287411)	Mesothelin	NCT03507452 (Phase I; completed)	Advanced recurrent serous ovarian, malignant peritoneal mesothelioma, pancreatic adenocarcinoma [358]
[^{227}Th]Th-trastuzumab (BAY2701439)	HER2+	NCT04147819 (Phase I; ongoing)	Cancer with HER2 + expression [359]
[^{227}Th]Th-epratuzumab (BAY1862864)	CD22	NCT02581878 (Phase I; completed)	Non-Hodgkin lymphoma [360]



cancers

MDPI

Article

Efficacy of a HER2-Targeted Thorium-227 Conjugate in a HER2-Positive Breast Cancer Bone Metastasis Model

Jenny Karlsson [1,*], Urs B. Hagemann [2], Véronique Cruciani [1], Christoph A. Schatz [2], Derek Grant [1], Christine Ellingsen [1], Alexander Kristian [1], Shirin Katoozi [1], Dessislava Mihaylova [1], Steinar R. Uran [1], Mari Suominen [3], Roger M. Bjerke [1], Olav B. Ryan [1] and Alan Cuthbertson [1]

Karlsson et al, 2023

Sharma, Pharmaceuticals **2023**, *16*, 1460.

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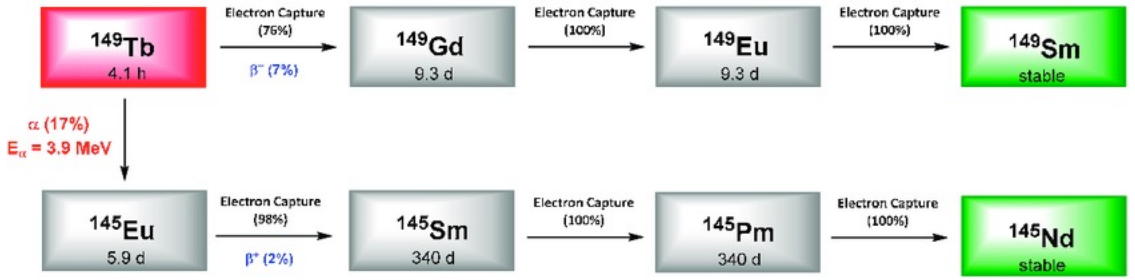
Terbium-149

149 Tb Terbium

Terbium-149



★★★★

Half-life of 4.1 hr

B+ 730 keV (7%) PET & Alpha

Alpha particles , no daughters

Stable DOTA coordination to small LMW

Easily cleared

Melanoma, leukemia, NET promising

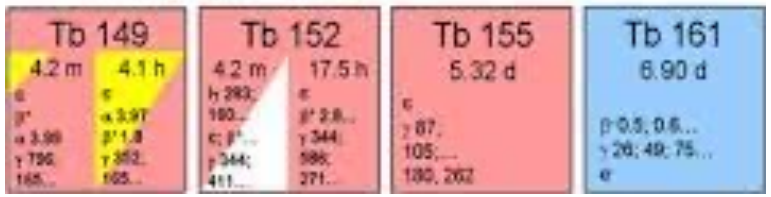
Short supply!

Only alpha-emitting Radio-isotope of Terbium
165 keV and B particle

Major concerns:
Large –scale production
Decay scheme to long-lived radionuclides

Terbium-149 production: a focus on yield and quality improvement towards preclinical application

C. Favaretto[1,2], P. V. Grundler[2], Z. Talip[2], U. Köster[3,4], K. Johnston[4], S. D. Busslinger[2], Sprung[5], C. C. Hillhouse[6], R. Eichler[6,7], R. Schibli[2,8], C. Müller[2,8] & N. P. van der Meulen[2]



PET SPECT Auger

Conclusions
In this study, the production and radiochemical purification of terbium-149 were optimized to provide terbium-149 in quantity and quality, to our knowledge, never achieved in the past, and sufficient for use in more extensive therapeutic preclinical studies than those previously conducted.

Major concern:
large scale production

Favaretto et al. Scientific reports (2024) 14:3284

Astatine-211

★★★★

Half-life of 7.21 hours

Single Alpha particle (simplifies dosimetry, less off-target)

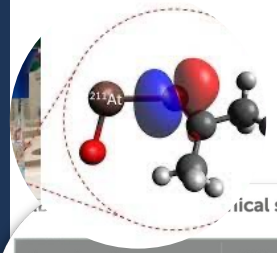
Flexible chemistry

Cyclotron production

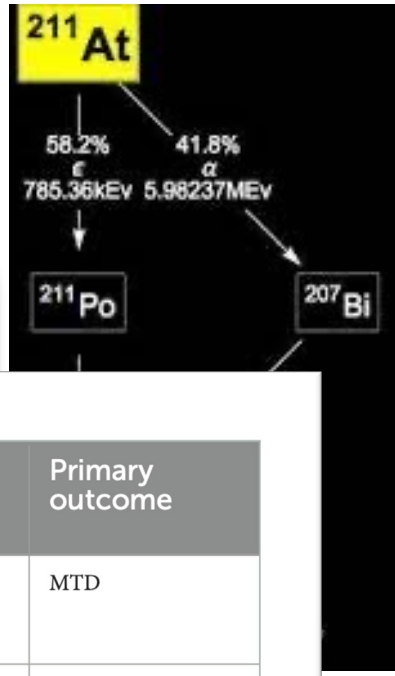
Stable DOTA coordination

Promising in Thyroid,

NET, hemat ca, Glioma



Astatine-211



...ical studies using ^{211}At. (*NTC number*) is the ClinicalTrials.gov identifier.

Institution, Reference	Clinical situation	Nb. Pts.	Study Objective	TAT-agent	Target	Adminis-tration	Act-ivity	Toxicity/ effect
Duke University Medical Center,	Recurrent surgically resected	18	Feasibility and safety	^{211}At-ch81C6	tenascin	Surgically created	71–347 MBq	MTD, Not reached

TABLE 2 Ongoing and planned clinical trials with ^{211}At. (NTC number) is the ClinicalTrials.gov identifier.

Institution, reference	Clinical situation	Planned size (nb Pts.)	Study objective(s)	TAT-agent/ Carrier	Target	Primary outcome
Fred Hutchinson Cancer Center, Seattle, USA (*NCT04466475*)	Multiple Myeloma	24	Feasibility and safety	^{211}At-OKT10-B10	CD38	MTD
Fred Hutchinson Cancer Center, Seattle, USA (*NCT04579523*)	Multiple Myeloma	30	Dose escalation	^{211}At-OKT10-B10	CD38	MTD
Fred Hutchinson Cancer Center, Seattle, USA (*NCT04083183*)	HCT for non-malignant disease	40	Dose escalation	^{211}At- BC8-B10	CD45	Graft rejection
Fred Hutchinson Cancer Center, Seattle, USA (*NCT03670966*)	High-risk acute leukemia or MDS	30	Dose-escalation	^{211}At- BC8-B10	CD45	Toxicity
Fred Hutchinson Cancer Center, Seattle, USA (*NCT03128034*)	High-risk AML, ALL, MDS or Mixed-phenotype acute leukemia	50	Dose-escalation	^{211}At- BC8-B10	CD45	Toxicity, MTD
Osaka University Hospital, Suita, Japan (*NCT05275946*)	Thyroid cancer	11	To establish recommended dose for Phase II trial	[^{211}At] NaAt	NIS	Treatment-related adverse events
Fukushima Medical University, Japan	Malignant pheochromocytoma	Up to 18	Dose escalation	^{211}At-MABG	Norepinephrine transporter	Toxicity, MTD

HCT, Hematopoietic cell transplantation.

Lead-212

★★★★★

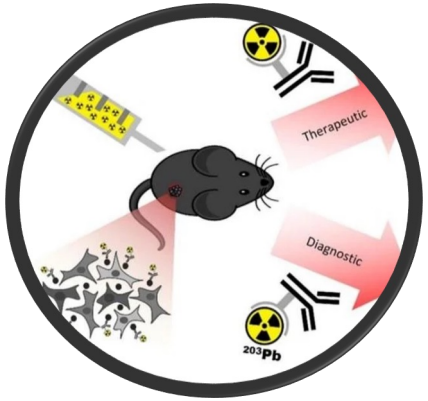
Physics: Half-life: 10.6 hrs

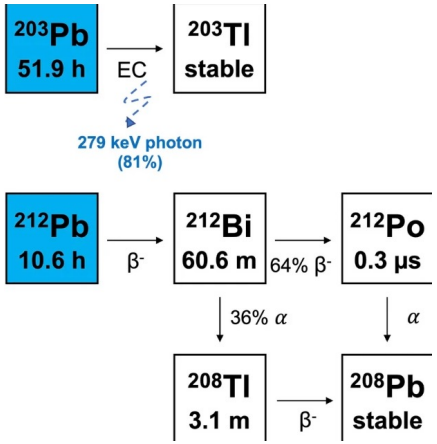
1x alpha, 2x beta emission

Production (3 generator possibilities)

Partner with Pb-203 (t1/2 51.9 hrs)

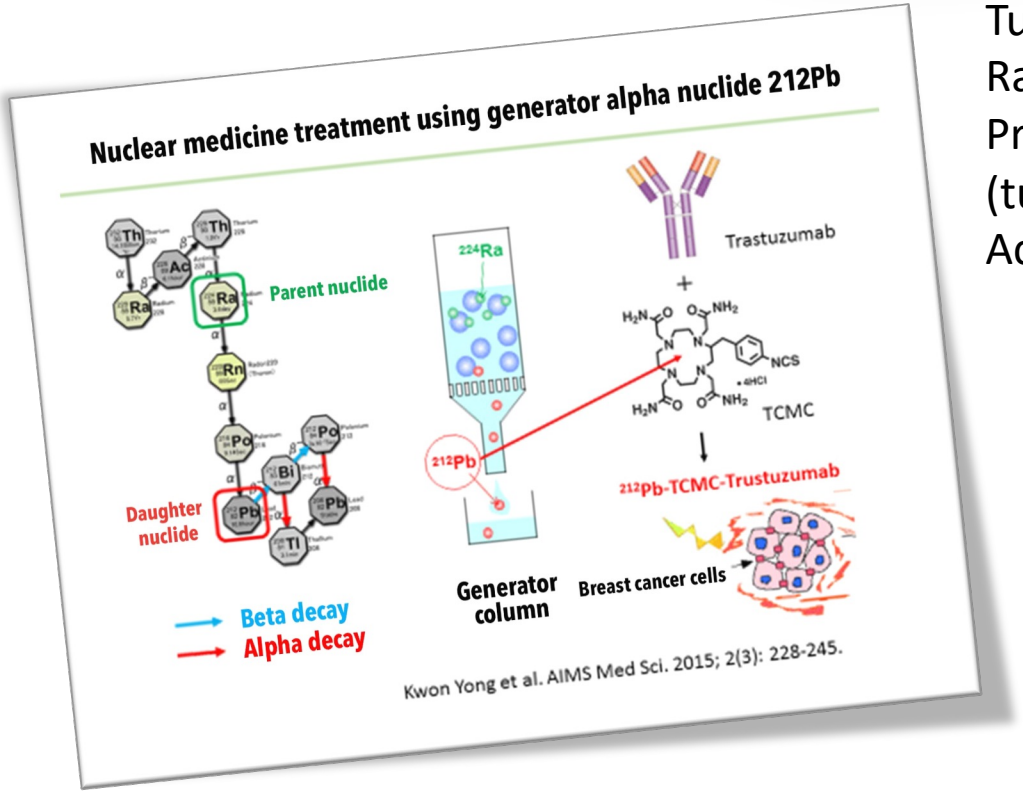
Pb-212





Potential Clinical applications

NET
Prostate cancer (RM2 peptide)
Metastatic melanoma
HER-2 expression (breast, ovarian, gastric)
Multiple myeloma



Plusses

Tumour cell internalization
Rapid normal tissue clearance
Promising pre-clin results (tumor growth)
Acceptable toxicity profile

Problems/ Precautions

Kidneys may be dose limiting

★★★★★

Lead-212

Dose Escalation and Dosimetry of First-in-Human α Radioimmunotherapy with ^{212}Pb-TCMC-Trastuzumab

Ruby Meredith[1], Julien Torgue[2], Sui Shen[1], Darrell R. Fisher[3], Eileen Banaga[2], Patty Bunch[1], Desiree Morgan[1], Jinda Fan[1], and J. Michael Straughn, Jr.[1]

[1]Department of Radiation Oncology, University of Alabama at Birmingham, Birmingham, Alabama; [2]AREVA Med, Bethesda, Maryland; and [3]Dade Moeller Health Group, Richland, Washington

J Nucl Med 2014; 55:1636–1642

Safety and Outcome Measures of First-in-Human Intraperitoneal α Radioimmunotherapy With ^{212}Pb-TCMC-Trastuzumab

American Journal of Clinical Oncology Volume 41, Number 7,2018

Ruby F. Meredith, MD, PhD, Julien J. Torgue, PhD,† Tania A. Rozgaja, PhD,† Eileen P. Banaga, MS,† Patty W. Bunch, OCN,‡ Ronald D. Alvarez, MD,‡ J. Michael Straughn Jr, MD,‡ Michael C. Dobelbower, MD, PhD,* and Andrew M. Lowy, MD§*

Phase 1 trial of Pb-212-VMT-alpha-NET in select metastatic or inoperable somatostatin receptor positive tumors

Frank I. Lin [1], Jaydira Del Rivero [1], Anish Thomas [1], Ramaprasad Srinivasan [1], Floudas Charalampos [1], Jorge Carrasquillo [1], Inna Shamis [1], Joy Zou [1], Baris Turkbey [1], Esther Mena [1], Liza Lindenberg [1], Clara Chen [4], Peter Herscovitch [4], Corina Millo [4] & Karel Pacak [2]

NANETS2023 › Trials In Progress (12 abstracts)

Phase 1/2 trial of Pb-212-VMT-alpha-NET in GI neuroendocrine tumors and pheochromocytoma/paraganglioma previously treated with radioligand therapy

Frank I. Lin [1], Jaydira Del Rivero [1], Jorge Carrasquillo [1], Inna Shamis [1], Joy Zou [1], Baris Turkbey [1], Joanna Klubo [2], Esther Mena [1], Liza Lindenberg [1], Clara Chen [4], Peter Herscovitch [4], Corina Millo [4] & Karel Pacak [2]

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Main challenges with TAT

Reliable supply

Internalization

Prospective data

Dosimetry

Waste management

Recoil

Delivery / Toxicity

Acceptance

Long-term follow-up

Chelators &
Delivery vehicles

Availability and Re-imbursement

Timing in Rx landscape

Combination Rx

Standardization of protocols

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Imaging Partner

Production & Cost

Clinical Guidelines

Preparation

Possibilities & Purpose

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Considerations for each isotope

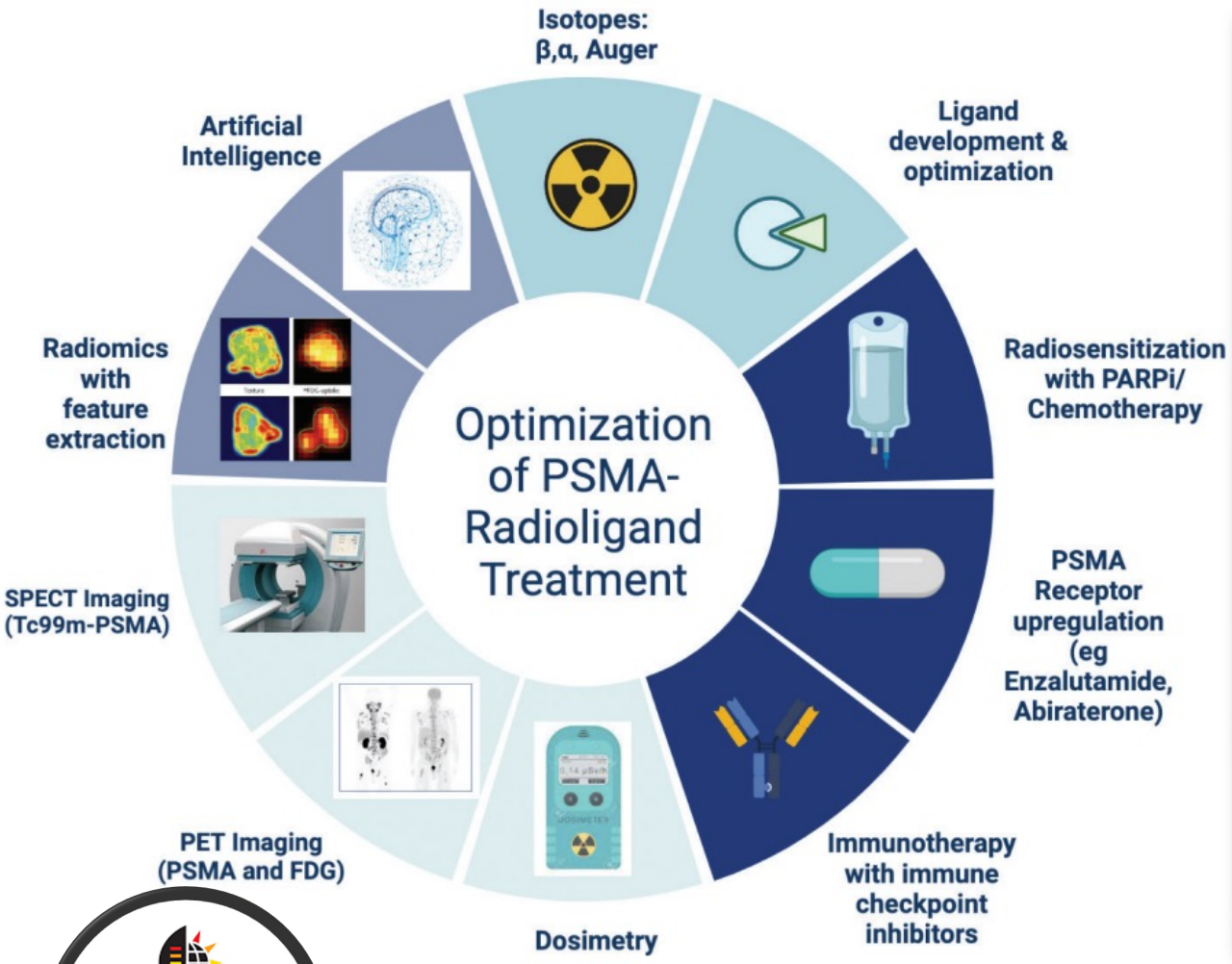
Ac-225

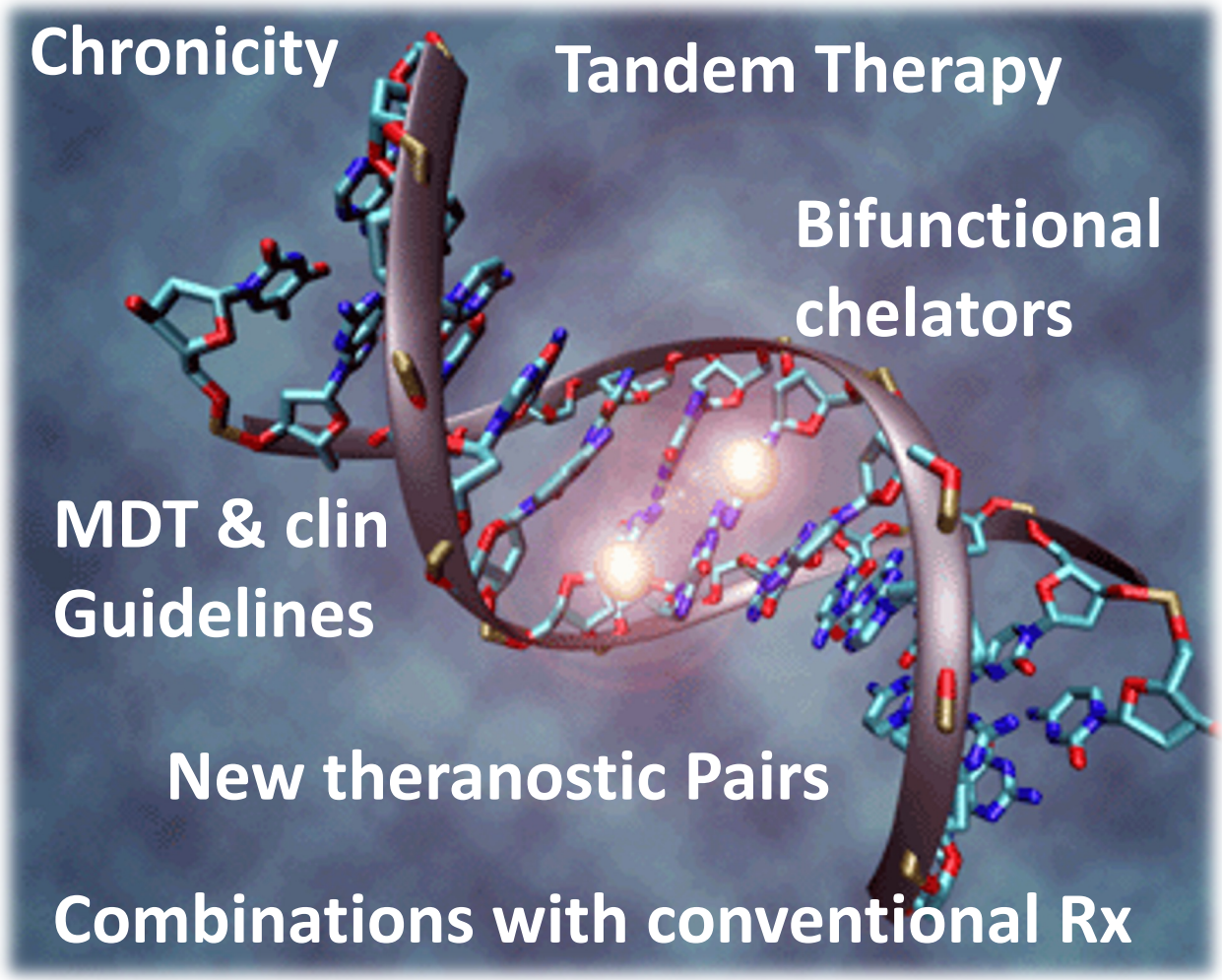
Pb-212

At-211

Tb-149

Future Perspectives





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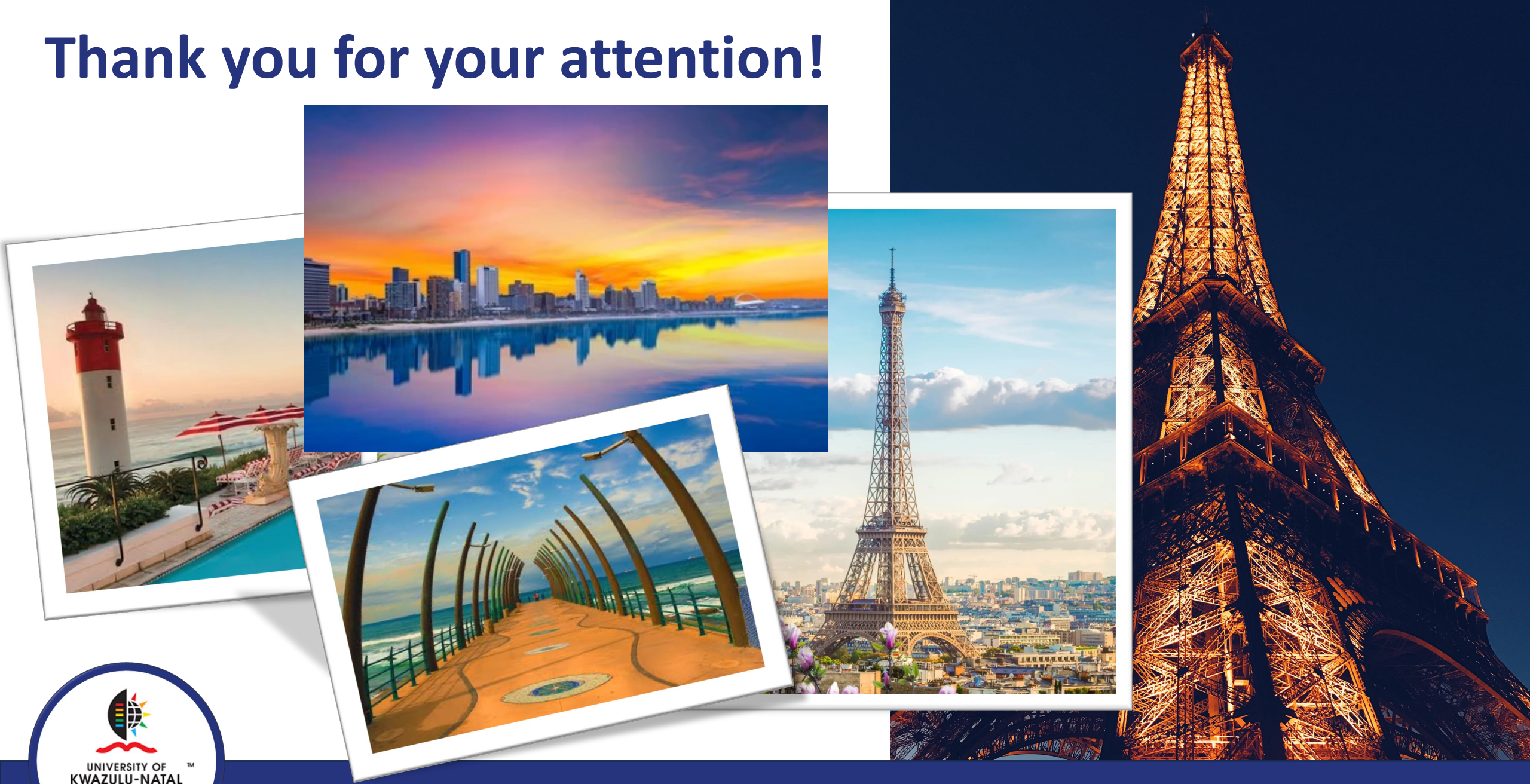
Vorster & Sathekge, 2021 Theranostics in mCRPC

Thank you for your attention!



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VorsterM1@ukzn/ marizavorster@gmail.com