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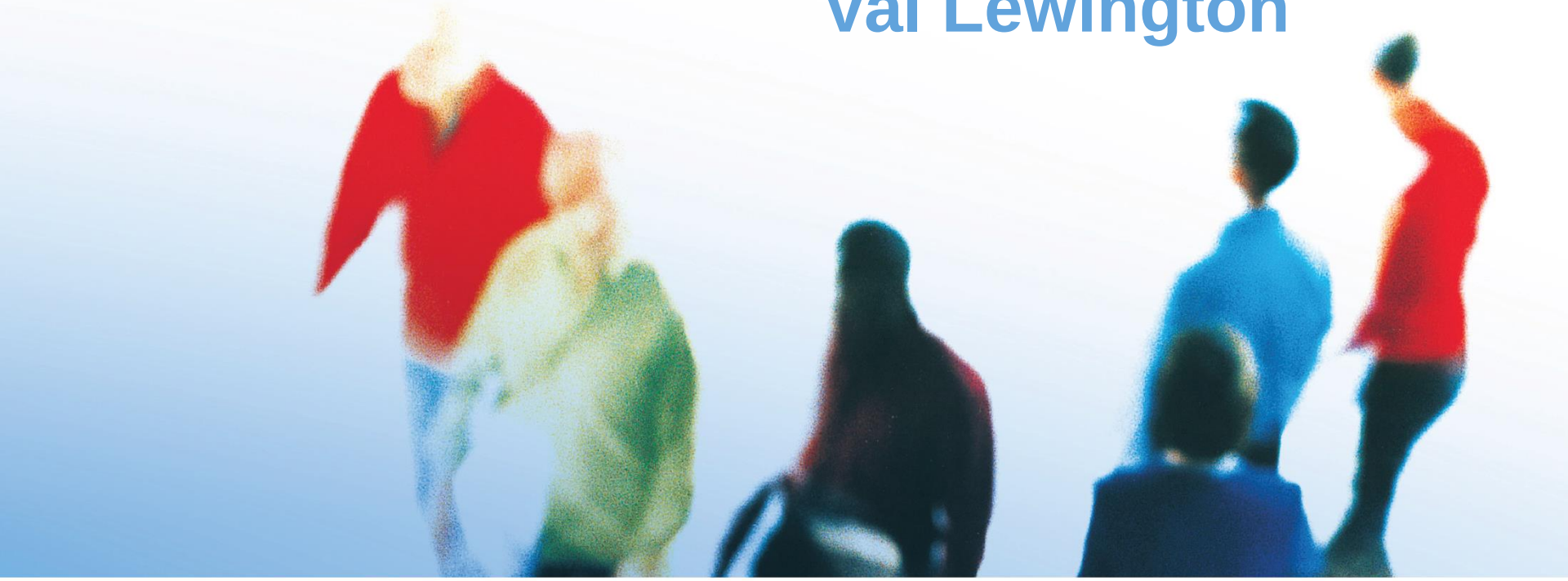
An Academic Health Sciences Centre for London

Pioneering better health for all

Recent advances in alpha particle therapy

Val Lewington



Disclosures

Speaker honoraria, Advisory Board member	Bayer AG
Advisory Board member	Oncoinvent
Advisory Board member and speaker honoraria	Advanced Accelerator Applications

Targeted alpha Therapy TαT

"An agent that delivers systemic radiation selectively to cancer cells and the tumour microenvironment to control cancer while minimising toxicity"

Targeted Alpha Therapy Working Group 2017

Alpha vs Beta particle characteristics

	Alpha
Relative particle mass	**7000**
Range in tissue (μm)	**40 - 100**
LET (keV/μm)	**60 - 300**
Ion pairs/μm	**2000 - 7000**

LET Linear energy transfer

Radiation induced DNA damage and cytotoxicity

Low LET eg β^-

- Sparse ionisation events
- Individual DNA lesions eg single strand DNA breaks
- Repairable using opposite strand as template
- Low probability of cell death

High LET eg α

- Multiple ionisation events
- Double strand DNA break clusters
- Difficult to repair
- Loss of chromosomal content and high probability of cell death

Relative radiobiological effectiveness

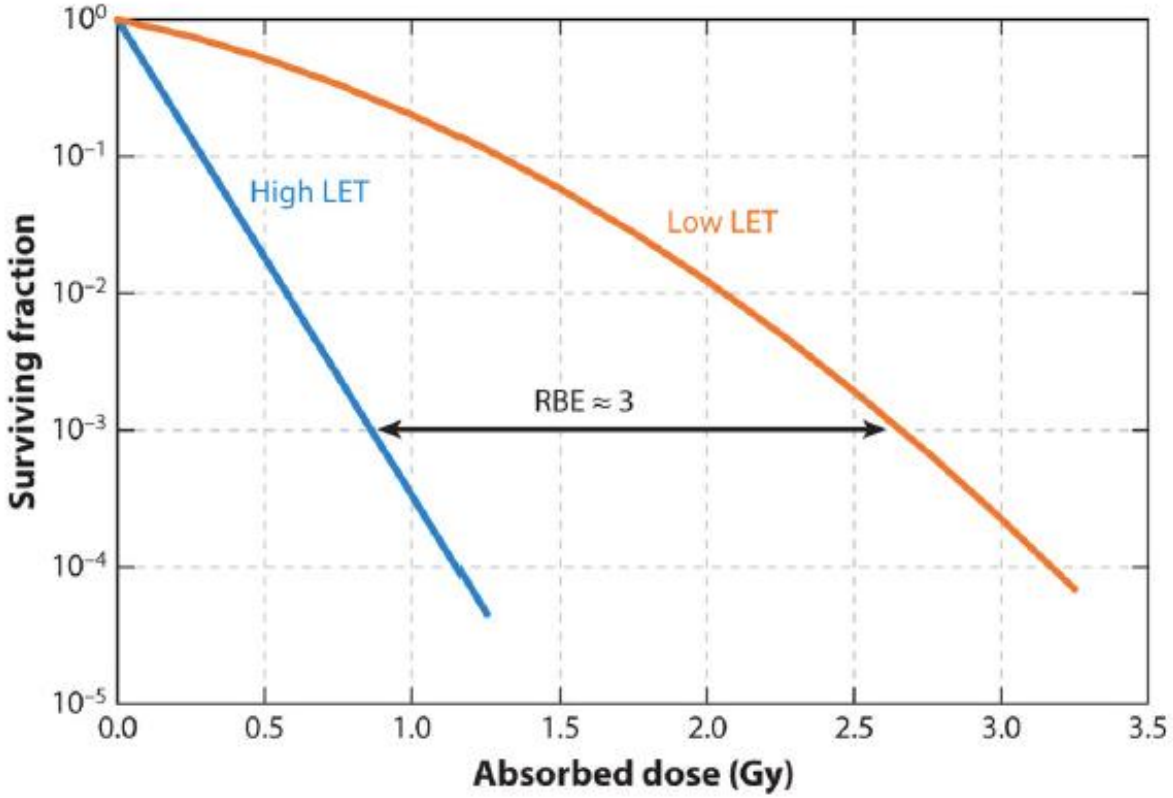
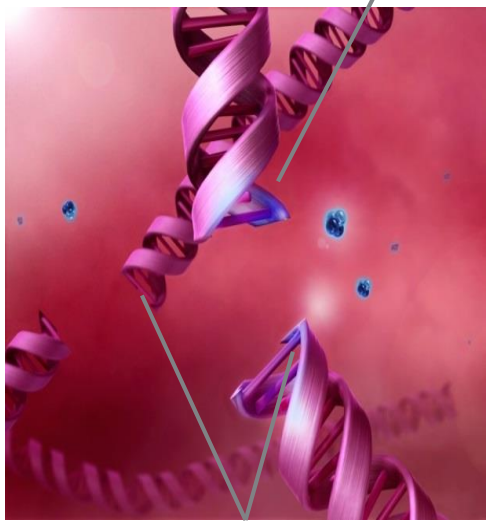


Figure 1.
Cell survival curves as a function of absorbed dose for high and low linear energy transfer (LET) emitters. Abbreviation: RBE, relative biological effectiveness.

Cellular Response to α irradiation [1]

DSB repair failure

- **Apoptosis** programmed cell death[2]
- **Necrosis** premature cell death by autolysis
- **Cell cycle arrest** cell cycle delay and arrest at cell cycle checkpoints[2]
- **Autophagy** intracellular components undergo lysosome-mediated self-digestion[3]



Double-stranded DNA break

DSB mis-repair

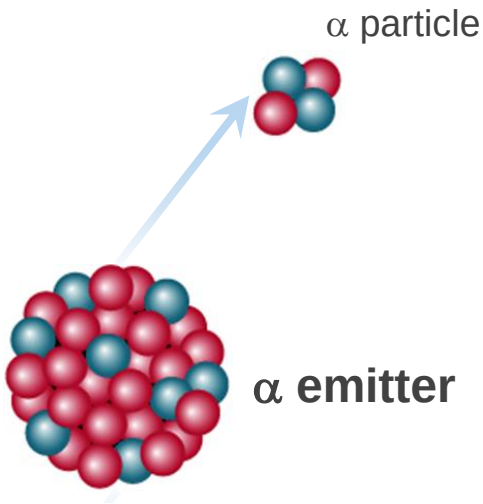
chromosome aberations & mitotic cell death

- No known mechanism of resistance to α particle irradiation
- Oxygen concentration independent
- Cell cycle independent

1. Dekempeneer Y *et al. Expert Opin Biol Ther* 2016;16:1035–1047. **2.** Kassis AI. *Semin Nucl Med* 2008;38:358–366. **3.** Netea-Maier R *et al. Autophagy* 2016;12:245–260. 4. Ceder J, Elgqvist J. *Front Oncol* 2017;6:1–6.

α particle biological impact

- Oxidising events via water radiolysis[1]
- High daughter isotope recoil energy[2]
- Unstable daughter isotope:chelator chemical bonds may allow daughter atom escape[2]



- Radiation-induced bystander effect
  - nontargeted cells damaged independently of direct radiation exposure[2]

1. Azzam EI, Jay-Gerin JP, Pain D. *Cancer Lett* 2012;48–60. **2.** Dekempeneer Y *et al*. *Expert Opin Biol Ther* 2016;16:1035–1047.

Immunogenic cell death

EBRT and photon therapy ↑ tumour sensitivity to cytotoxic T lymphocytes

Sub lethal ^{223}Ra exposure in vitro (prostate, breast, lung cancer cell lines)

- increased CTL mediated lysis via specific antigens
- Increased protein expression to enhance antigen presentation

→ Potential for combining α treatment with immunotherapies eg cancer vaccines that expand endogenous antigen-specific T cell populations

CTL cytotoxic T lymphocytes

Optimising α emitting isotope selection

Physical half life

- short - to deliver high dose rate
  - to mitigate radiation toxicity
- long - to allow production, preparation, distribution, administration

Daughter isotope characteristics

- short half life to ensure - rapid clearance
  - decay energy confined to tumour target

Chemical properties - biodistribution

- compounding

Biological Sites of Deposition

Essential considerations

- Physiological uptake

  Biological sites of deposition

  - potential for normal tissue toxicity

- *In vivo* radioconjugate stability

  Radioconjugates susceptible to catabolism and radiolysis

α-particle-emitting radionuclide	Biological uptake
Actinium-225	Bone and liver
Astatine-211	Thyroid, gut, and lungs
Bismuth-213	Kidney
Lead-212	Red blood cells and bone
Radium-223	Bone
Thorium-227	Bone

Currently available α particle emitting radionuclides

Isotope	Daughter isotopes	Physical half-life	Emission (%)
^{211}At	–	7.2 h	α (41.8%)
	^{211}Po	516 ms	α (100%)
^{225}Ac	–	10 d	α (100%)
	^{221}Fr	4.9 min	α (100%)
	^{217}At	32.3 ms	α (99.98%)/β (0.01%)
→	^{213}Bi	45.6 min	α (2.2%)/β (97.8%)
	^{213}Po	4.2 μs	α (100%)
^{213}Bi	–	45.6 min	α (2.2%)/β (97.8%)
	^{213}Po	4.2	α (100%)
^{212}Bi	–	61 min	α (36%)/β (64%)
	^{212}Po	298 ns	α (100%)
^{212}Pb	–	10.64 h	β (100%)
	^{212}Bi	61 min	α (36%)/β (64%)
	^{212}Po	0.3 μs	α (100%)
^{223}Ra	–	11.4 d	α (100%)
	^{219}Rn	4 s	α (100%)
	^{215}Po	1.8 ms	α (100%)
	^{211}Bi	2.14 min	α (99.7%)/β (0.3%)
^{227}Th	–	18.72 d	α (100%)
→	^{223}Ra	11.4 d	α (100%)
	^{219}Rn	4 s	α (100%)
	^{215}Po	1.8 ms	α (100%)
	^{211}Bi	2.14 min	α (99.7%)/β (0.3%)

Dekempeneer Y *et al. Expert Opin Biol Ther* 2016;16:1035–1047.

α particle emitting Isotope production

Isotope	Source
Actinium-225	• Natural decay of uranium-233 in Oak Ridge National Laboratory[1] • Accelerator-based methods[1]
Astatine-211	• Bombardment of natural bismuth with α-particles in a cyclotron[1]
Bismuth-213	• Purified from actinium-225 generator[1]
Radium-223	• Purified from actinium-227 generator[2]
Thorium-227	• Purified from actinium-227 generator[3]

1. Dekempeneer Y *et al. Expert Opin Biol Ther* 2016;16:1035–1047 **2.**Brechbiel MW. *Dalton Trans* 2007;43:4918–4928. 3. Abbas N *et al. EJNMMI Res* 2011;1:18.

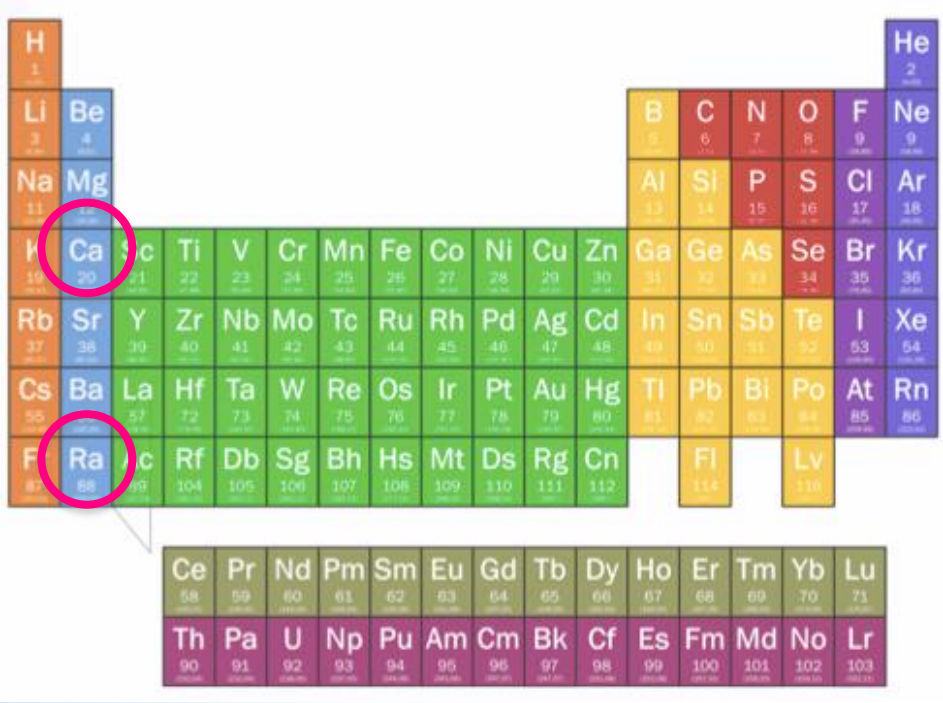
Targeting options

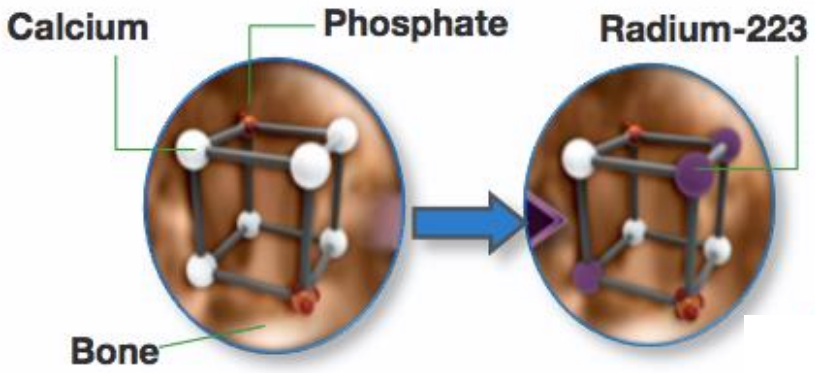
Stable radio conjugation in vivo

- α emission energy
- recoil daughter kinetic energy
- daughter isotope binding to chelator

i Molecular targeting

Radium 223





Selective hydroxyapatite binding at sites of increased bone turnover

Radium-223 physical properties

Ca^{2+} analogue

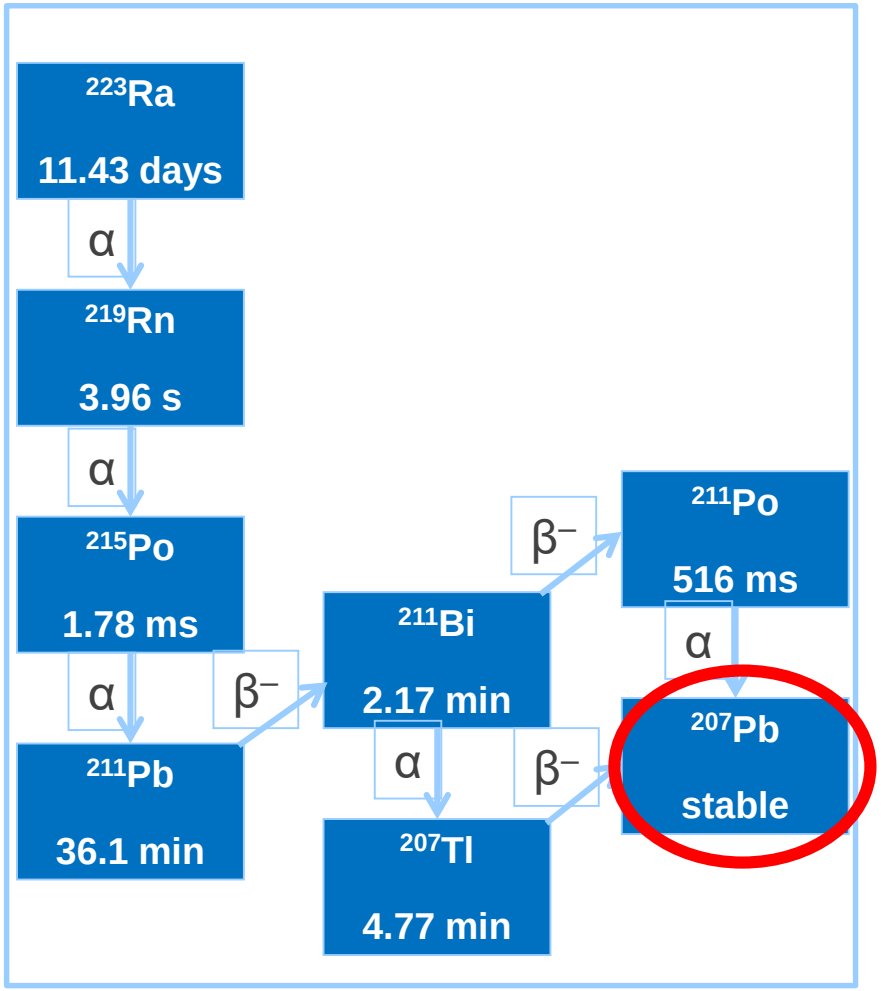
$t_{1/2}$ = 11.4 days

95.3% α

3.6% β-

1.1% γ or x rays

27.4 MeV decay energy

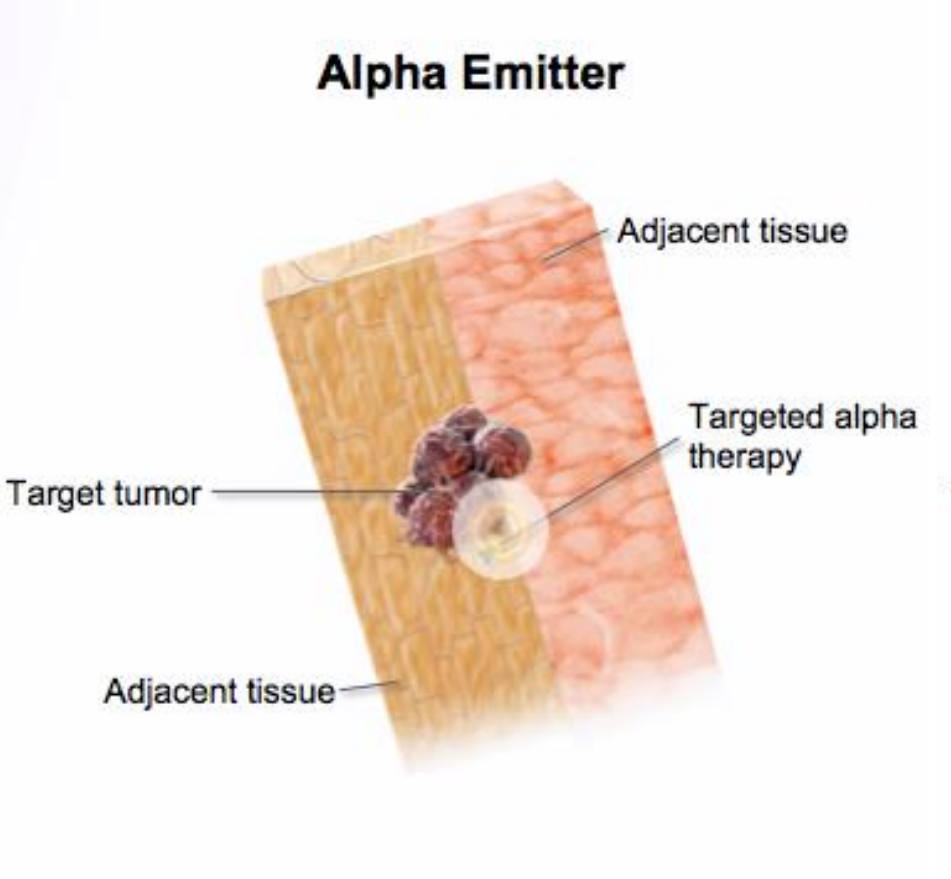


Adapted from Henriksen et al. Cancer Res 2002;62:3120–5.

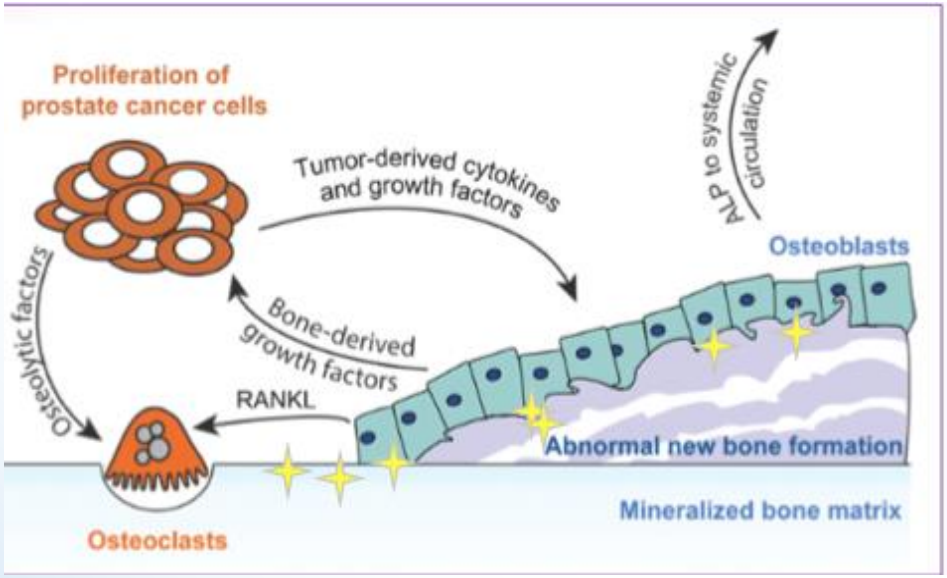
Nuclides 2000. Nuclide Explorer, Institute of Transuranium Elements, Karlsruhe, Germany (1999) Version 1.0

Kassis AI. Semin Nucl Med 2008;38:358–66 ;
Brechbiel. Dalton Trans 2007;43:4918–28.

Decay energy distribution



^{223}Ra Dual mode of action

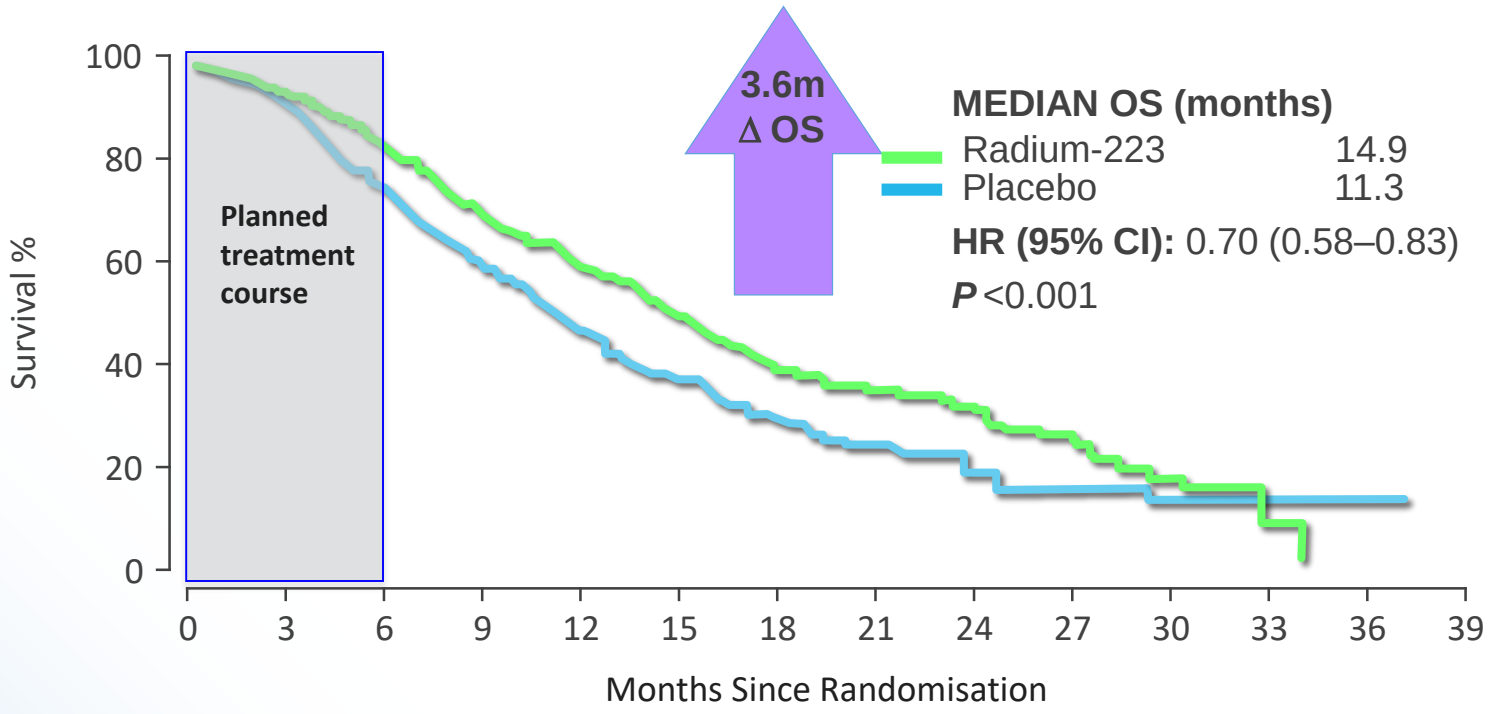


^{223}Ra impact

- Direct effect on CaP cells
- Suppresses tumour induced abnormal bone formation

ALSYMPCA Primary endpoint Overall Survival

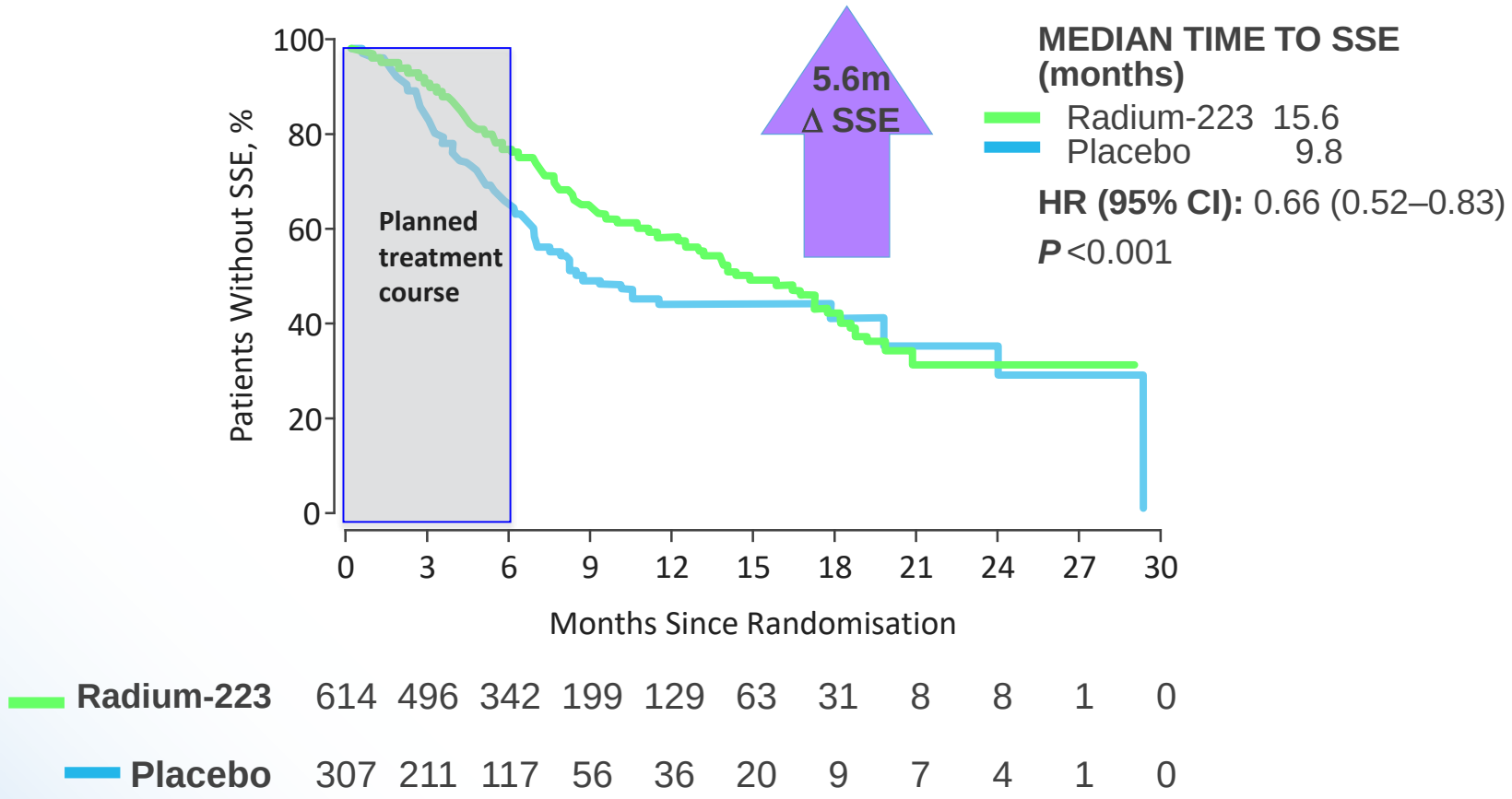
30% reduction in risk of death (HR=0.70) for patients treated with ^{223}Ra



CI, confidence interval; HR, hazard ratio; OS, overall survival.

Parker C, et al. *N Engl J Med.* 2013;369(3):213–223.

ALSYMPCA Secondary endpoint Time to 1st SSE



BSoC, Best standard of care; CI, confidence interval; HR, hazard ratio; SSE, symptomatic skeletal event

Parker C, et al. *N Engl J Med.* 2013;369(3):213–223

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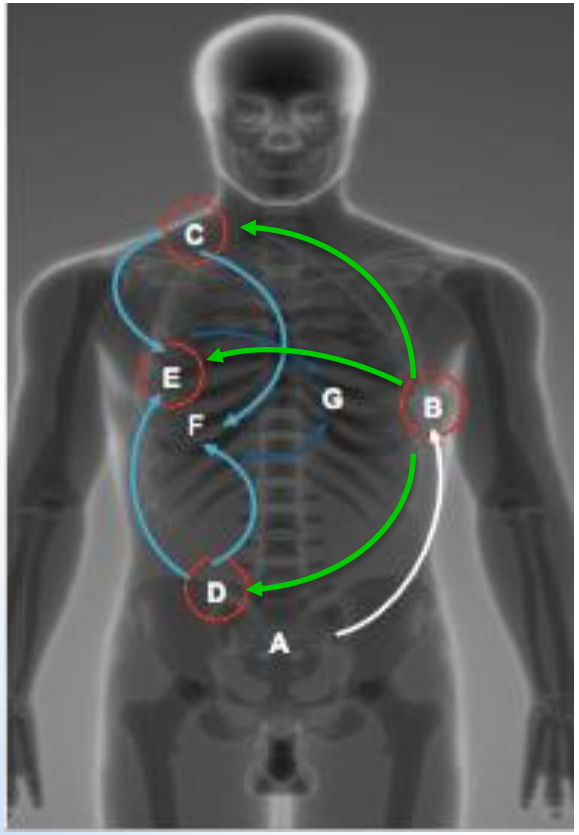
ALSYMPCA Adverse events

Adverse Events n (%)	All Grades		Grades 3 or 4	
	^{223}Radium (n = 600)	Placebo (n = 301)	^{223}Radium (n = 600)	Placebo (n = 301)
Haematological				
Anaemia	187 (31)	92 (31)	76 (13)	39 (13)
Neutropaenia	30 (5)	2 (1)	13 (3)	2 (1)
Thrombocytopaenia	69 (12)	5 (2)	38 (6)	6 (2)

Parker C. N Engl J Med. 2013;369:213-223

Radium 223 survival gain Rationale



- CaP cells metastasise from prostate (A) to bone (B)[1]
- Tumour cells circulate via bloodstream from (B) to other skeletal sites (C-E)[2]
- Metastases move between distant sites rather than as waves from the primary tumour[2]
- Metastatic spread to non skeletal tissues (F)[1] occurs late and often involves the liver (G)[1]

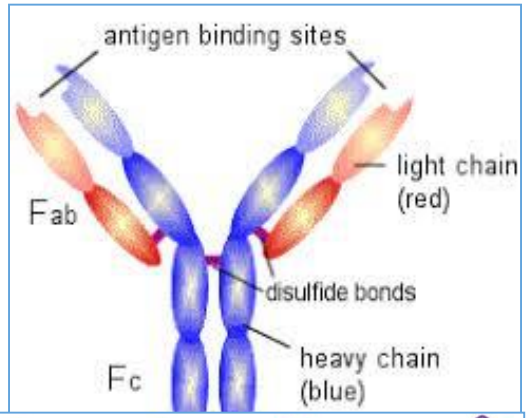
→ **Bone is the source of further metastases**

1 Pezaro CJ, et al. Eur Urol. 2014;65:270-273
2 Gundem G, et al. Nature. 2015;520(7547):353-357

2. Monoclonal antibody mediated targeting

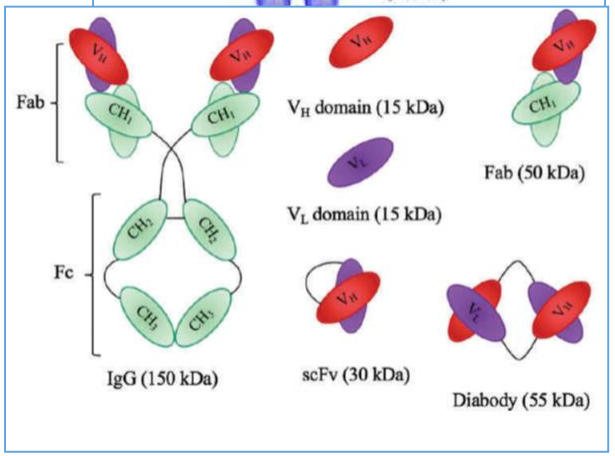
Whole antibodies

- High molecular weight
- Slow plasma clearance
- Non specific reticuloendothelial uptake (Fc region) – myelosuppression, hepatotoxicity



Antibody fragments

- Shorter serum half life
- Higher tumour penetration
- Improved therapeutic ratio



Protein scaffolds, nanobodies, lysosomes

α Radioimmunotherapy trials

Isotope	T 1/2	α emission	Vehicle	Phase / Study population

1. https://www.clinicaltrials.gov/ct2/show/NCT02581878.
2. Jurcic JG et al *Blood.* 2014;124:5293
3. Jurcic JG et al *Blood.* 2002;100(4):1233–1239
4. Zalutsky MR et al *J Nucl Med.* 2008;49(1):30–38
5. Andersson H et al *J Nucl Med.* 2009;50(7):1153–1160

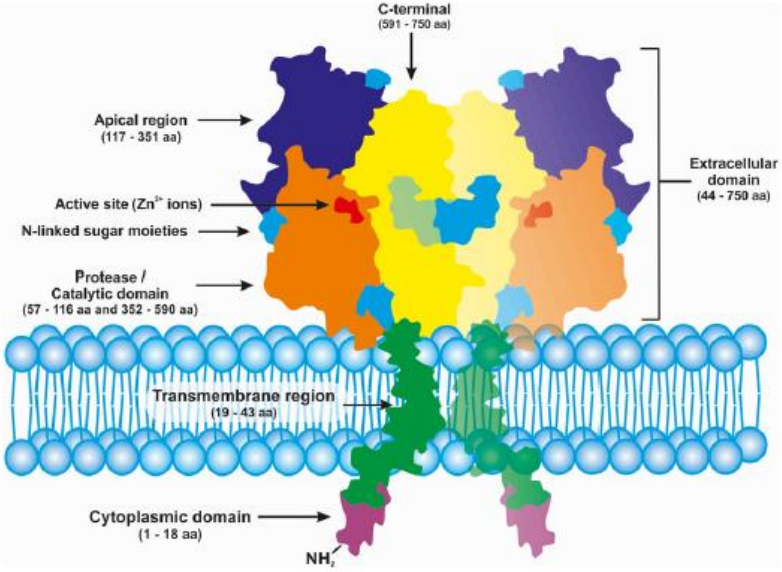
* poor in vivo stability

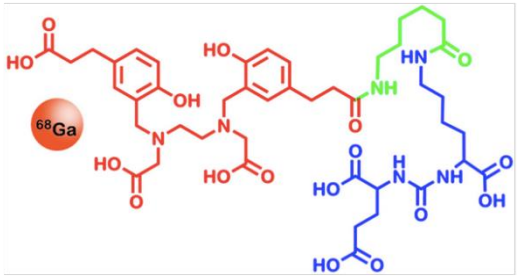
3. Peptide / small molecule mediated TαT

Prostate specific membrane antigen (PSMA)

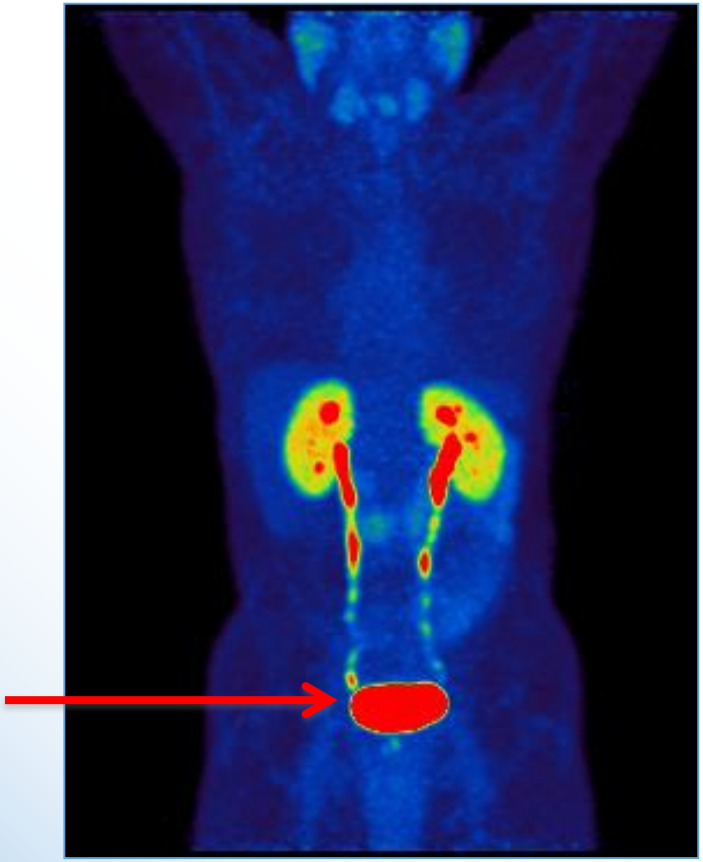
- Overexpressed on CaP cells
- Expression correlates with
  - higher tumour grade
  - metastases
  - hormone refractory disease
  - poor outcome

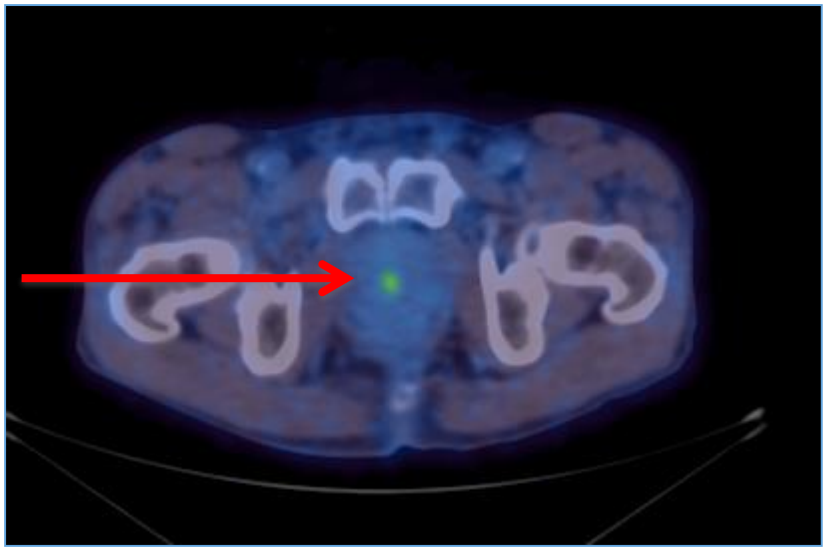
→ Radiolabelled PSMA imaging **/ therapy**





Gallium 68 PSMA PET CT Imaging

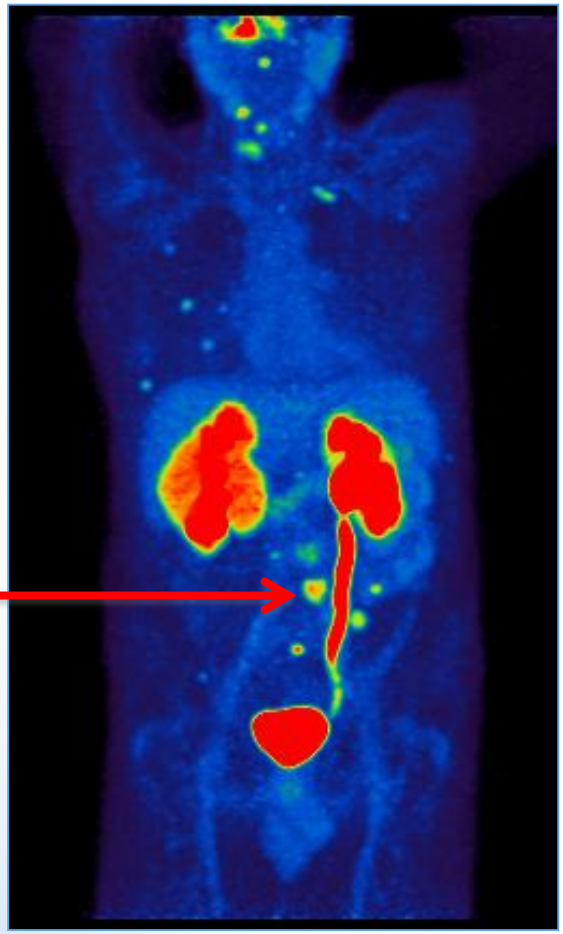




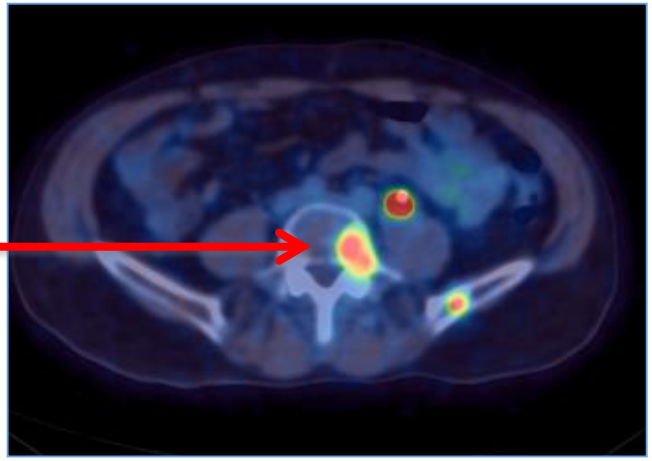
Maximum intensity projected image

Transaxial ^{68}Ga PSMA CT fusion

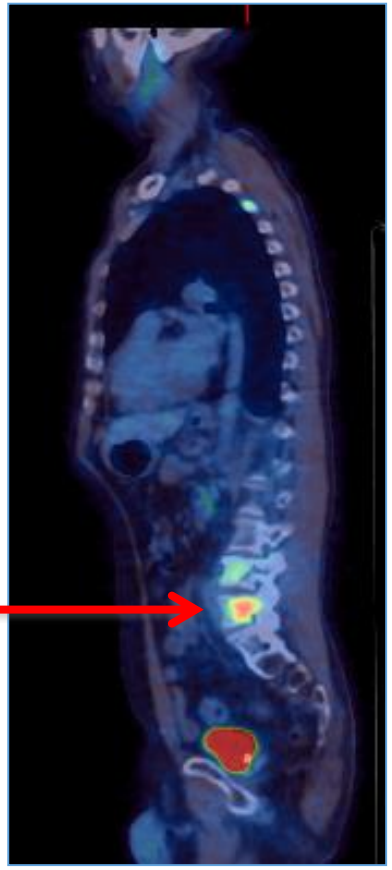
Gallium 68 PSMA PET CT Imaging



Maximum intensity projected image



Transaxial fusion



Saggital fusion

PSMA targeted therapy

Lutetium-177 PSMA

Potential advantage vs ^{223}Ra - target bone and soft tissue metastases

^{177}Lu PSMA Retrospective German Multicentre Study

n = 145 mCRPC

1- 4 cycles ^{177}Lu PSMA-617

Primary endpoint >50% PSA decline from baseline

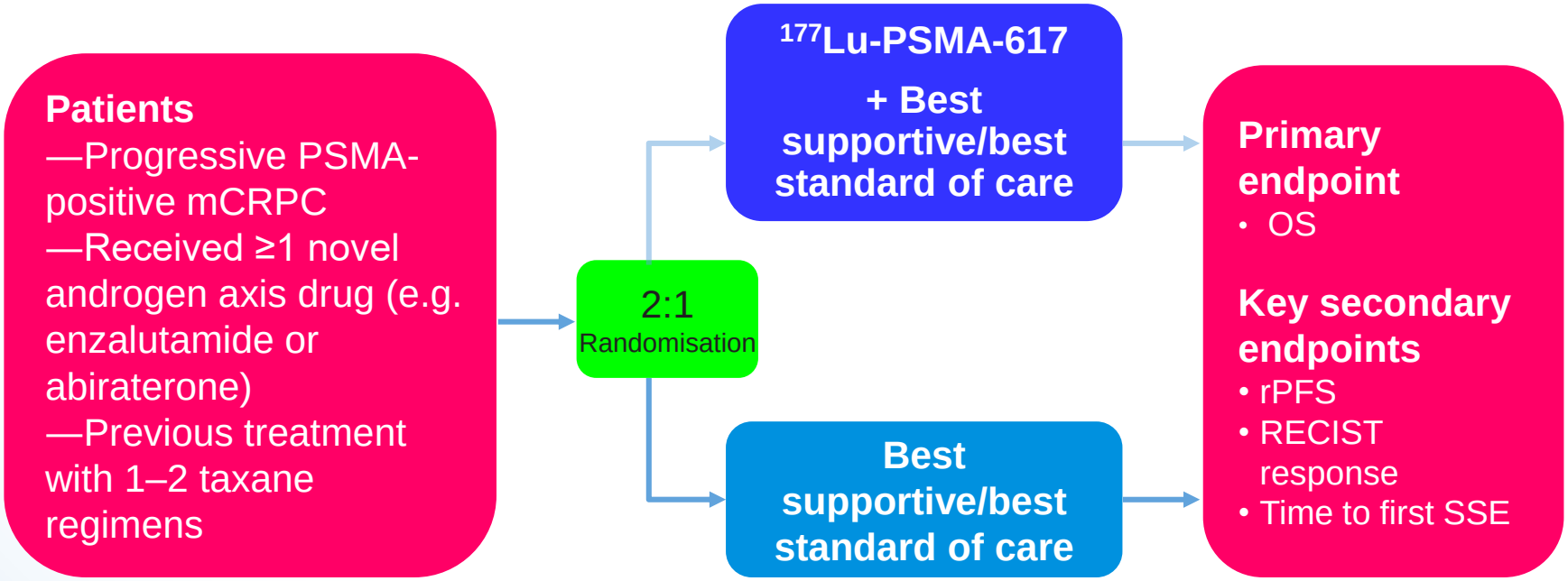
248 ^{177}Lu PSMA-617 cycles delivered

Overall response 45%

Adverse events 12% Grade 3-4 haematological toxicity

8% Xerostomia (dry mouth)

First Phase III Open-label, Randomised Controlled Trial ^{177}Lu-PSMA-617 (VISION)[1,2]



mCRPC, metastatic castration-resistant prostate cancer; **OS**, overall survival; **PSMA**, prostate-specific membrane antigen; **RECIST,** Response Evaluation Criteria in Solid Tumors; **rPFS**, radiographic progression-free survival; **SSE**, symptomatic skeletal event.

1. ClinicalTrials.gov. NCT03511664. Available at https://clinicaltrials.gov/ct2/show/NCT03511664?term=Lu-PSMA-617&rank=1. Accessed May 2018. **2**. GlobeNewswire. Endocyte Announces Enrollment of First Patient in Phase 3 VISION Trial of 177Lu-PSMA-617 in Prostate Cancer.

PSMA targeted α therapy

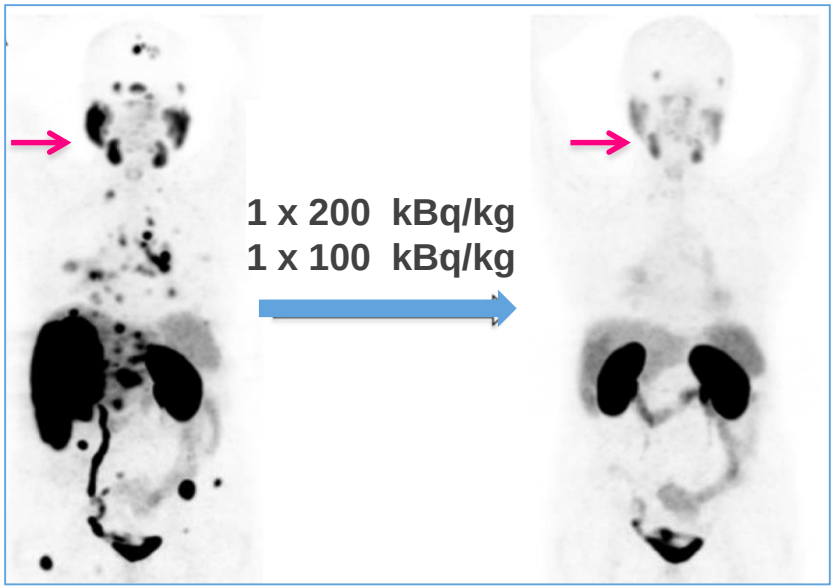
Actinium-225 PSMA	Limited clinical experience (anecdotal)

^{225}Ac-PSMA-617 Targeted Alpha Therapy mCRPC

Study

Retrospective, observational, single-centre ^{225}Ac-PSMA-617 salvage therapy

n = 14 patients



PSA response

PSA-response observed in 75% patients

No dose-response correlation

Adverse events

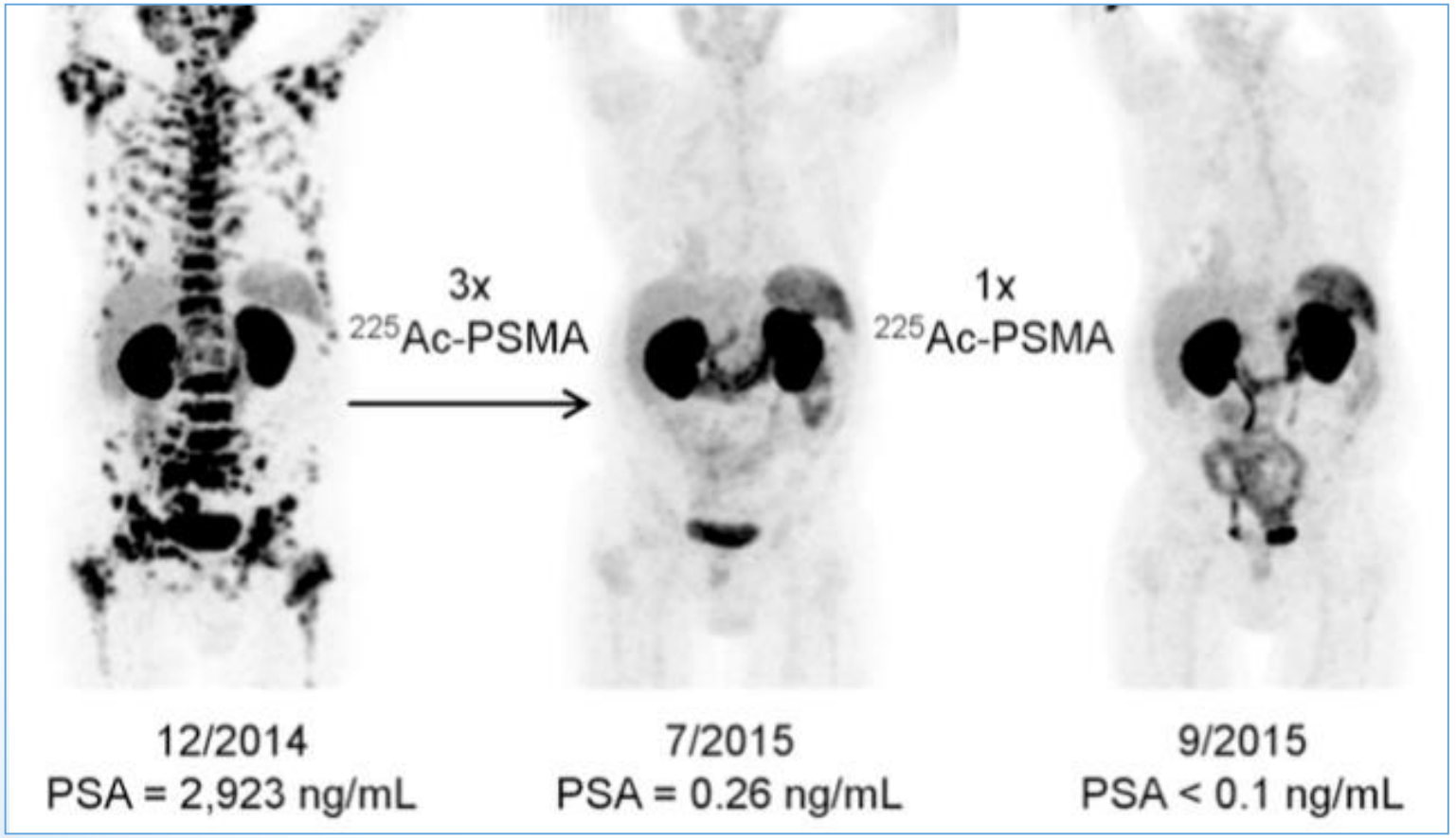
Haematological toxicity 43 %

Dry eyes, dry mouth 57 %

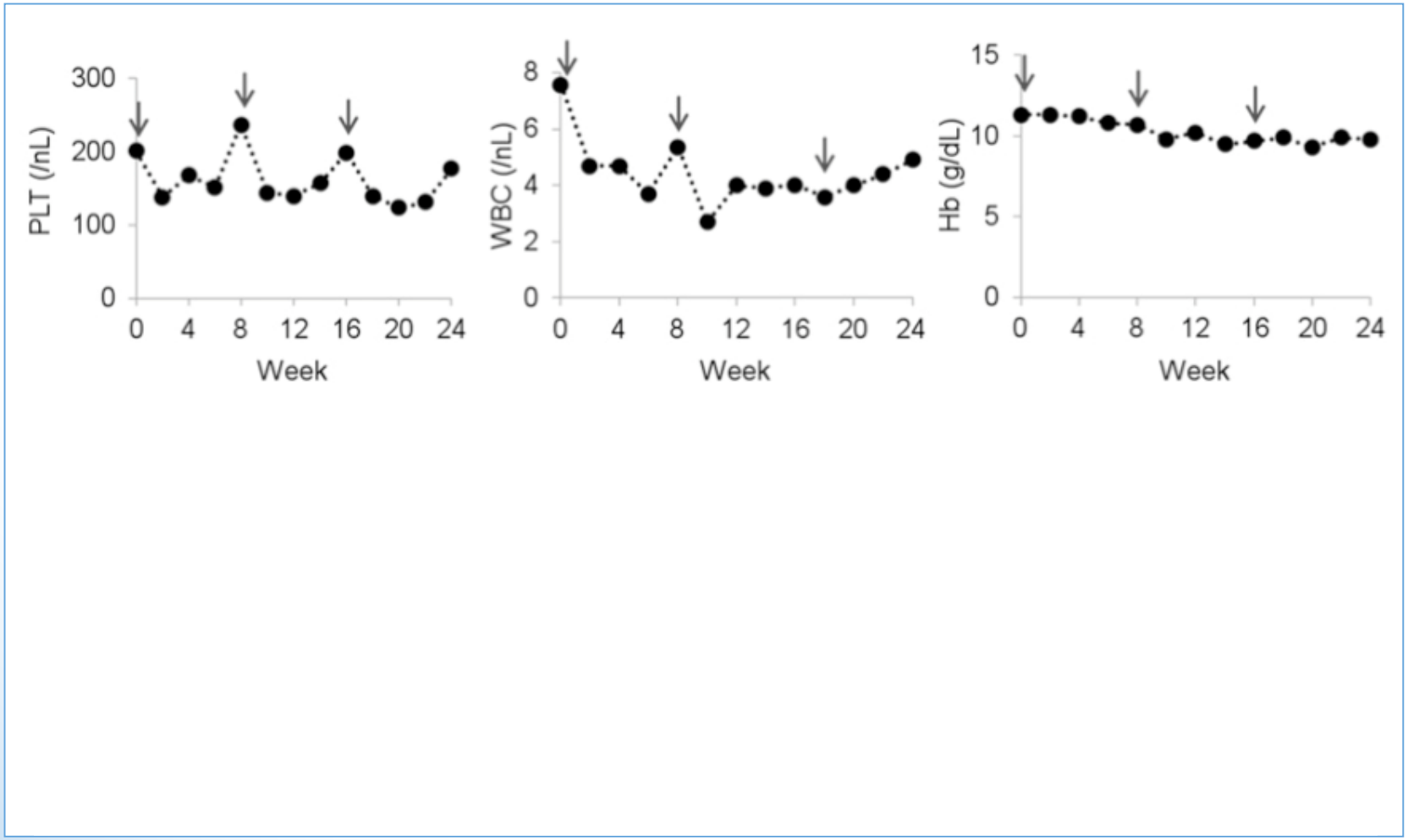
kBq, kilobecquerel; **mCRPC**, metastatic castration-resistant prostate cancer; **PSA**, prostate-specific antigen; **PSMA**, prostate-specific membrane antigen.

Kratochwil C *et al. J Nucl Med* 2017; 58:1624–1631.

^{225}Ac PSMA Early clinical experience



^{225}Ac PSMA Early clinical experience



Kratochwil C et al J Nucl Med 2016 57:1941-44

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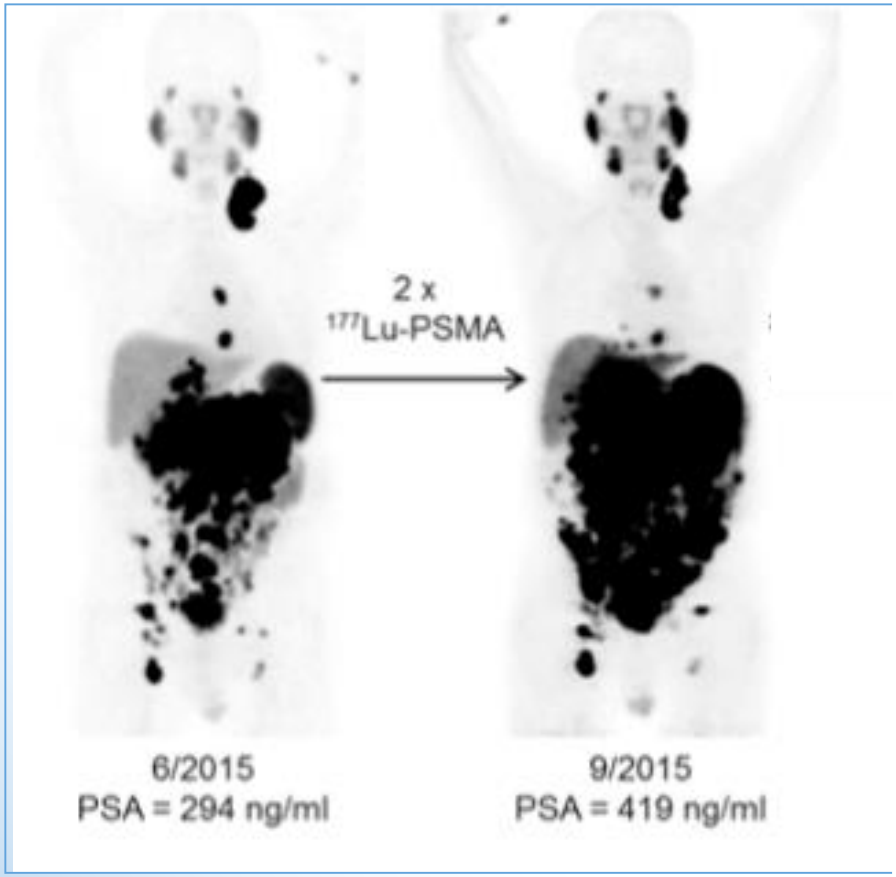
^{177}Lu PSMA refractory mCRPC

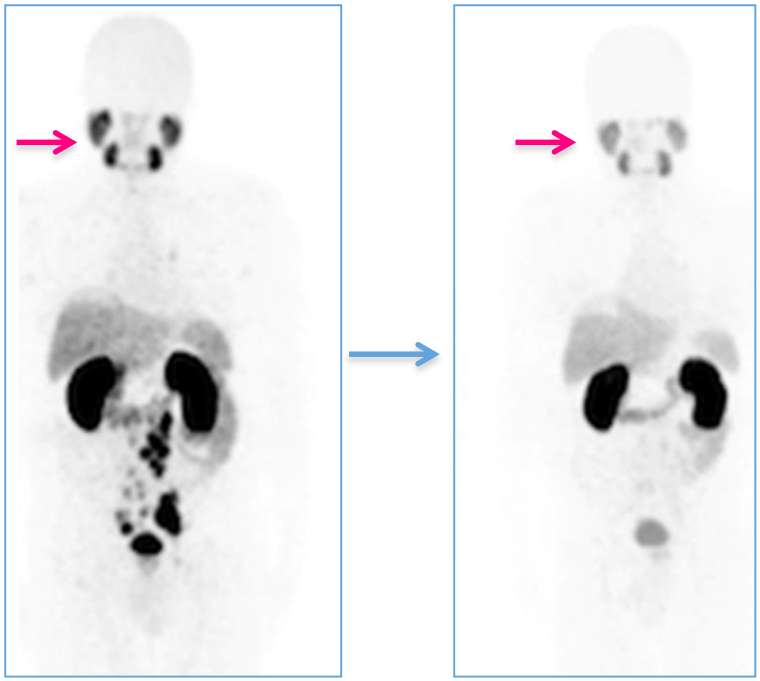
Serial ^{68}Ga PSMA PET CT scans



Kratochwil C et al J Nucl Med 2016 57:1941-44

^{213}Bi PSMA-617

- ^{213} Bi PSMA 617 x 2 cycles
- Cumulative activity 592 MBq
- Molecular imaging response after 11m
- PSA decline 237 ug/L to 43 ug/L



MBq, megabecquerel; **mCRPC**, metastatic castration-resistant prostate cancer; **PSA**, prostate-specific antigen; **PSMA**, prostate-specific membrane antigen

.

Sathekge M *et al. Eur J Nucl Med Mol Imaging* 2017;44:1099–1100.

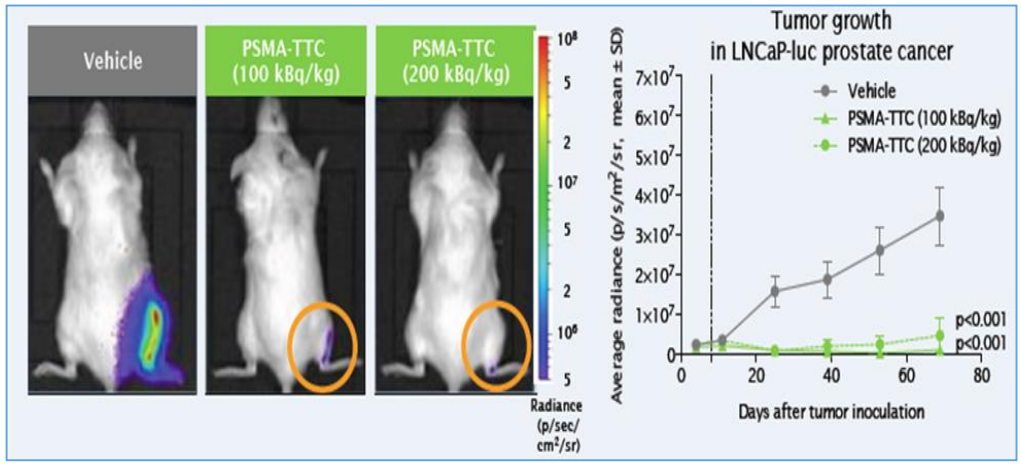
Thorium-227 PSMA mAb Preclinical

ST1273 patient-derived prostate cancer model

- Double strand DNA breaks
- Upregulated immunogenic cell death markers

LNCaP-luc osseous prostate cancer xenograft model

- Objective tumour regression
- PSA decrease



Single dose PSMA-TTC : strong anti-tumour activity *in vivo* in

- several prostate cancer xenograft models with variable PSMA expression
- model mimicking prostate cancer with bone metastasis
- models sensitive or resistant to the standard-of-care drug enzalutamide[1,2]

In vivo stability

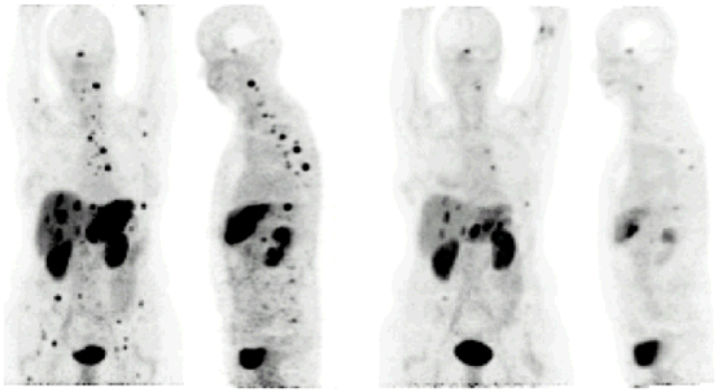
PSMA-TTC accumulated selectively in tumours and increased over time

→ **Clinical translation feasible**

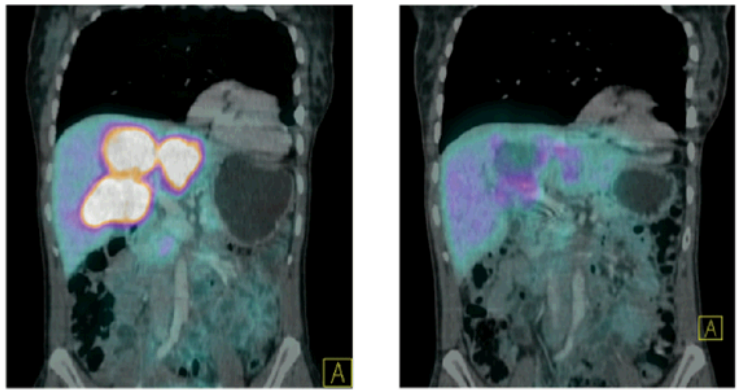
TTC Thorium targeted complex

TαT peptide receptor therapy

Remarkable responses to Bi-213-DOTATOC observed in tumors resistant to previous therapy with Y-90/Lu-177-DOTATOC



Case I: Shrinkage of liver lesions and bone metastases after i.a. therapy with 11 GBq Bi-213-DOTATOC

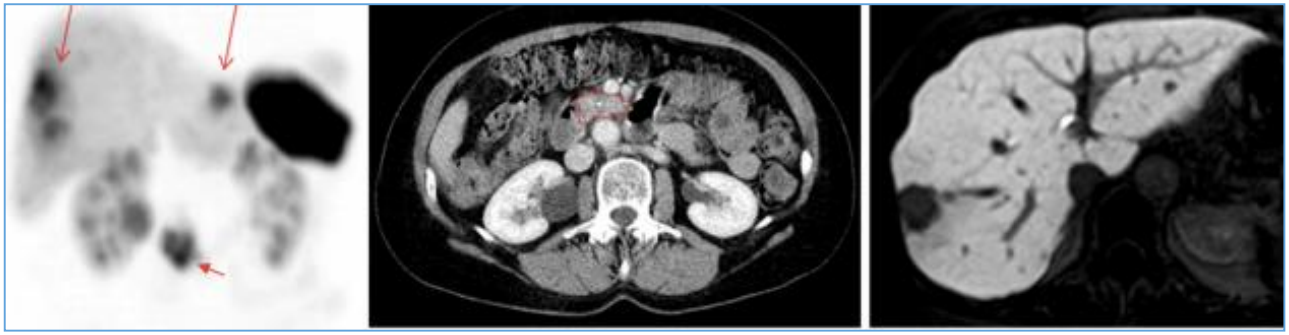


Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq Bi-213-DOTATOC

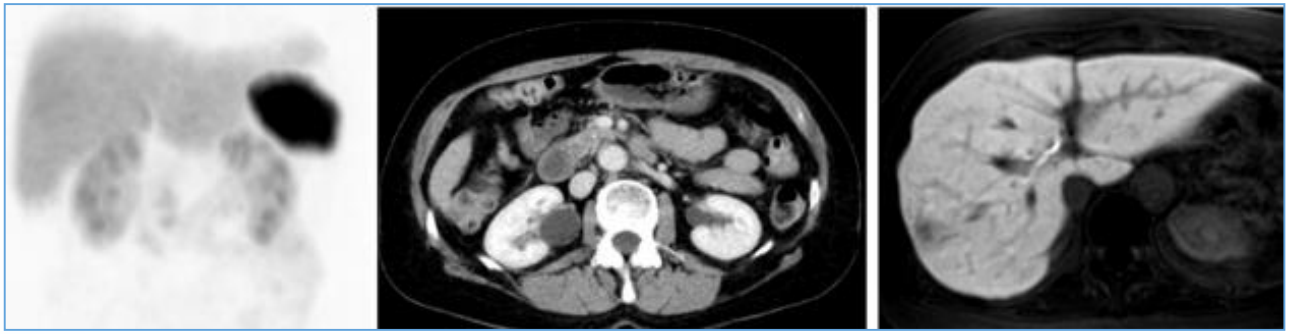
2012 SNMMI Image of the Year Morgenstern A et al
SNM 59th Annual Meeting, June 9-13, 2012

^{213}Bi DOTATOC Refractory neuroendocrine tumour

^{213}Bi DOTATOC
x 3 cycles



Cumulative activity
4GBq



Summary

>100 α-particle emitters – minority appropriate for medical use

α-particle emitters in clinical trials

- Actinium-225
- Astatine-211
- Bismuth-212/bismuth-213
- Radium-223
- Thorium-227

Targeting options include

- Physiological uptake
- Chelation and radio conjugation to mAbs, peptides, or small molecules

Changing perspectives

- Cancer defined by molecular phenotype vs site of origin
- Molecular phenotype (biopsy) presumed representative

- Cancer imaging phenotypes - tumour-specific probes
  - → Unique, specific imaging signature: diagnosis, staging, response assessment
  - → Conversion to targeted molecular therapy
  - → Growing TαT potential, single agent and in combination