ENETS Centers of Excellence
ENETS CoE
Assuring Quality since 2009
Endo-ERN
European Reference Network on Rare Endocrine Conditions
WWW.IO.GLIWICE.PL

# Radionuclide Therapy in Oncology: From Beta to Alpha

Daria Handkiewicz-Junak
Zakład Medycyny Nuklearnej
i Endokrynologii Onkologicznej
NIO– PIB im. Marii Skłodowskiej-Curie, Oddział w Gliwicach






# From β-therapy to α-therapy in oncology

Selected milestones in targeted radionuclide therapy

## 1940s–1960s

### Radioiodine

$^{131}$I

Thyroid cancer targeting
Landmark metastatic response reported in 1946

Seidlin et al. JAMA 1946

## 1980s–2000s

### Radioimmunotherapy

$^{90}$Y / $^{131}$I-labelled antibodies

Anti-CD20 targeting in B-cell lymphoma

## 1990s–2010s

### SSTR / PSMA β-therapy

$^{90}$Y-DOTATOC / $^{177}$Lu-DOTATATE

PRRT for SSTR-positive NETs
PSMA radioligands in the 2010s

Kwekkeboom 2008; Strosberg 2017

## 2013

### Radium-223

$^{223}$Ra

First approved α therapy
Survival benefit in mCRPC with bone metastases

## 2016–2022

### Targeted α-therapy expands

$^{225}$Ac-PSMA / $^{212}$Pb-DOTAMTATE*

Early responses in mCRPC / NETs
Other α platforms: $^{213}$Bi, $^{211}$At

Kratochwil 2016; Delpassand 2022

## 2024–2026

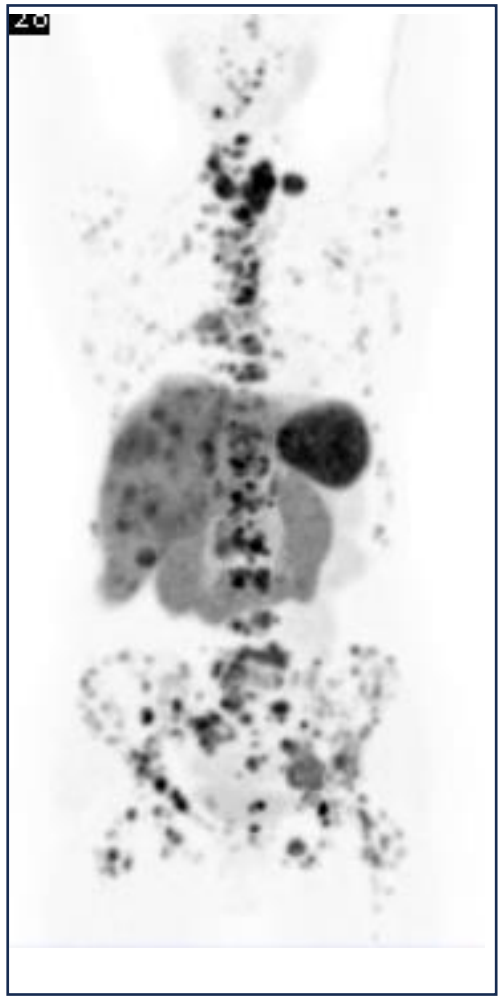
### Investigational RLT

β + α combinations

PRRT + immunotherapy
$^{212}$Pb and $^{227}$Th platforms
$^{161}$Tb: β + Auger electrons

WWW.IO.GLIWICE.PL

# What determines therapeutic efficacy?



RADIONUCLIDE

Which type of radiation?

TARGETING LIGAND

How can we deliver radiation to the tumour?

ABSORBED DOSE AND TUMOUR RESPONSE

What dose is needed for tumour control?

Tumour radiosensitivity and normal-tissue tolerance

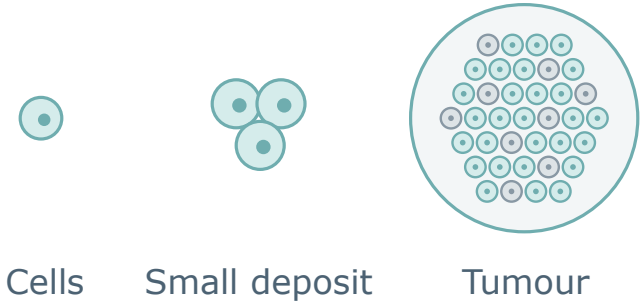


WWW.IO.GLIWICE.PL

# Tumour biology and radiation response

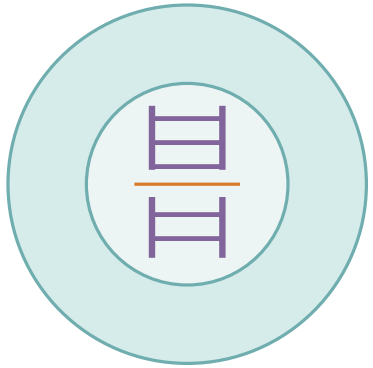
WWW.IO.GLIWICE.PL

## Size and distribution




Lesion dimensions
Localised or disseminated disease

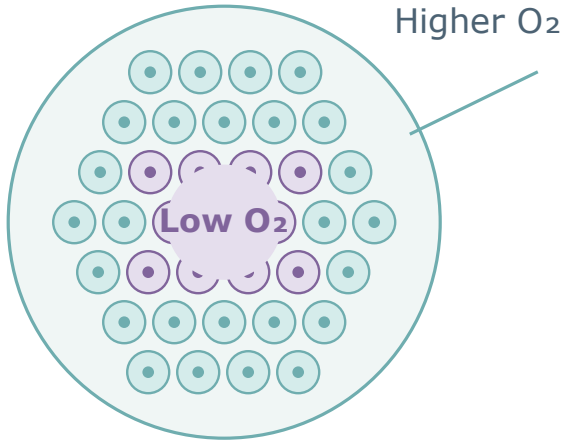
## Intrinsic radiosensitivity



DNA damage and repair

DNA repair capacity
Proliferation and repopulation

## Oxygenation and hypoxia




Spatially variable oxygenation
Relevant to low-LET response

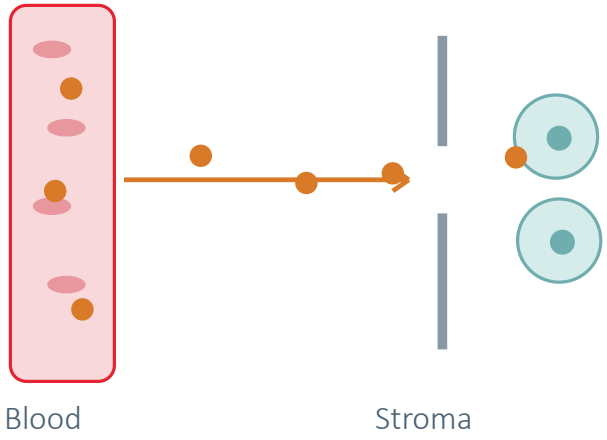
## The same absorbed dose can produce different tumour responses

Sgouros et al. Nat Rev Drug Discov 2020; Ruigrok et al. EJNMMI 2022.

# Radiopharmaceutical delivery to the tumour

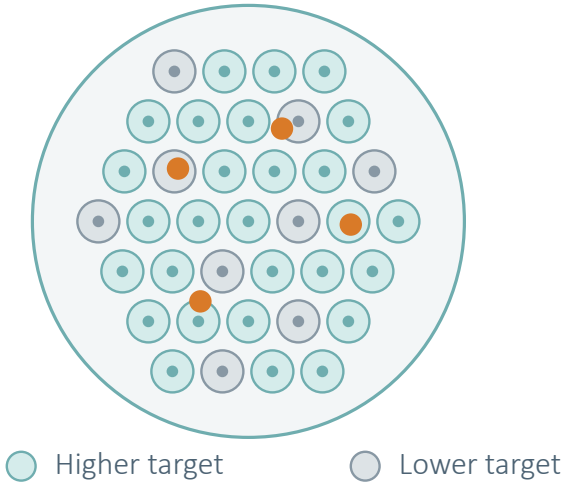
WWW.IO.GLIWICE.PL

## Access to the tumour



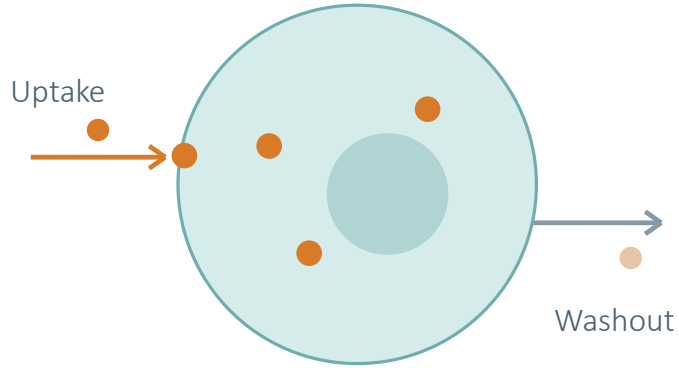

Perfusion and tissue penetration
Barriers to uniform delivery

## Target heterogeneity




Variation within lesions
and between metastases

## Uptake and retention




Tumour accumulation
Residence time

## Tumor uptake must results in sustained irradiation

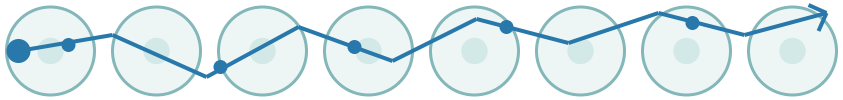
Buteau et al. Lancet Oncol 2022; Sgouros et al. 2020.

# Beta and alpha radiation: physical properties

WWW.IO.GLIWICE.PL

## $\beta^-$ Beta particles

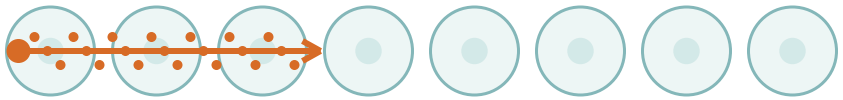
Electron · charge −1



Longer track, sparse ionisation

## α Alpha particles

Helium nucleus · charge +2



Short track, dense ionisation

| | | |
|---|---|---|
| Particle energy | Continuous spectrum<br>Emax: $^{177}$Lu ≈0.50, $^{90}$Y ≈2.28 MeV | Discrete energies<br>Typically ≈5–9 MeV per α particle |
| Range in tissue | Maximum: $^{177}$Lu ≈2 mm<br>$^{90}$Y ≈11 mm | Typically ≈50–100 µm<br>A few cell diameters |
| LET | Low, typically ≈0.2 keV/µm | High, typically ≈80 keV/µm |

**Range and ionisation density determine where and how energy is deposited**

# Beta and alpha radiation: effects within the cell

WWW.IO.GLIWICE.PL

## $\beta^-$ Low-LET radiation

## α High-LET radiation

Schematic cell, nucleus and enlarged DNA segment.



| | | |
|---|---|---|
| DNA damage | More dispersed lesions<br>Single- and double-strand breaks | More clustered lesions<br>Complex double-strand breaks |
| Repair | Greater scope for repair | More difficult and slower repair |
| Oxygen effect | Greater oxygen dependence | Lower oxygen dependence |

## Biological potency must be balanced against normal-tissue toxicity

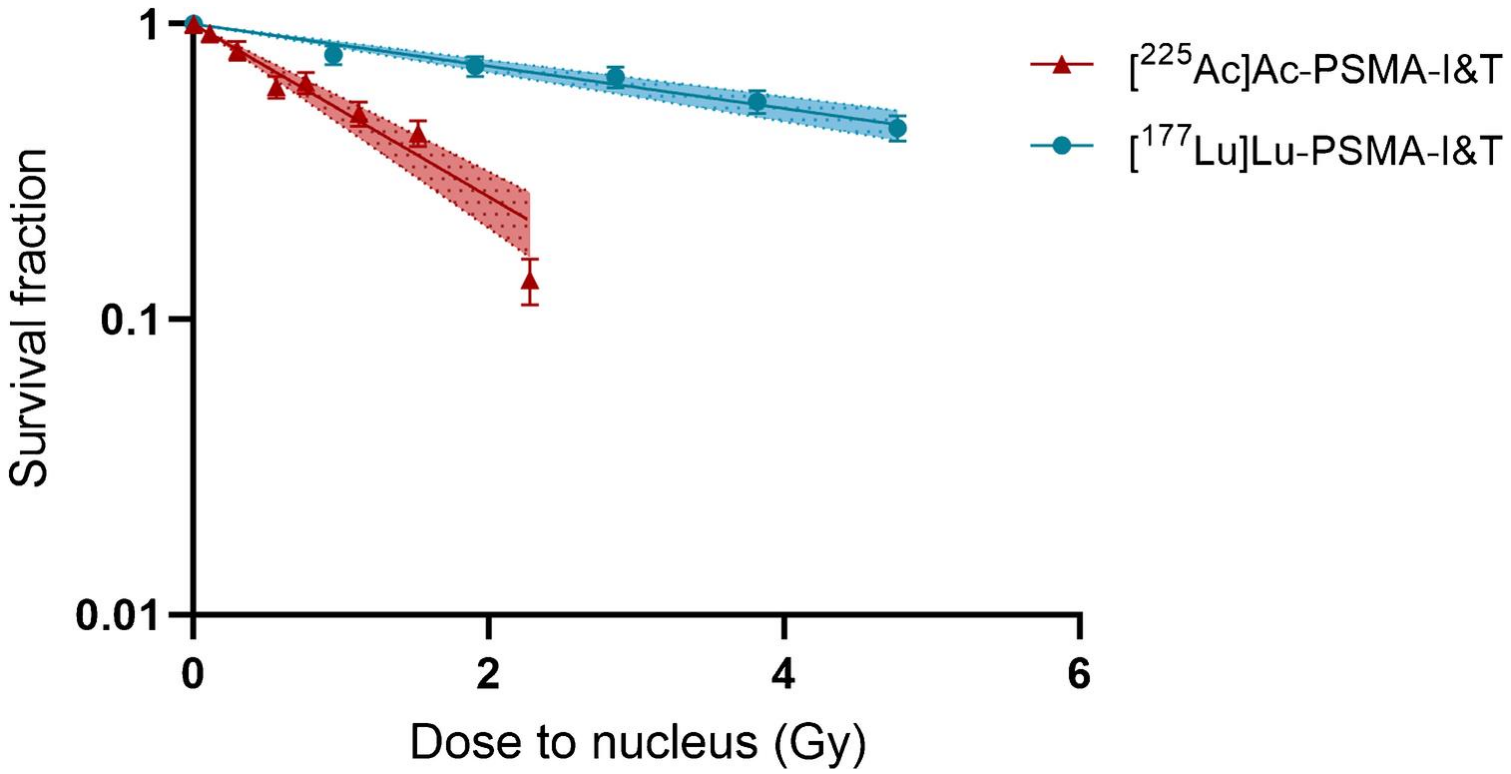


Sgouros et al. J Nucl Med 2010; Ruigrok et al. Eur J Nucl Med Mol Imaging 2022

# $^{225}$Ac versus $^{177}$Lu-PSMA-I&T: in vitro evidence

WWW.IO.GLIWICE.PL

PSMA-expressing PC3-PIP prostate cancer cells




**Relative biological effectiveness**

**4.2 ± 0.46**

Absorbed-dose comparison for the same biological effect

**Similar ligand binding**

These findings come from an in vitro model and require clinical validation



Ruigrok EAM et al. Eur J Nucl Med Mol Imaging. 2022

# Normal-tissue effects: beta versus alpha therapy

WWW.IO.GLIWICE.PL

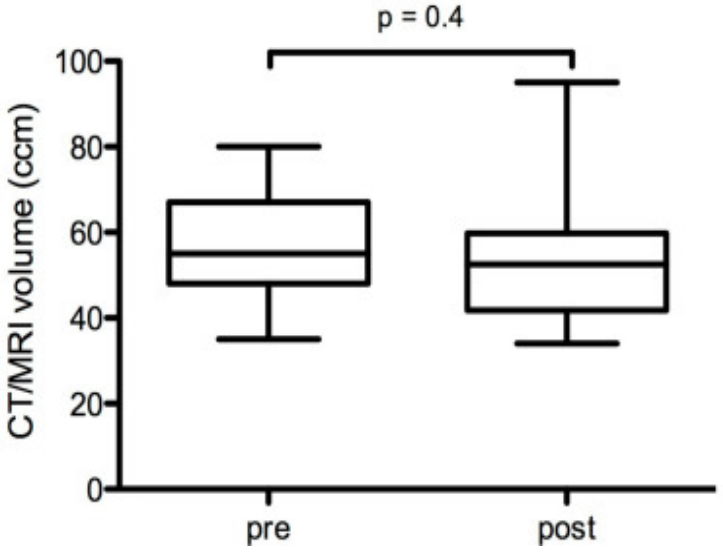
Wild et al., 2011 · mouse model

Greater antitumour efficacy with α therapy; renal injury depended on the radiopharmaceutical.

## Salivary-gland volume · Feuerecker et al., 2023

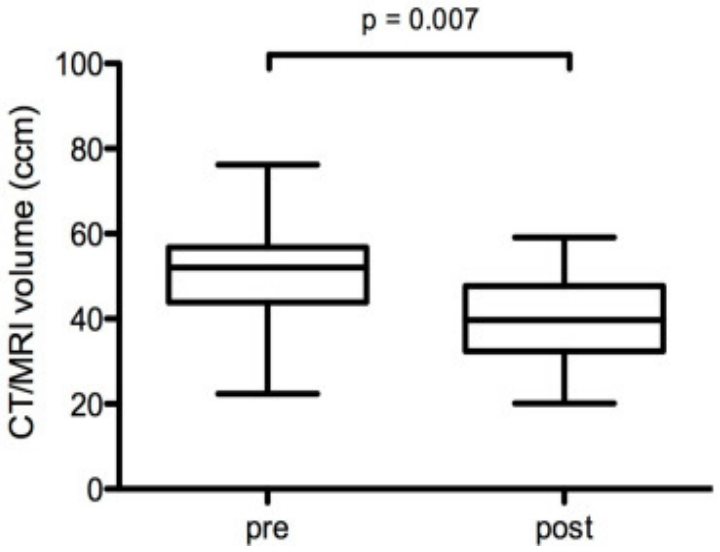
**$^{177}$Lu-PSMA-I&T**

2 cycles · n = 15



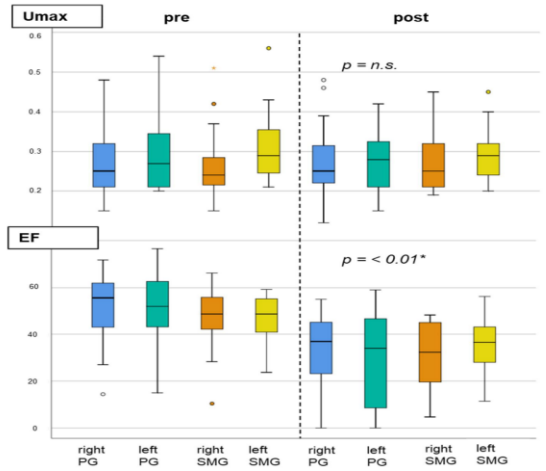

**$^{225}$Ac-PSMA-617**

1 cycle · n = 21




## Functional evidence: Langbein et al., 2022

Scintigraphy: reduced excretion after α/β tandem, no significant change after $^{177}$Lu alone.




## The clinical goal: meaningful clinical benefit with acceptable toxicity

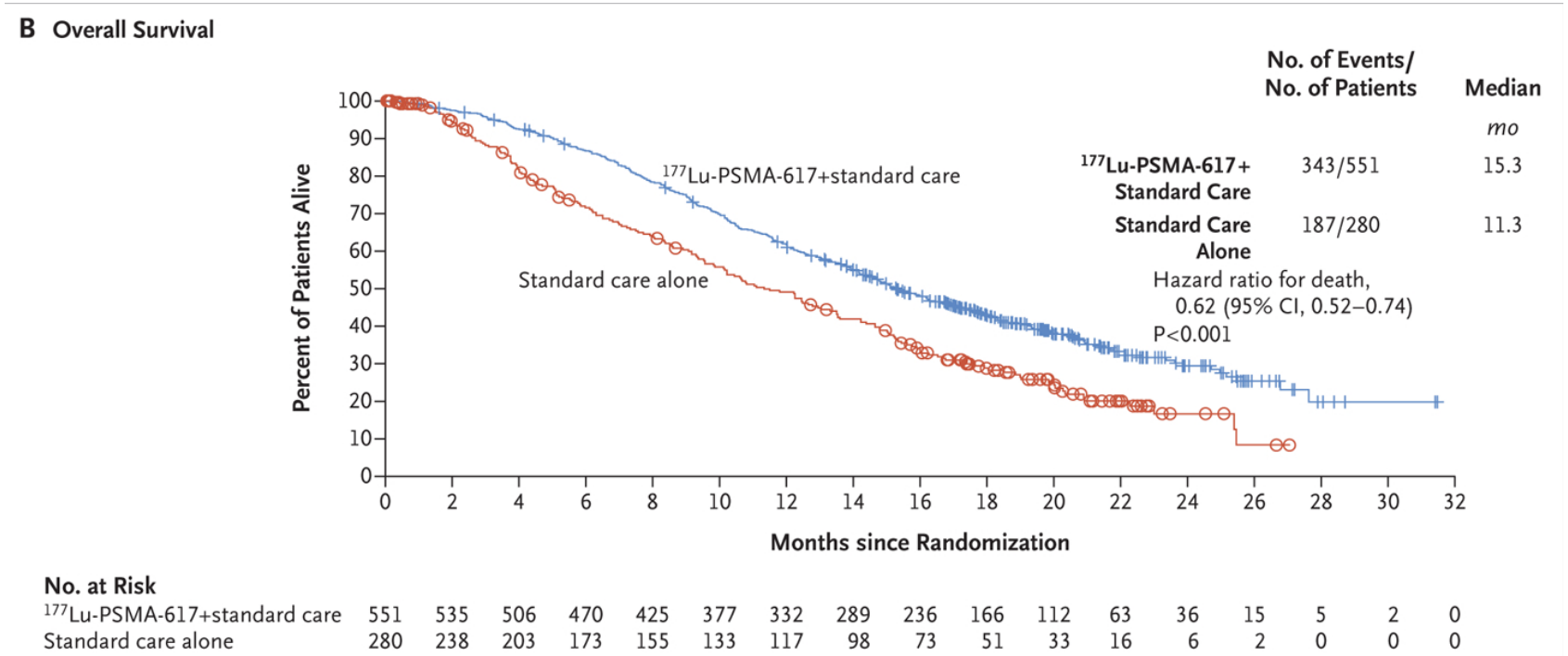
Wild et al. Cancer Res 2011; Feuerecker et al. IJMS 2023

# What does beta therapy achieve for patients?

WWW.IO.GLIWICE.PL

## VISION: $^{177}$Lu-PSMA-617 in advanced prostate cancer

Randomised phase III trial, 831 patients




**Median overall survival (months)**

**15.3**

$^{177}$Lu-PSMA-617 + standard care

**11.3**

Standard care alone

PSMA-positive metastatic castration-resistant prostate cancer after hormonal therapy and taxane chemotherapy

## Adding $^{177}$Lu-PSMA-617 prolonged survival

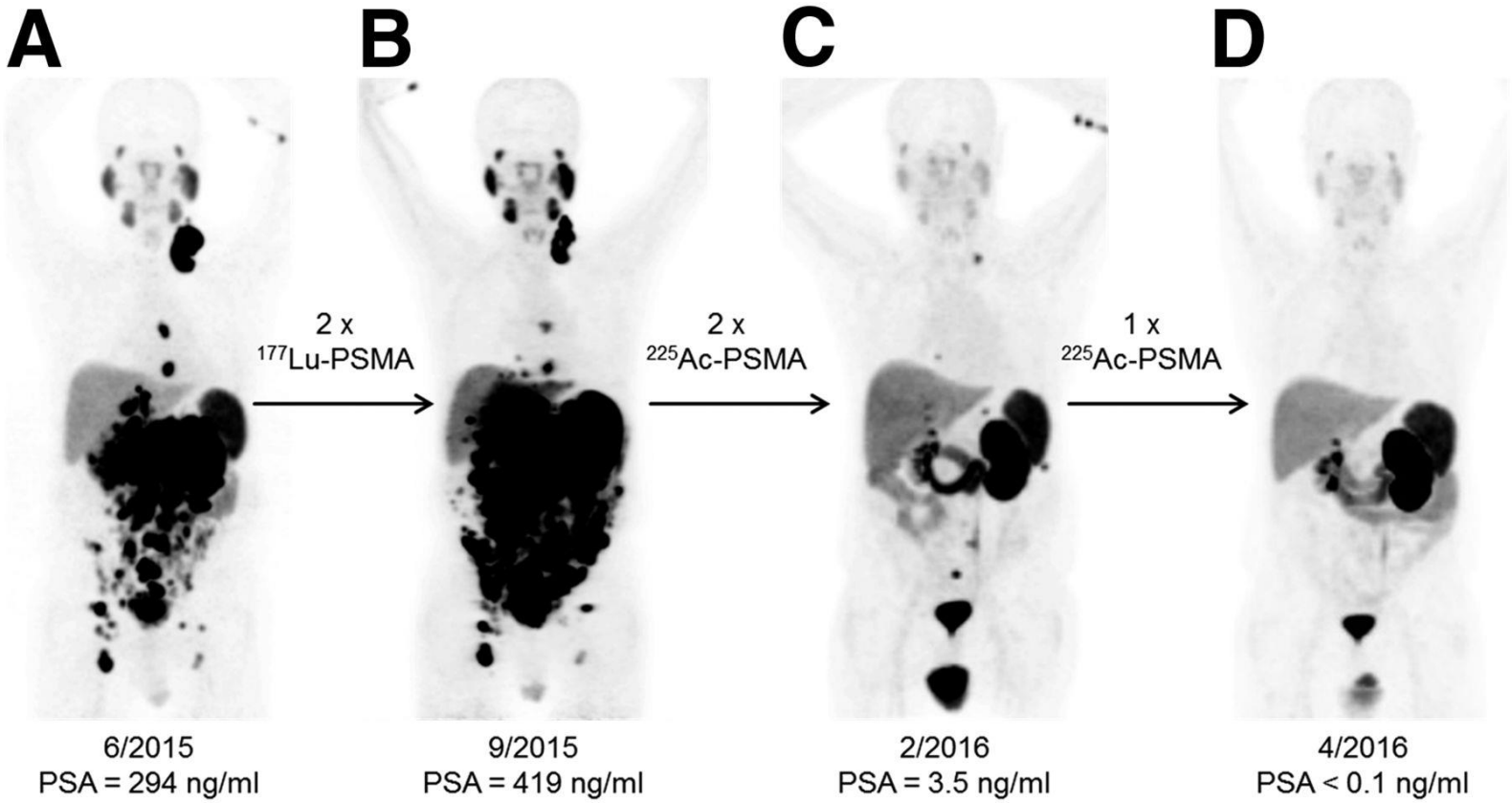


Sartor et al. N Engl J Med 2021

# What can alpha therapy add?

WWW.IO.GLIWICE.PL

## Response to $^{225}$Ac-PSMA-617 after progression on $^{177}$Lu-PSMA-617




## A rationale for trials of alpha therapy after beta-therapy progression

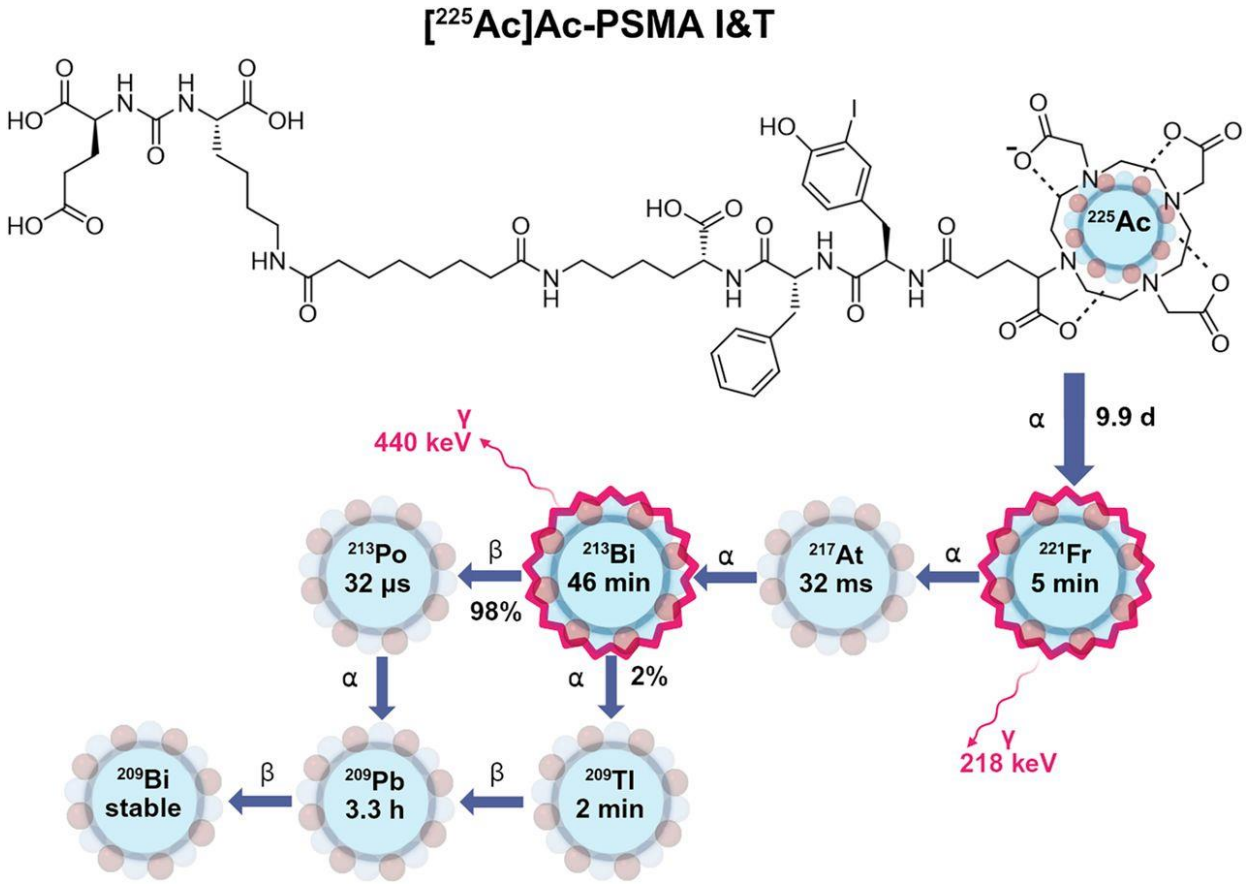


Kratochwil et al. J Nucl Med 2016

# $^{225}$Ac decay: where is the energy released?

WWW.IO.GLIWICE.PL

## The targeting molecule determines the initial delivery




### After the first α decay

Recoil releases $^{221}$Fr from the targeting molecule

### Daughter retention

Further decays within the tumour

### Daughter redistribution

Further decays may irradiate other tissues

A short α-particle range does not guarantee local retention of daughter nuclides



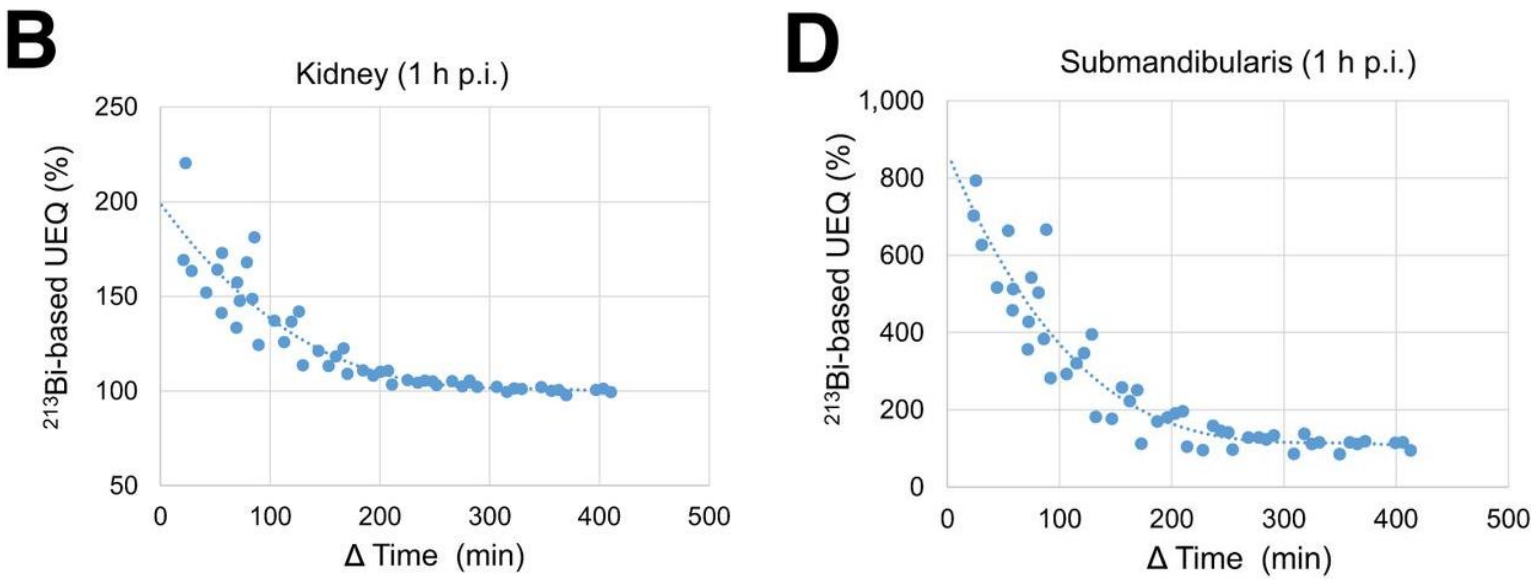
Wurzer et al. J Nucl Med 2025;66:1964–1969. doi:10.2967/jnumed.125.269744. Figure 1. © SNMMI.

# Daughter redistribution: effects on organ dose

WWW.IO.GLIWICE.PL

## Wurzer et al., 2025: $^{225}$Ac-PSMA I&T in mice

Organ sampling 1 h after injection (n = 5)




100% = equilibrium activity. Time axis = minutes after sacrifice.

### Modelled dose increase*

**Kidneys ×1.3**

**Salivary glands ×2.5**

*$^{221}$Fr uptake scenario, relative to local decay of all progeny. Mouse-to-human extrapolation.

No detectable daughter loss from tumour tissue in this model

**Lutetium-177 decays to stable hafnium-177. With actinium-225, however, we also need to consider radioactive daughter nuclides and where their subsequent decays occur.**



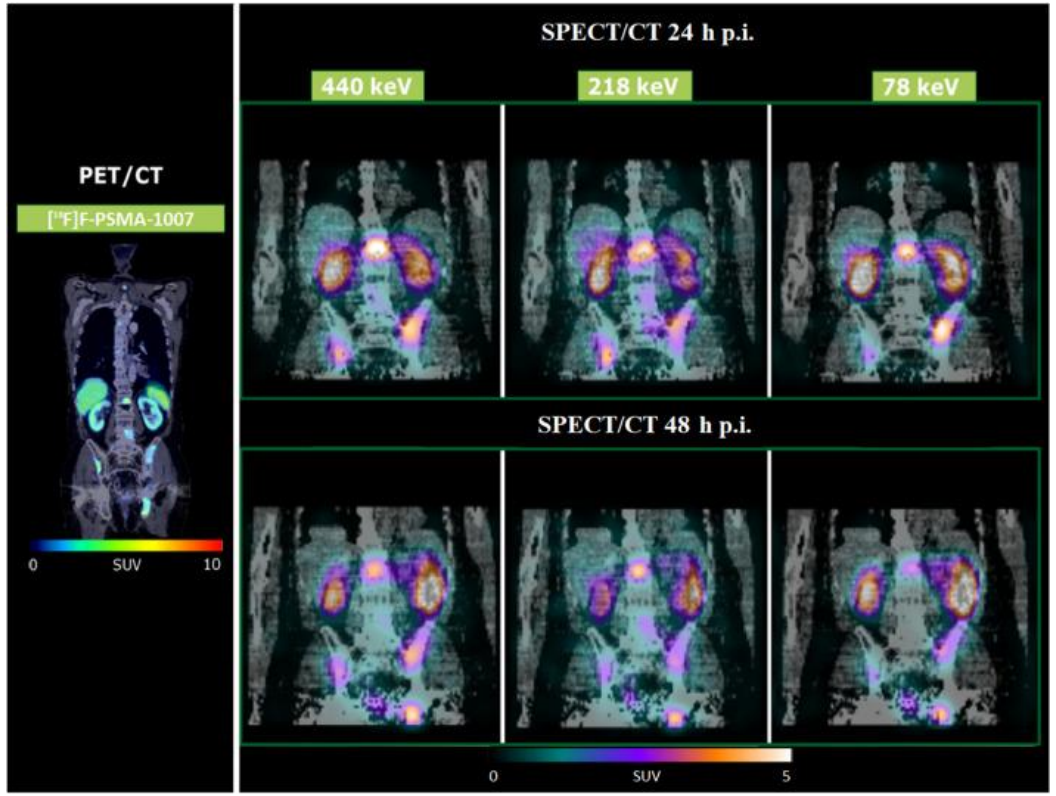
Wurzer et al. J Nucl Med 2025;66:1964–1969. doi:10.2967/jnumed.125.269744. Fig. 4B,D, cropped. © SNMMI.

# Daughter redistribution: evidence in patients

WWW.IO.GLIWICE.PL

## Liubchenko et al. 2024: $^{225}$Ac-PSMA-I&T

5 patients: quantitative SPECT/CT and urine analysis at 24 and 48 h




**Up to 10%**

Differences in daughter-specific kinetics

**Within 8%**

Differences in dose estimates for kidneys and lesions across methods

Small cohort and later measurements
No salivary-gland dosimetry

Limited impact on kidney and lesion dose estimates in this small cohort



Liubchenko et al. Eur J Nucl Med Mol Imaging 2024;51:2504–2514. doi:10.1007/s00259-024-06681-2. Figure 1, CC BY 4.0.

# What is needed to bring theranostics to more patients?

WWW.IO.GLIWICE.PL



**Reliable radionuclide supply**

Sufficient production capacity and dependable delivery

Validated manufacturing and consistent quality



**Clinical evidence**

Prospective trials
Treatment optimisation
Long-term safety



**Capacity and patient access**

Trained teams, treatment facilities and sustainable funding

NCBJ / POLATOM

IFJ PAN

Cyclotrons (Bydgoszcz, Gliwice, Katowice…)

## How can Poland connect isotope production, research and clinical care?



Al-Ibraheem et al. Semin Nucl Med. 2025. doi:10.1053/j.semnuclmed.2025.07.005.

# What clinicians need

WWW.IO.GLIWICE.PL

$^{225}Ac$

## $^{225}Ac$: the α-therapy bottleneck

- Limited global supply restricts clinical use
- Simpler waste handling and regulatory approval

$^{67}Cu$
$^{47}Sc$

## Matched theranostic pairs

- $^{67}Cu$ via $^{68}Zn(\gamma,p)$: $\beta^-$ therapy, paired with $^{64}Cu$ PET
- $^{47}Sc$ via $^{48}Ti(\gamma,p)$: $\beta^-$ therapy, paired with $^{43}Sc/^{44}Sc$ PET
- **Same ligand, different radionuclide:** identical chemistry for imaging and therapy

GMP

## What the clinic needs

- **Radionuclidic purity:** no long-lived impurities
- **High specific activity:** no carrier competing for the target
- **Reliable, scheduled supply** with batch-to-batch consistency



Radchenko V et al. J Nucl Med 2021;; Mikołajczak R et al. EJNMMI Radiopharm Chem 2021.

# From accelerator to patient: a more resilient Polish theranostics system




## Two complementary outcomes

### NEW THERAPIES

- Earlier access to novel radionuclides
- Investigator-initiated translational studies
- Polish multicentre clinical innovation
- Research independence for selected radionuclides

### SUPPLY RESILIENCE

- Local production of selected radionuclides
- Shorter supply chains
- Reduced dependence on external suppliers
- Backup capacity during supply

An accelerator can produce radionuclides.
A connected national system can produce new therapies — and make their supply more resilient.

# From beta to alpha: a clinical research agenda

WWW.IO.GLIWICE.PL

## Clinical need should guide radionuclide selection

Build on the clinical success of beta therapy and investigate where alpha-emitting radioligands may offer additional benefit.

## Production must support biological evaluation

Link radionuclide quality and radioligand stability to tumour delivery, dosimetry and normal-tissue toxicity.

## The research programme should be multidisciplinary

Physics, radiochemistry and radiobiology together with clinical teams to test clearly defined therapeutic hypotheses.