



Deutsche
Gesellschaft
für Nuklearmedizin
e.V.



Translational Research in Molecular Imaging and Radionuclid Therapy

September 4 – 6, 2014

Exampels for Translational Research Projects:

PSMA – a Theragnostic Approach

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University Hospital Heidelberg, Dept. Nuclear Medicine

- Some information about the “target” PSMA
- Tracer development and optimization of the ligands
- Improving biodistribution by co-medication? Nephroproction?
- First clinical results with PSMA targeted Radionuclide Therapy

The “target” PSMA:

- PSMA was originally identified as the ligand of the Prostate specific monoclonal antibody 7E11-C5 in 1987

Table 2 PSMA expression in normal tissues

Tissue	PSMA
Genitourinary organs	
Kidney	
Glomeruli	-
Tubules	+
Bladder	
Transitional epithelium	-
Smooth muscle	-
Prostate	
Epithelium	+
Stroma	-
Testis	-
Cervix	-
Breast	-
Digestive system	
Parotid	-
Stomach	-
Duodenum	+
Ileum	-
Colon	+
Liver	-
Pancreas	-
Hematological system	
Lymph node	-
Bone marrow	-
Skin	-
Skeletal muscle	-
Endocrine organs	
Thyroid	-
Adrenal	
Cortex	-
Medulla	-
Pancreatic islets	-
Nervous system	
Frontal cortex	-
Cerebellum	-
Eye	-
Peripheral ganglion	-

Horoszewicz, Anticancer Res, 1987

Silver, Clin Cancer Res, 1997

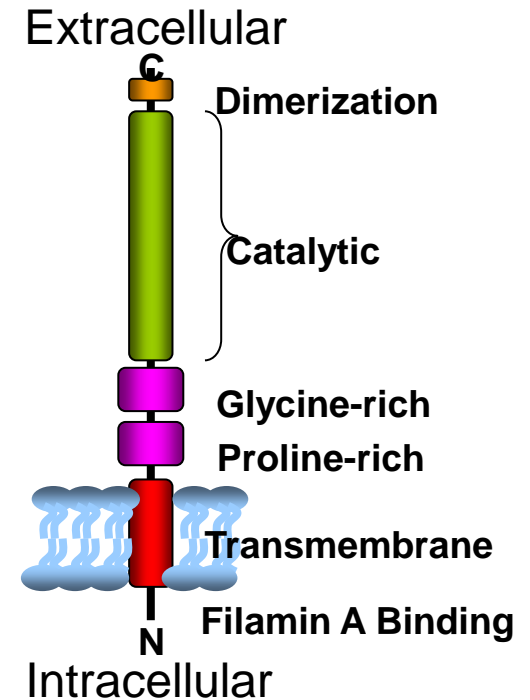
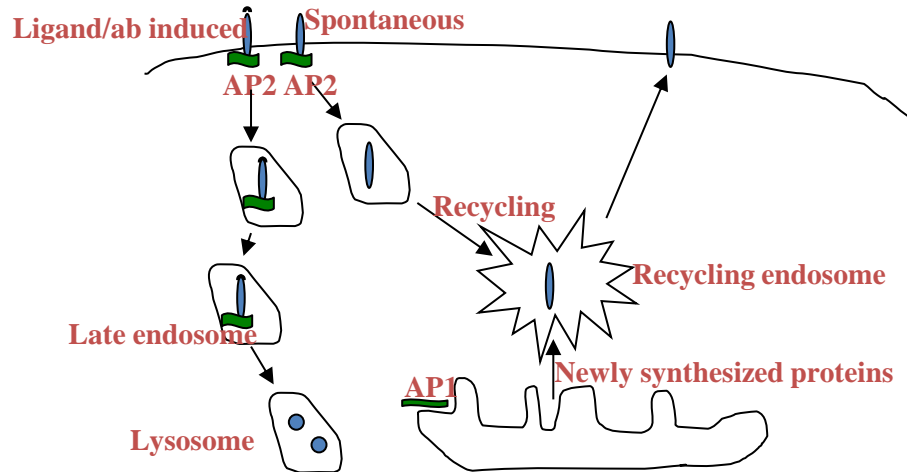
The “target” PSMA:

- PSMA was originally identified as the ligand of the Prostate specific monoclonal antibody 7E11-C5 in 1987
- PSMA is expressed in >90% of PCa

# Cases Studied	% Cases Reported to be PSMA Positive	Reference
251	94%	Wright et al
184	100%	Bostwick et al
51	84%	Mannweiler, et al
42	88%	Kusumi, et al
21	100%	Ananias, et al
905	99.9%	Loda, et al

The “target” PSMA:

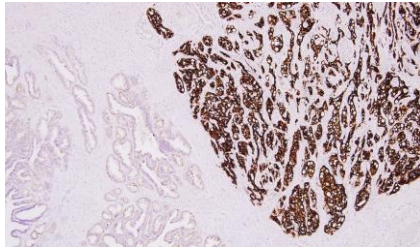
- PSMA was originally identified as the ligand of the Prostate specific monoclonal antibody 7E11-C5 in 1987
- Has a large extra-cellular part
- Internalisation after binding of an ligand or mAB



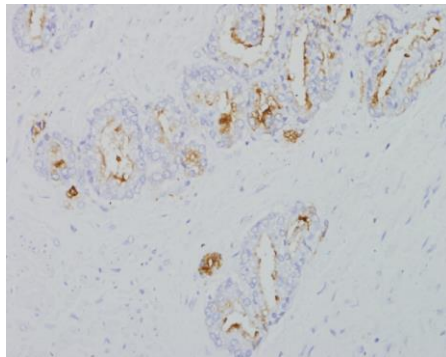
The “target” PSMA:

- PSMA was originally identified as the ligand of the Prostate specific monoclonal antibody 7E11-C5 in 1987
- PSMA expression increases progressively in:
 - a) High grade tumors
 - b) Metastases
 - c) Hormon-refractory PCa

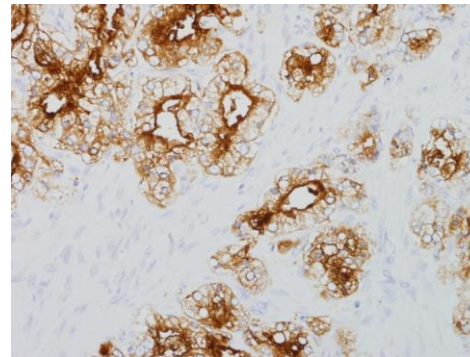
BPH



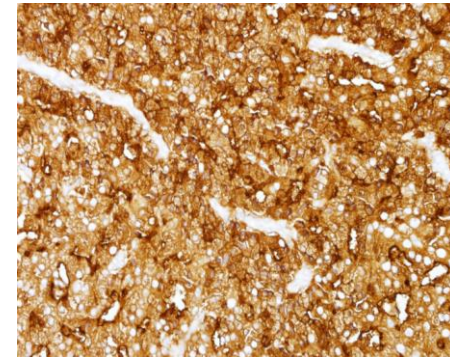
PCa



Gleason 3



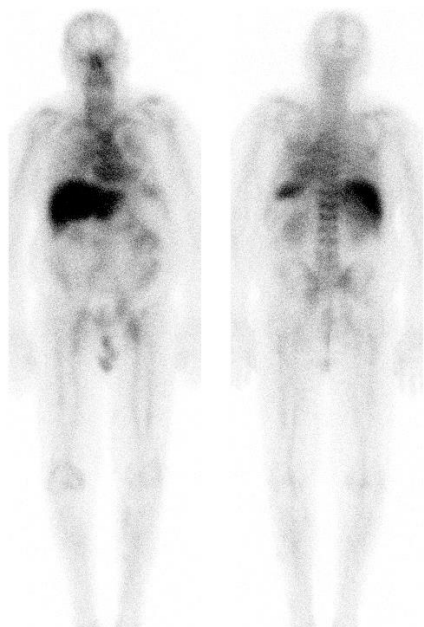
Gleason 4



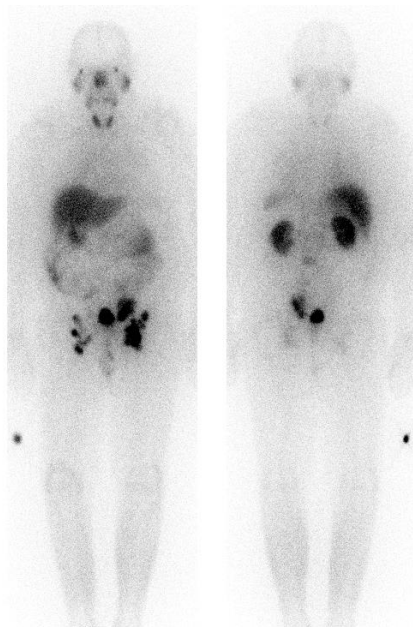
Gleason 5

The “target” PSMA:

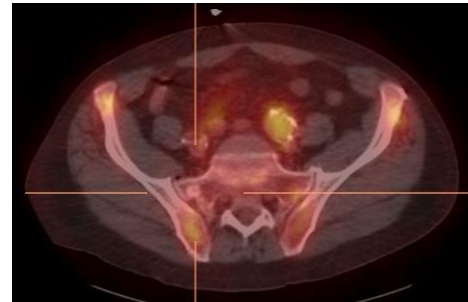
- PSMA was originally identified as the ligand of the Prostate specific monoclonal antibody 7E11-C5 in 1987
- The mAB labeled with ^{111}In was FDA approved as ProstaScint in 1996



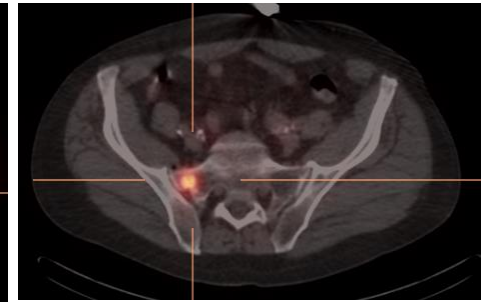
^{111}In -Prostascint (5d)



^{123}I -MIP1072 (3h)



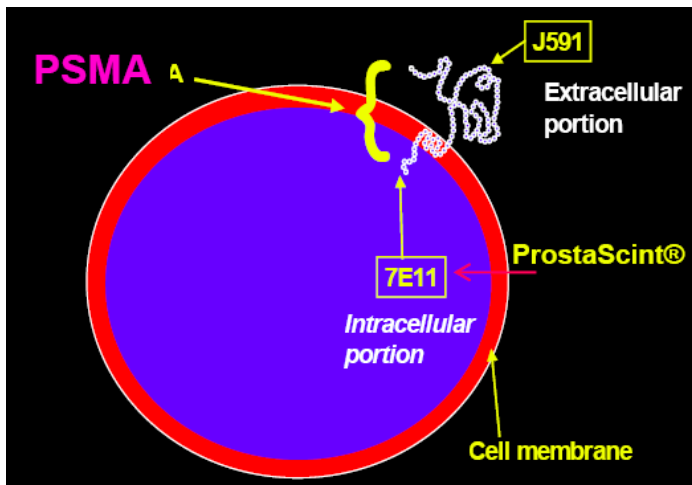
^{111}In -Prostascint (5d)



^{123}I -MIP1072 (3h)

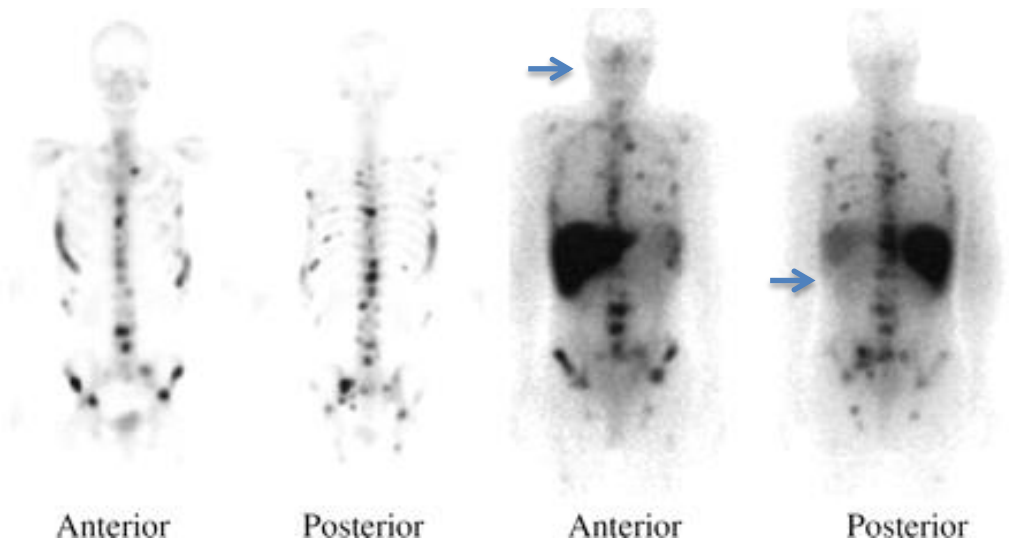
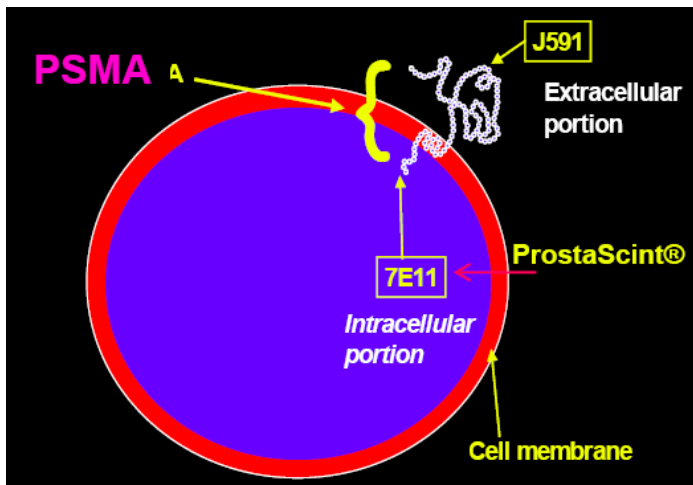
The “target” PSMA:

- PSMA was originally identified as the ligand of the Prostate specific monoclonal antibody 7E11-C5 in 1987
- The mAB labeled with ^{111}In was FDA approved as ProstaScint in 1996
- But targeting an intracellular domain of PSMA its clinical impact is not significantly different from zero.



The “target” PSMA:

- The deimmunized antibody J591 targets the extracellular domain of PSMA
- But is limited by the slow pharmacokinetics of an antibody



MDP

^{177}Lu -J591 (7d)

Vallabhajosula, JNM, 2005

Limitations of antibody tracers:

- long circulating half-life (hematotoxicity)
- poor tumor penetrability (particularly for bone metastases)

Advantages of small molecule tracers:

- faster normal tissue clearance (improving bone marrow dose)
- higher permeability in solid tumors

- Some information about the “target” PSMA
- Tracer development and optimization of the ligands
- Improving biodistribution by co-medication? Nephroproction?
- First clinical results with PSMA targeted Radionuclide Therapy

PSMA – a Theragnostic Approach

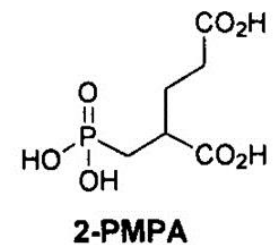
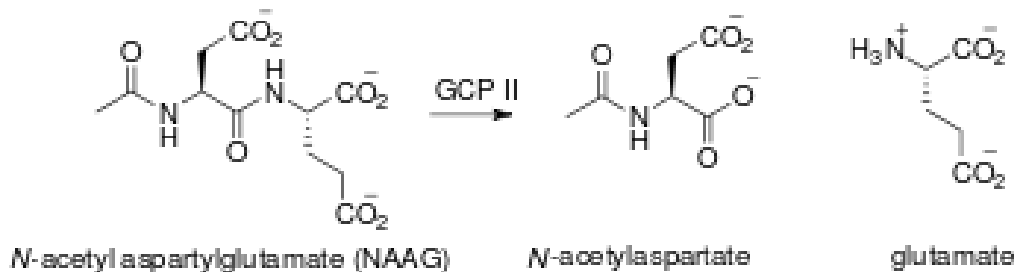
Glutamate carboxypeptidase II (GCPII) =

N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I) =

NAAG peptidase =

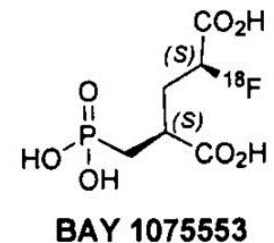
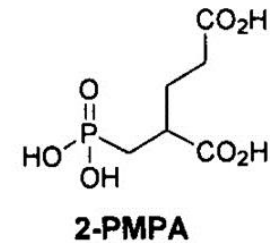
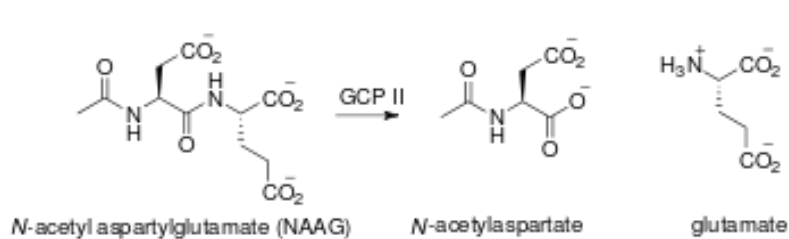
Folate hydrolase 1 (FOLH1) =

Prostate-specific membrane antigen (PSMA)



GCP II - Inhibitor

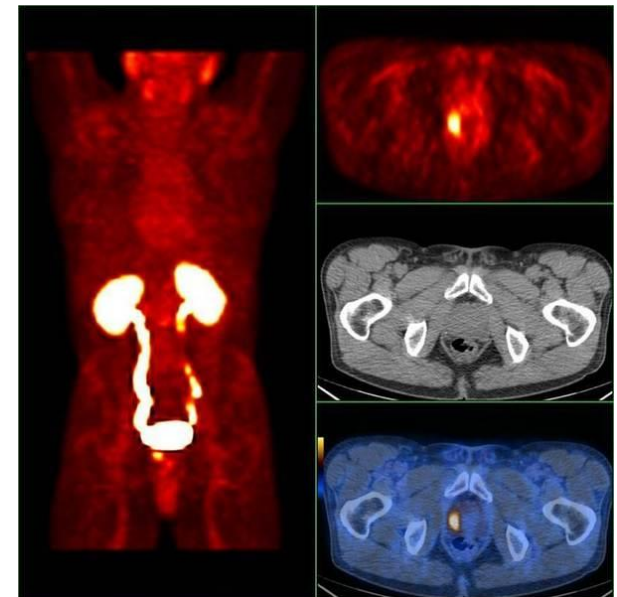
PSMA – a Theragnostic Approach



Even before the structure of the catalytic domain of PSMA was completely evaluated,

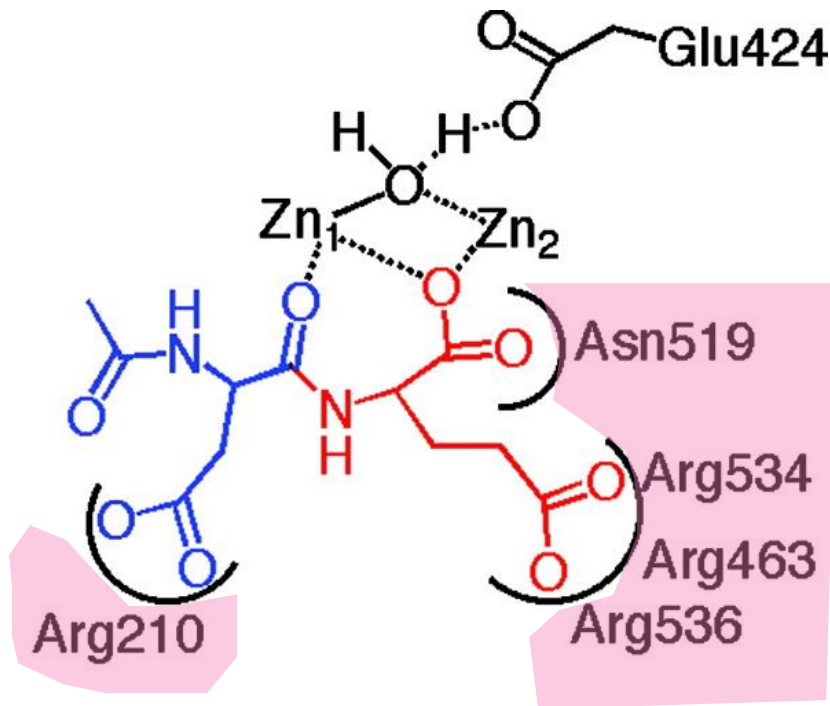
known inhibitors of the enzymatic function of GCP II served as basic structure for the first small molecule PSMA tracers.

However, these compounds failed to be superior in comparison with Choline-PET



Beheshti, WMIS convention, 2013

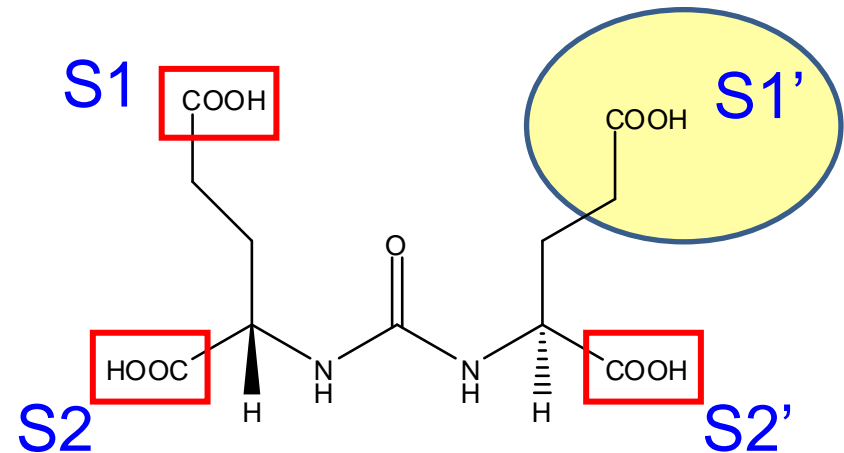
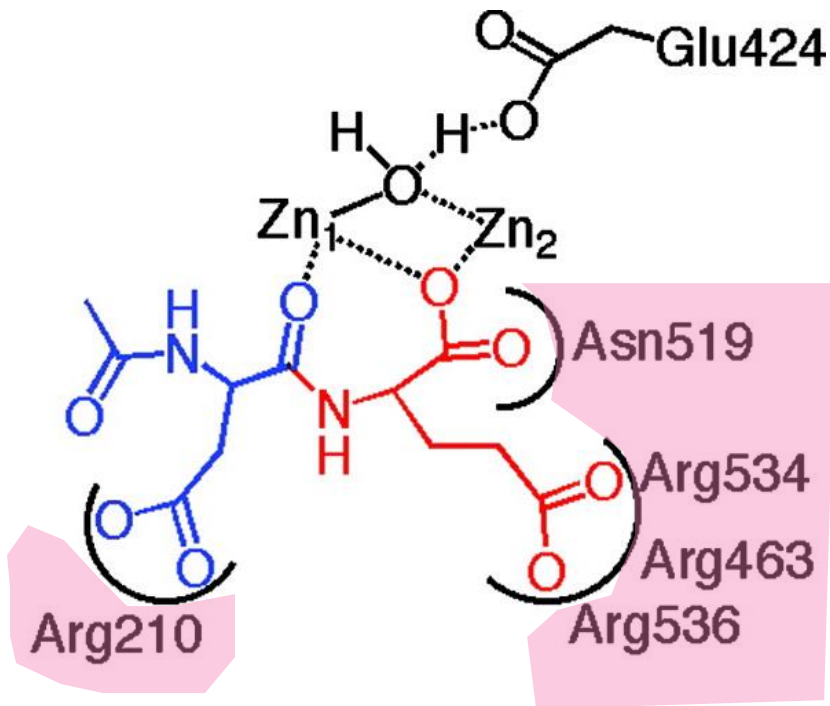
PSMA – a Theragnostic Approach



- Substrate binding domain contains two basic sub-pockets.
- First pocket binds glutamate (via electrostatic interactions)
- Catalytic domain contains a bi-nuclear zinc binding site (coordinating a water molecule where hydrolysis of peptide bond occurs)

Davis Proc. Natl. Acad. Sci. USA 2005
Mesters EMBO J. 2006

PSMA – a Theragnostic Approach

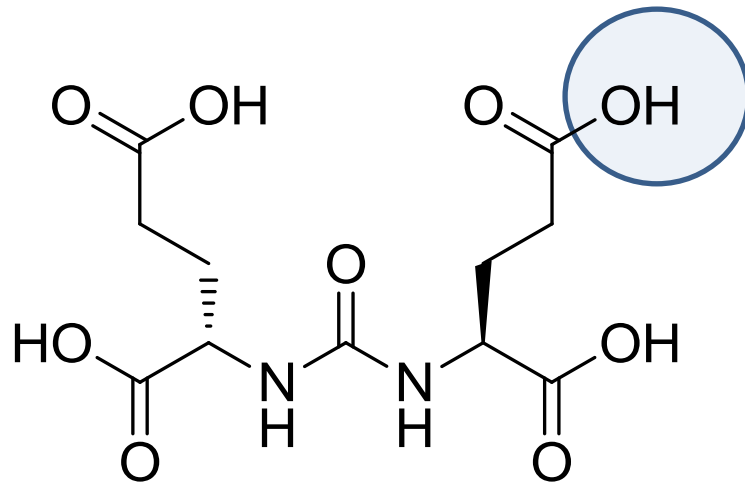


- It appears necessary to keep one glutamic acid unit intact
- S2 and S2' are intolerant to structural changes
- Assuming S1, S2 and S2' intact, S1' is tolerant to increase steric bulk

Davis Proc. Natl. Acad. Sci. USA 2005

Mesters EMBO J. 2006

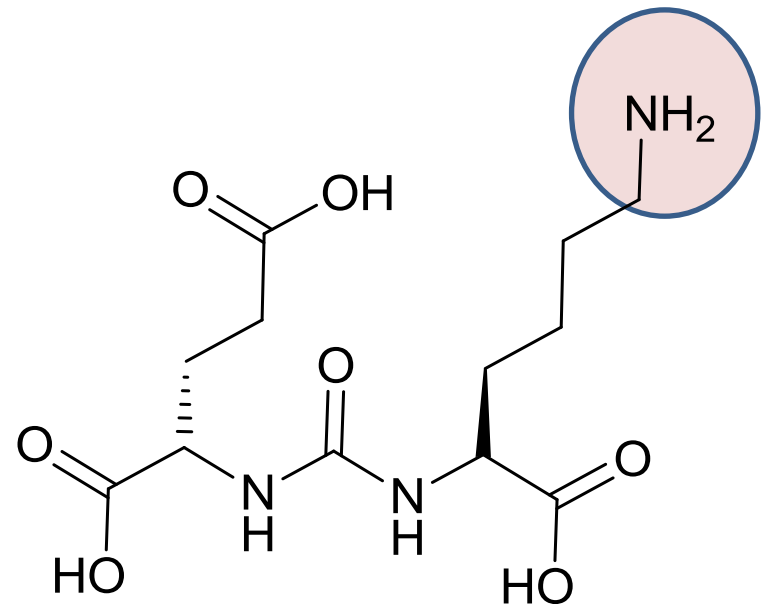
Glu-urea-Glu



403 nM

Kozikowski et al. J Med Chem. 2001

Glu-urea-Lys

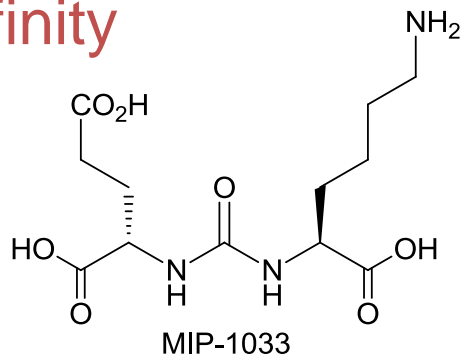


497 nM

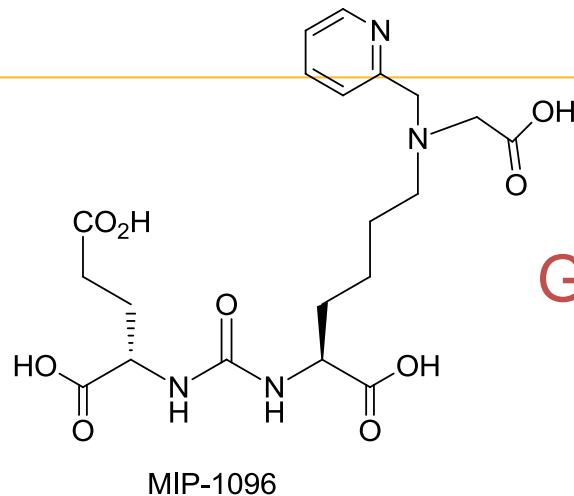
Maresca KP, et al. J Med Chem. 2009

PSMA – a Theragnostic Approach

Modest Affinity



497 nM

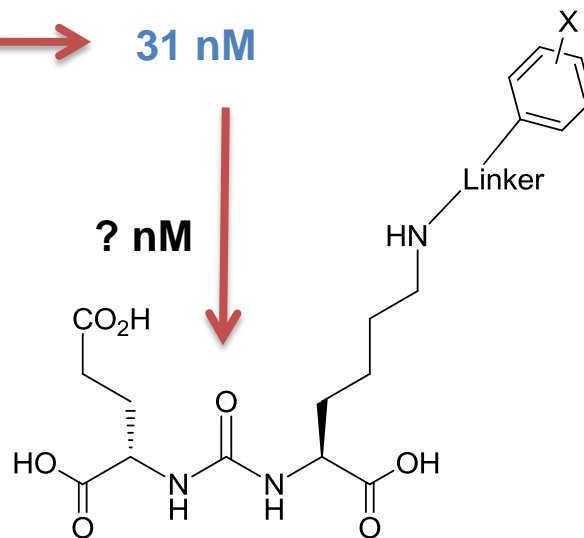


Good Affinity

31 nM

Can affinity be tuned with
haloaromatic substituents?

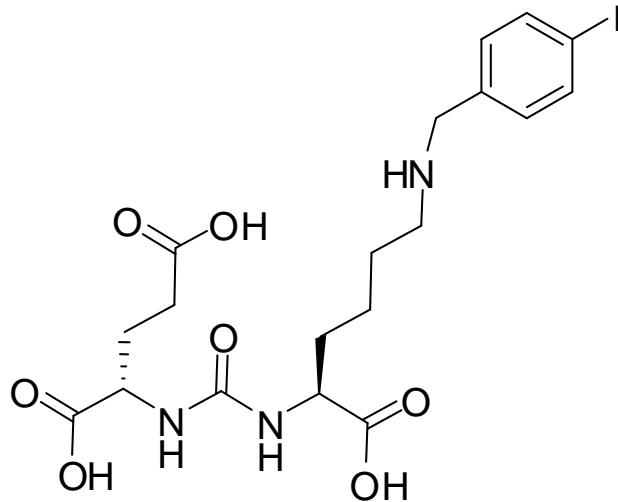
What will be the effect on PK?



X; F, Cl, Br, I

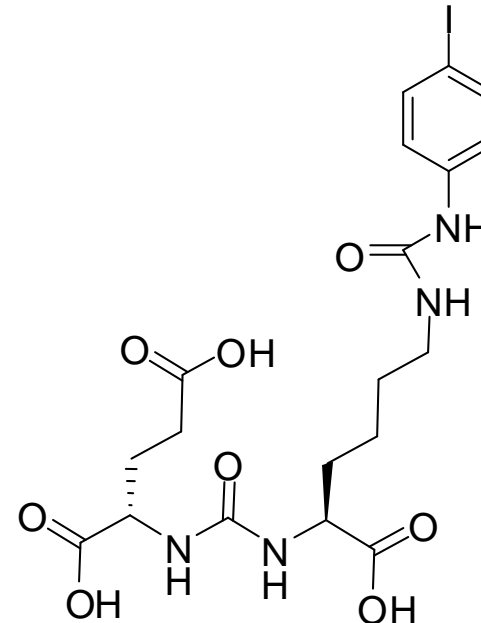
PSMA – a Theragnostic Approach

123 | / 131 |



MIP-1072

2-(3-(1-carboxy-5-(4-iodo-benzylamino)-
pentyl)-ureido)-pentanedioic acid



MIP-1095

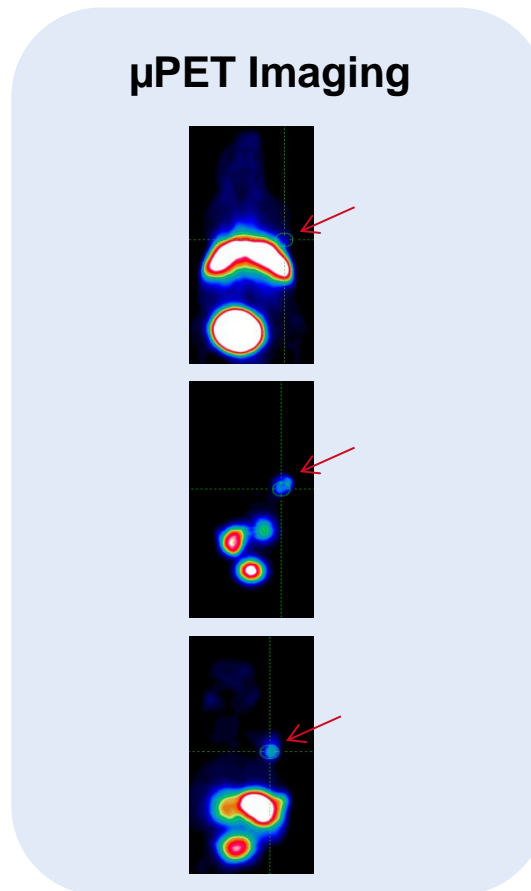
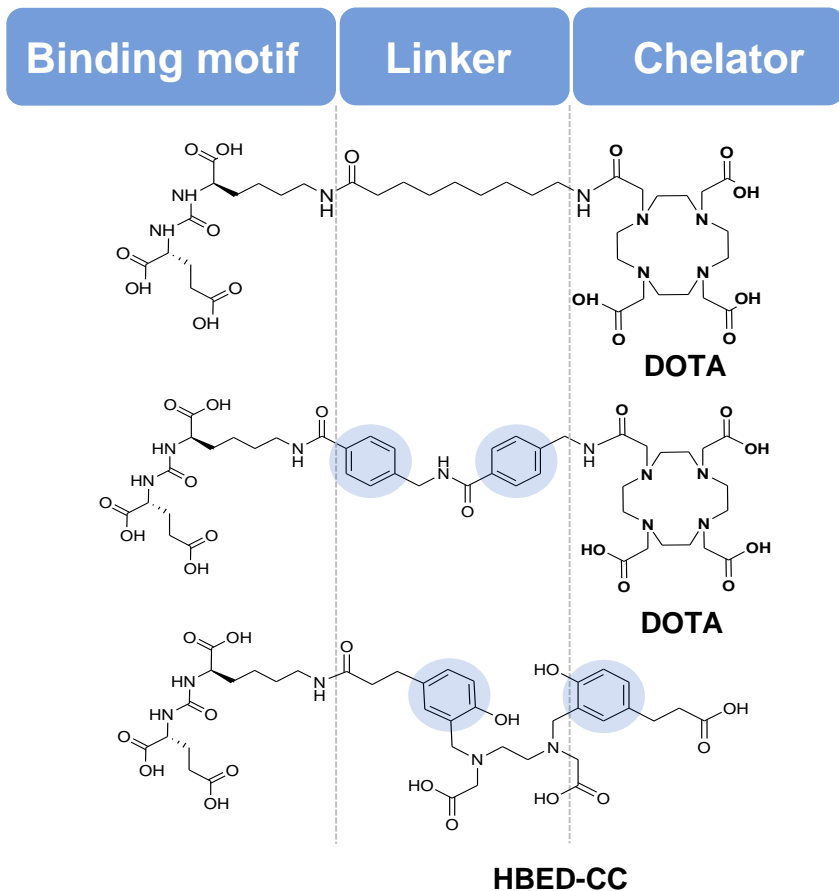
(S)-2-(3-(R)-1-carboxy-5-(3-(4-iodophenyl)
ureido)pentyl)ureido)pentanedioic acid

NAALADase Inhibition (K_i)

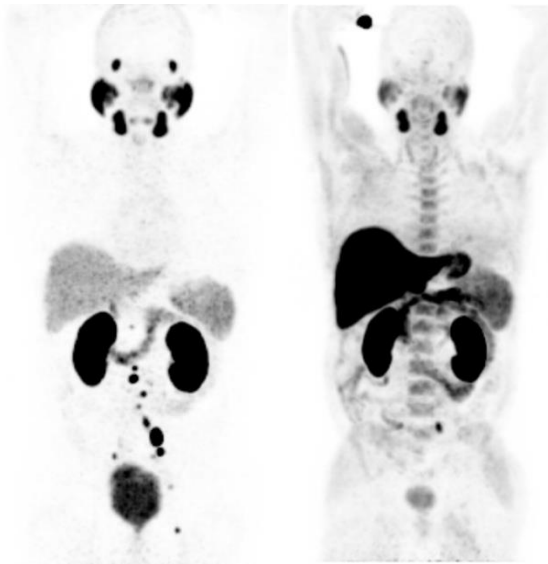
MIP-1072 **6 nM**

MIP-1095 **0.3 nM**

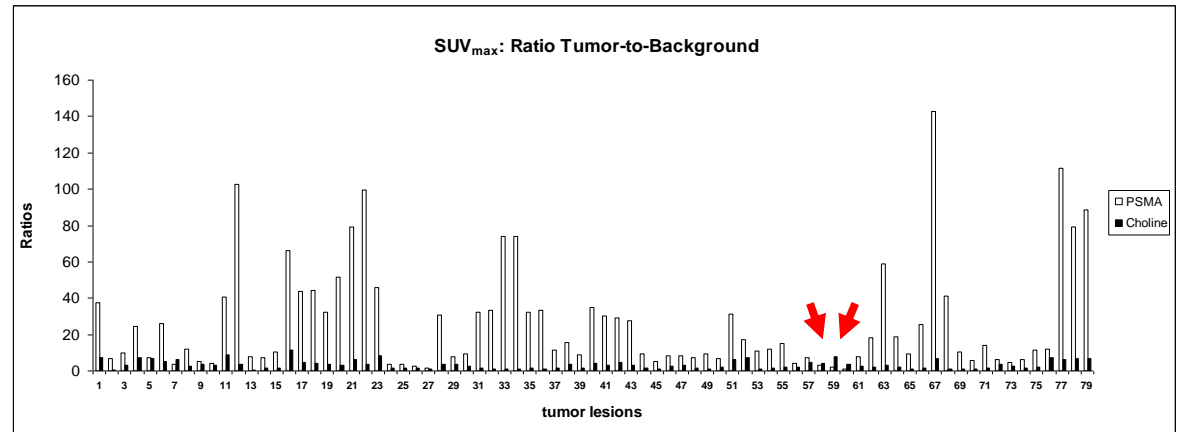
Chelator HBED-CC interacting with lipophilic binding pocket



^{68}Ga -HBED-CC



^{68}Ga -HBED-CC ^{18}F -FMCh



Higher sensitivity or at least contrast ratios in
77/79 pt. in comparison to Cholin-PET

PSMA617

Binding affinity

(LNCaP cell line)

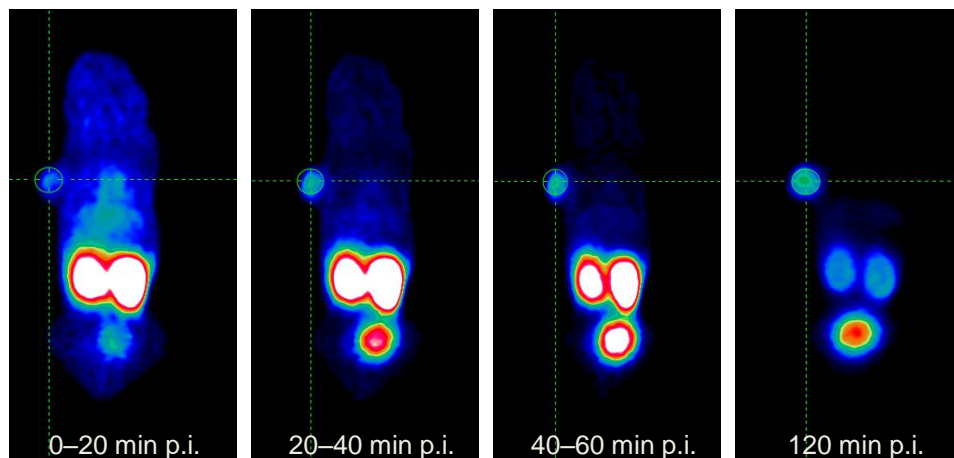
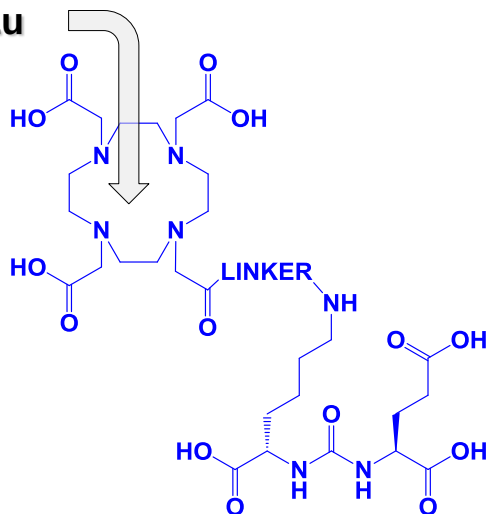
Comp.	IC ₅₀ [nM]
PSMA617	0.13 ± 0.02

Internalization

(LNCaP cell line)

Comp.	Cell surface [%]	Lysate [%]
PSMA617	14.5 ± 0.5	48.3 ± 1.4

⁶⁸Ga, ⁹⁰Y, ¹⁷⁷Lu
²¹³Bi, ²²⁵Ac

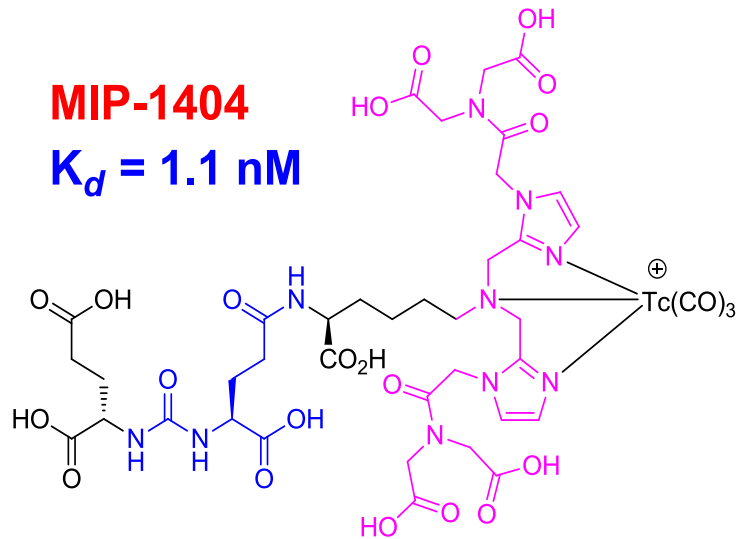


P 1123, EPA Patent Application EP 13004991; date of filing October 18th 2013.

^{99m}Tc / ^{186}Re , ^{188}Re

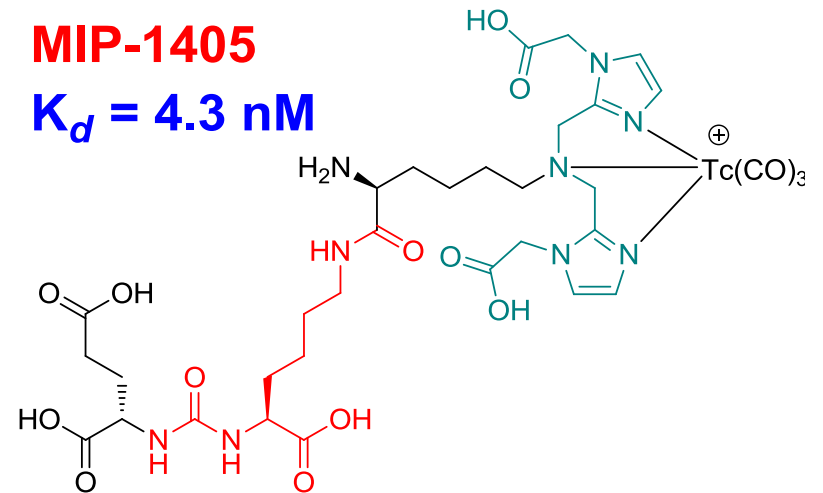
MIP-1404

$K_d = 1.1 \text{ nM}$



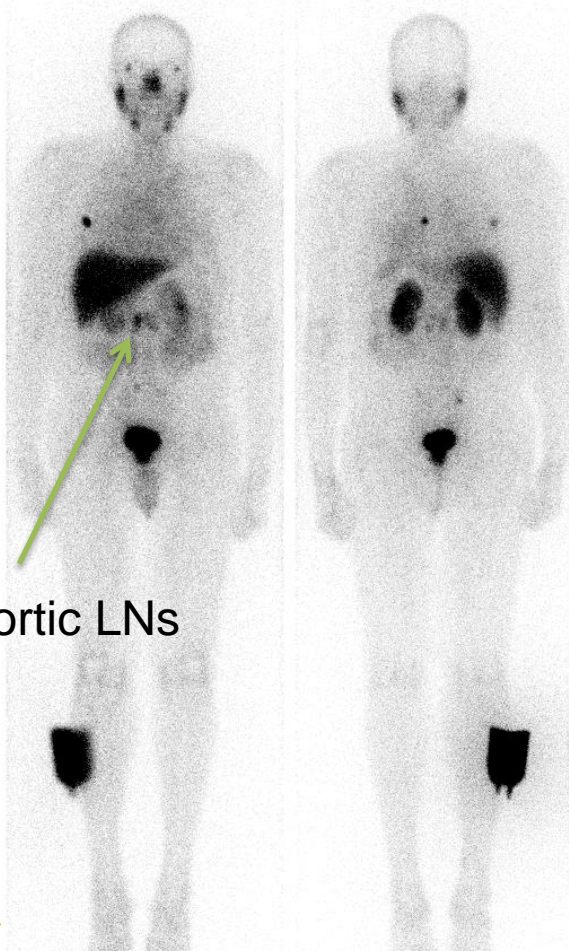
MIP-1405

$K_d = 4.3 \text{ nM}$



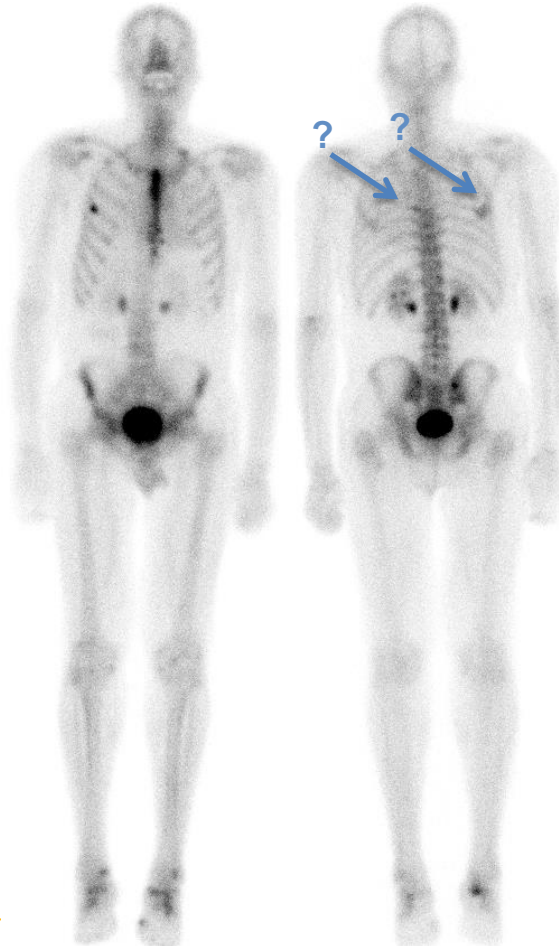
PSMA – a Theragnostic Approach

^{123}I -MIP-1072 4 hrs pi baseline

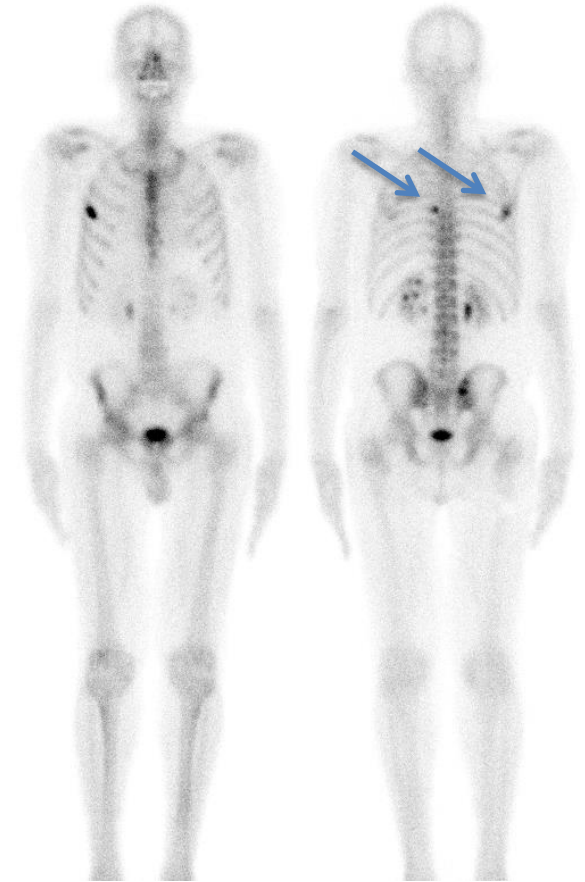


Periaortic LNs

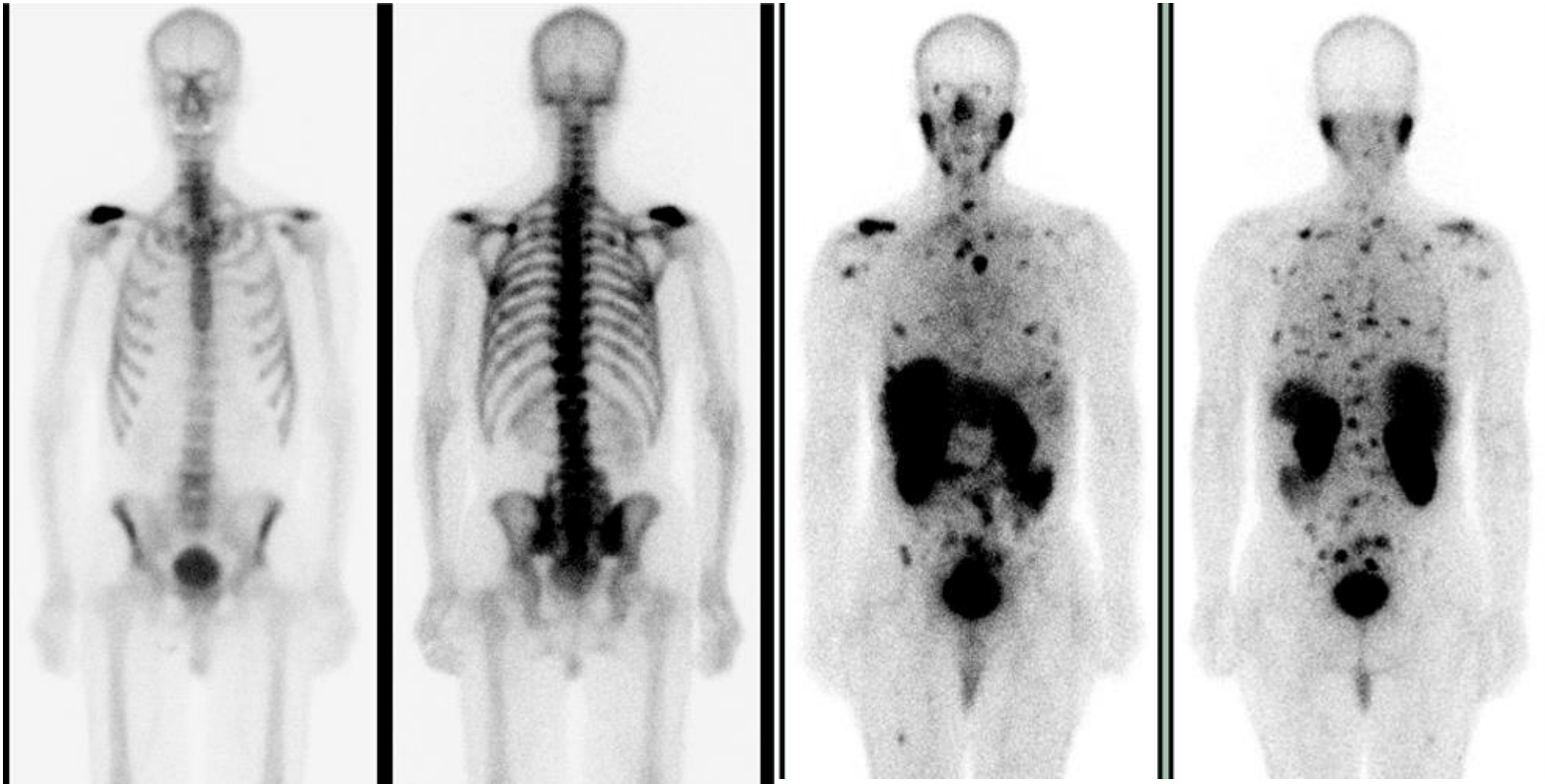
Bone Scan - Initial



F/U Bone Scan @ 12 weeks



PSMA – a Theragnostic Approach



Tc-MDP

Tc-MIP-1405

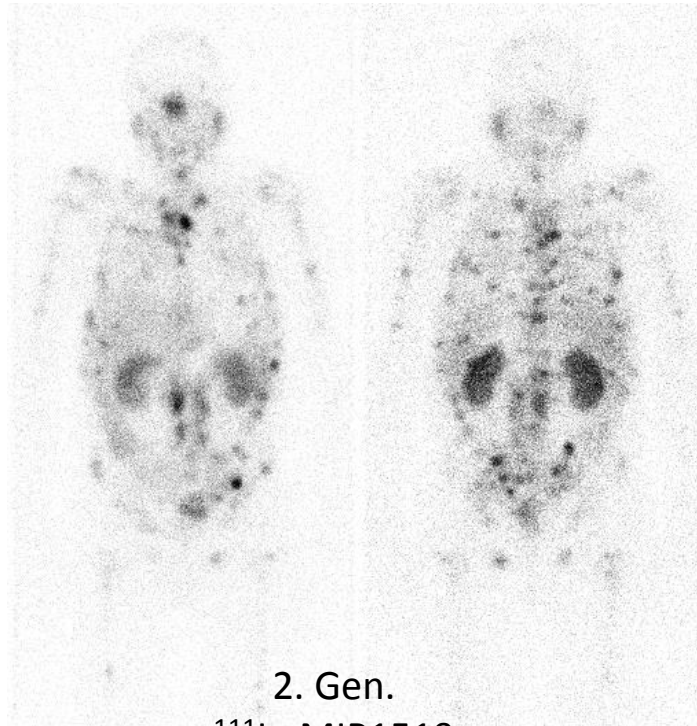
- Some information about the “target” PSMA
- Tracer development and optimization of the ligands
- Improving biodistribution by co-medication? Nephroproction?
- First clinical results with PSMA targeted Radionuclide Therapy

PSMA – a Theragnostic Approach

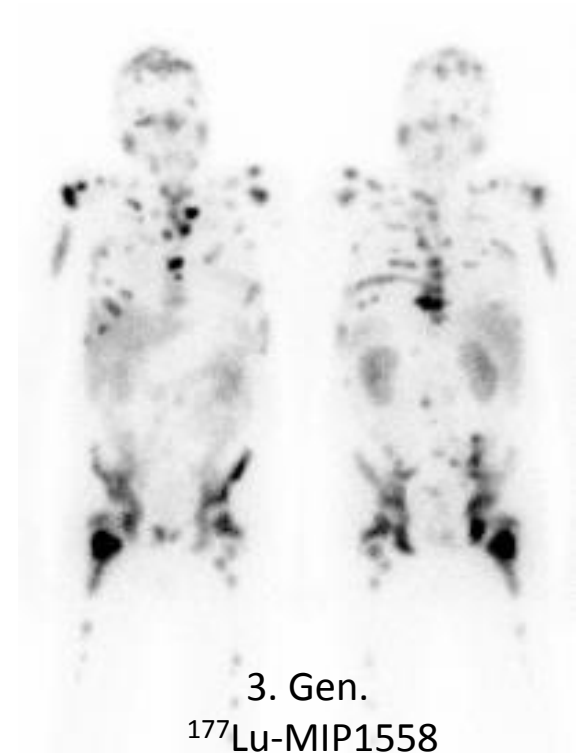
- Kidneys can be dose limiting
- Optimization of the radiopharmcon can only improve non-specific binding



1. Gen.
⁶⁸Ga HBED-CC



2. Gen.
¹¹¹In MIP1519



3. Gen.
¹⁷⁷Lu-MIP1558

PSMA – a Theragnostic Approach

- Optimization of the radiopharmcon can only improve non-specific binding
- Specific binding to kidney PSMA remains challanging

Table 2 PSMA expression in normal tissues

Tissue	PSMA
Genitourinary organs	
Kidney	-
Glomeruli	-
Tubules	+
Bladder	-
Transitional epithelium	-
Smooth muscle	-
Prostate	+
Epithelium	+
Stroma	-
Testis	-
Cervix	-
Breast	-
Digestive system	
Parotid	-
Stomach	-
Duodenum	+
Ileum	-
Colon	+
Liver	-
Pancreas	-
Hematological system	
Lymph node	-
Bone marrow	-
Skin	-
Skeletal muscle	-
Endocrine organs	
Thyroid	-
Adrenal	-
Cortex	-
Medulla	-
Pancreatic islets	-
Nervous system	
Frontal cortex	-
Cerebellum	-
Eye	-
Peripheral ganglion	-

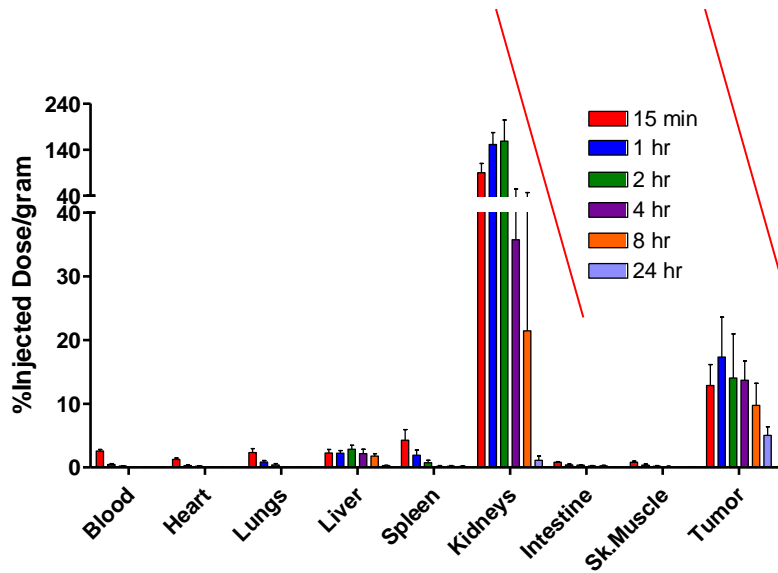
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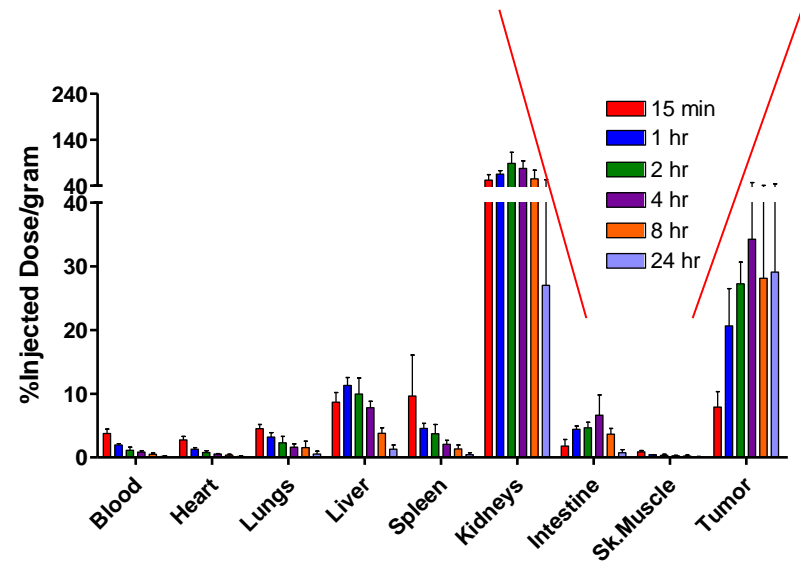
Silver Clin Cancer Res 1997

PSMA – a Theragnostic Approach

- Different kinetics between kidney and tumor
- Depends on internalisation rate



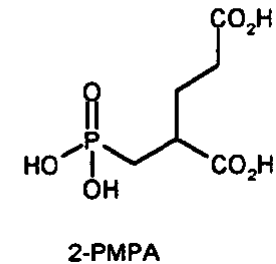
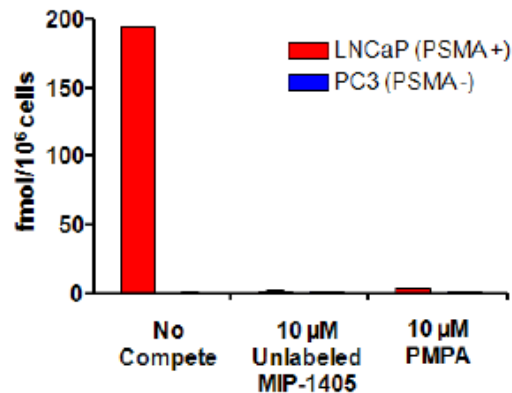
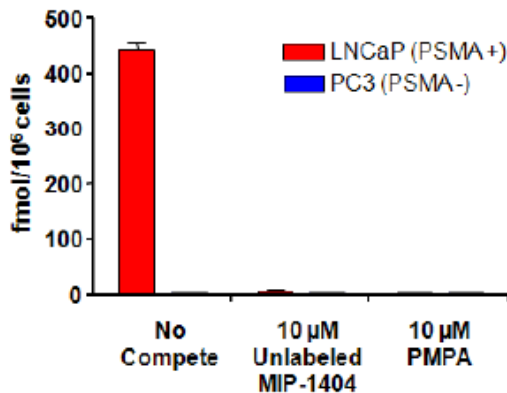
Tissue Distribution in LNCaP Bearing Mice:
[¹²³I]MIP-1072



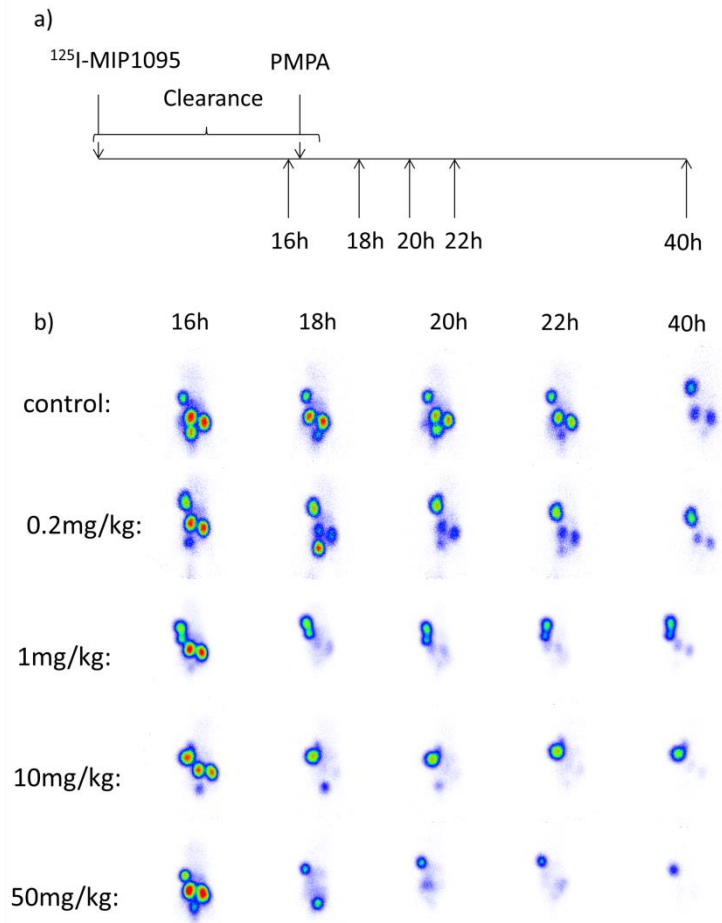
Tissue Distribution in LNCaP Bearing Mice:
[¹²³I]MIP-1095

PSMA – a Theragnostic Approach

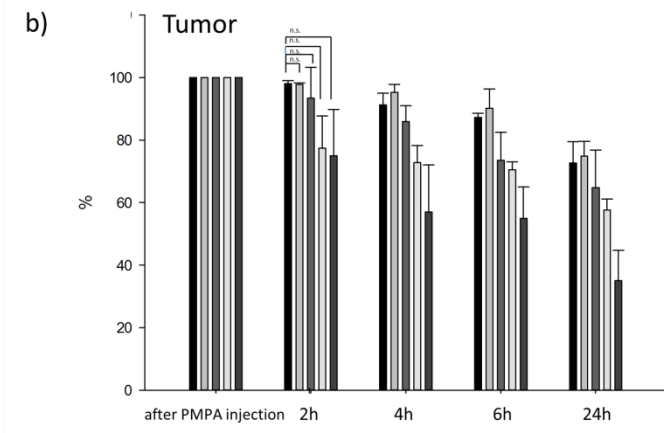
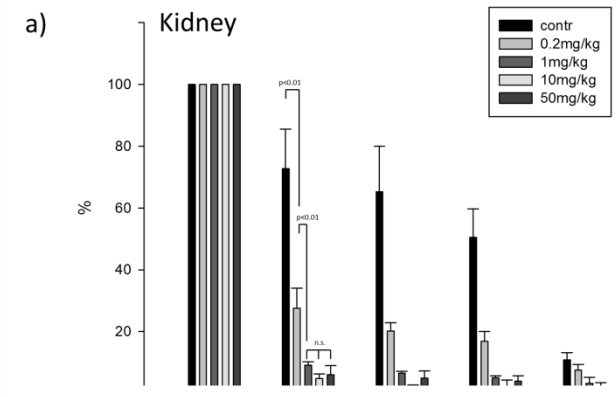
- Thesis: After the rapid internalization of PSMA-ligand into tumor cells a subsequent injection of a competitive PSMA inhibitor might still displace the none or “not-yet“ internalized ligand from the kidneys without decreasing tumor dose.
- PMPA (2-(Phosphonomethyl)-Pentanedioic acid) is a structurally unrelated PSMA inhibitor with long term experience in neurological evaluation.



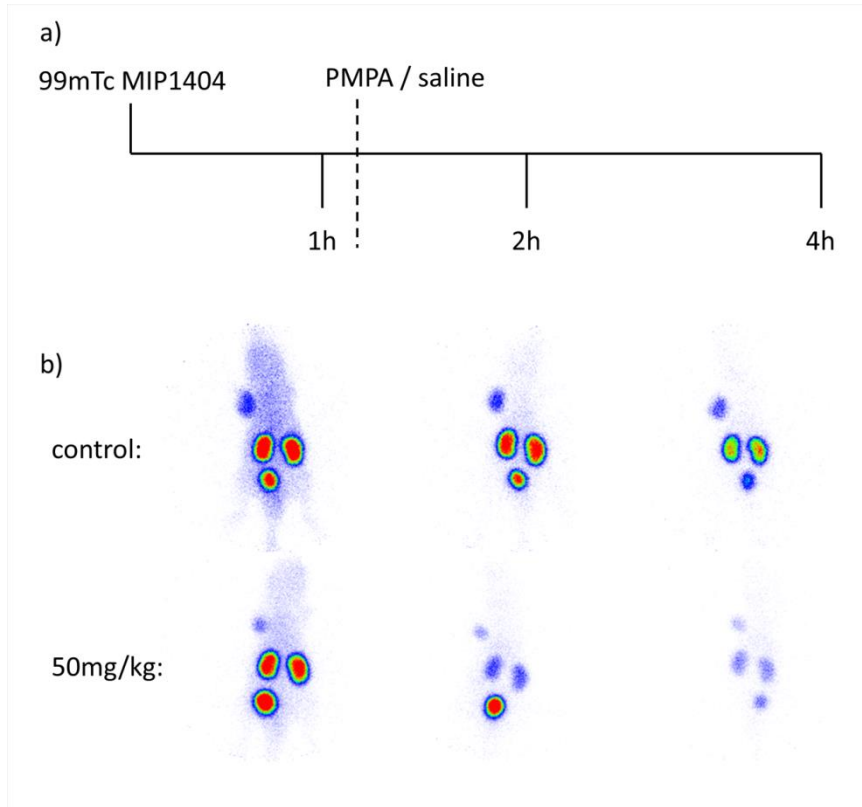
PSMA – a Theragnostic Approach



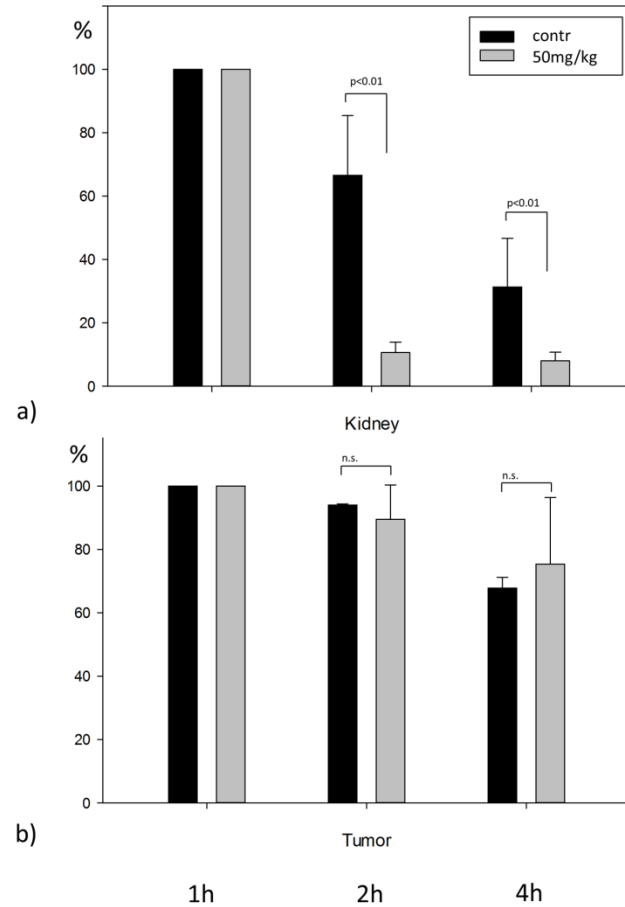
MIP1095



PSMA – a Theragnostic Approach



MIP1404

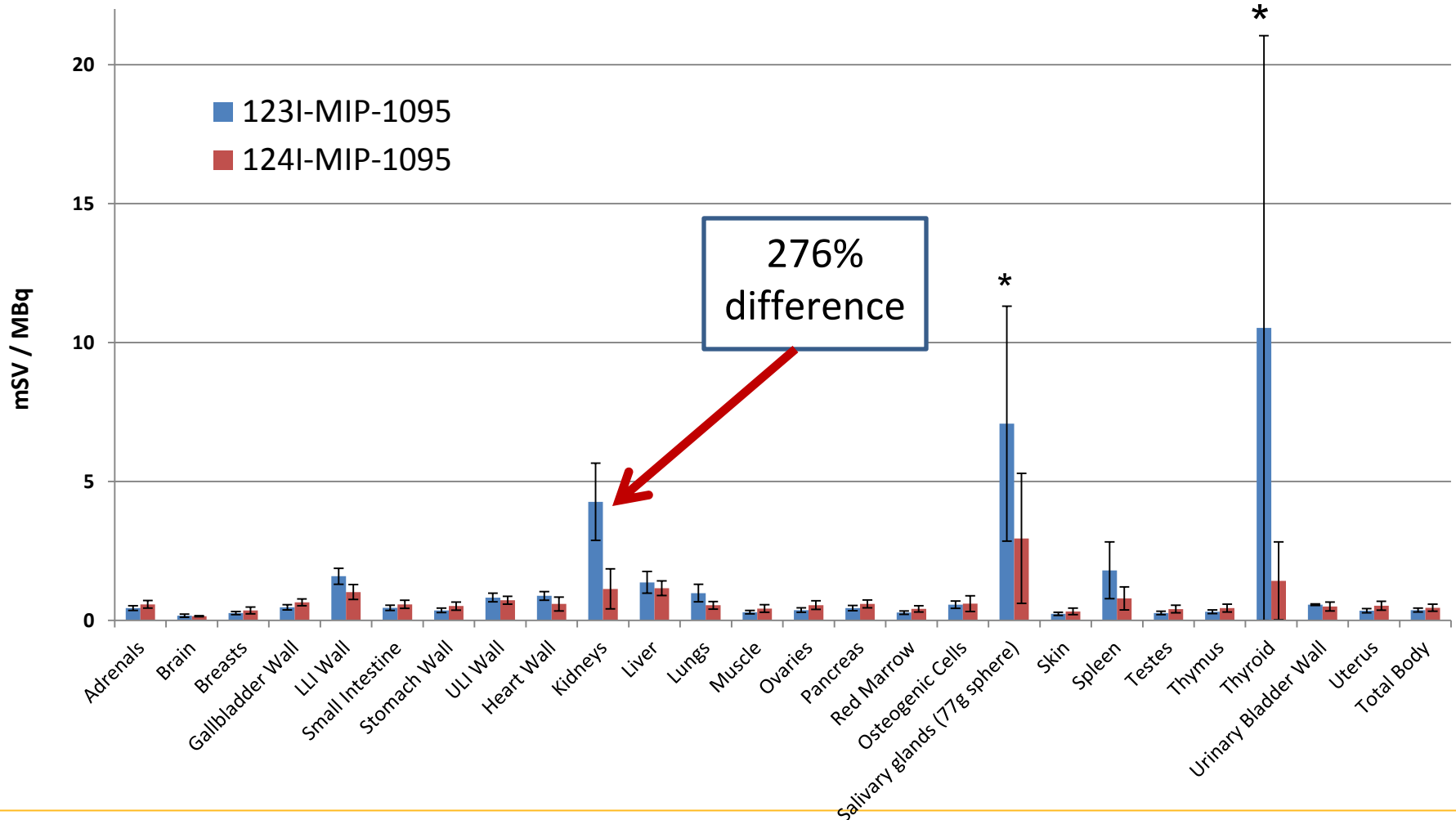


- Some information about the “target” PSMA
- Tracer development and optimization of the ligands
- Improving biodistribution by co-medication? Nephroproction?
- **First clinical results with PSMA targeted Radionuclide Therapy**

Methods for Dosimetry:

- ^{123}I -MIP-1095
 - 7 patients with Prostate Cancer enrolled in clinical trial MIP-TX-P101
 - 333 – 444 MBq administered i.v.
 - Anterior and posterior planar whole-body images collected through 72 hrs p.i.
 - Conjugate view method (2D ROIs)
- ^{124}I -MIP-1095
 - 7 patients with Prostate Cancer
 - 26 - 66 MBq administered i.v.
 - Axial slices of whole-body PET images collected through 72 hrs p.i.
 - Volumetric method (3D VOIs)

Estimated Organ Doses Extrapolated to ^{131}I -MIP-1095

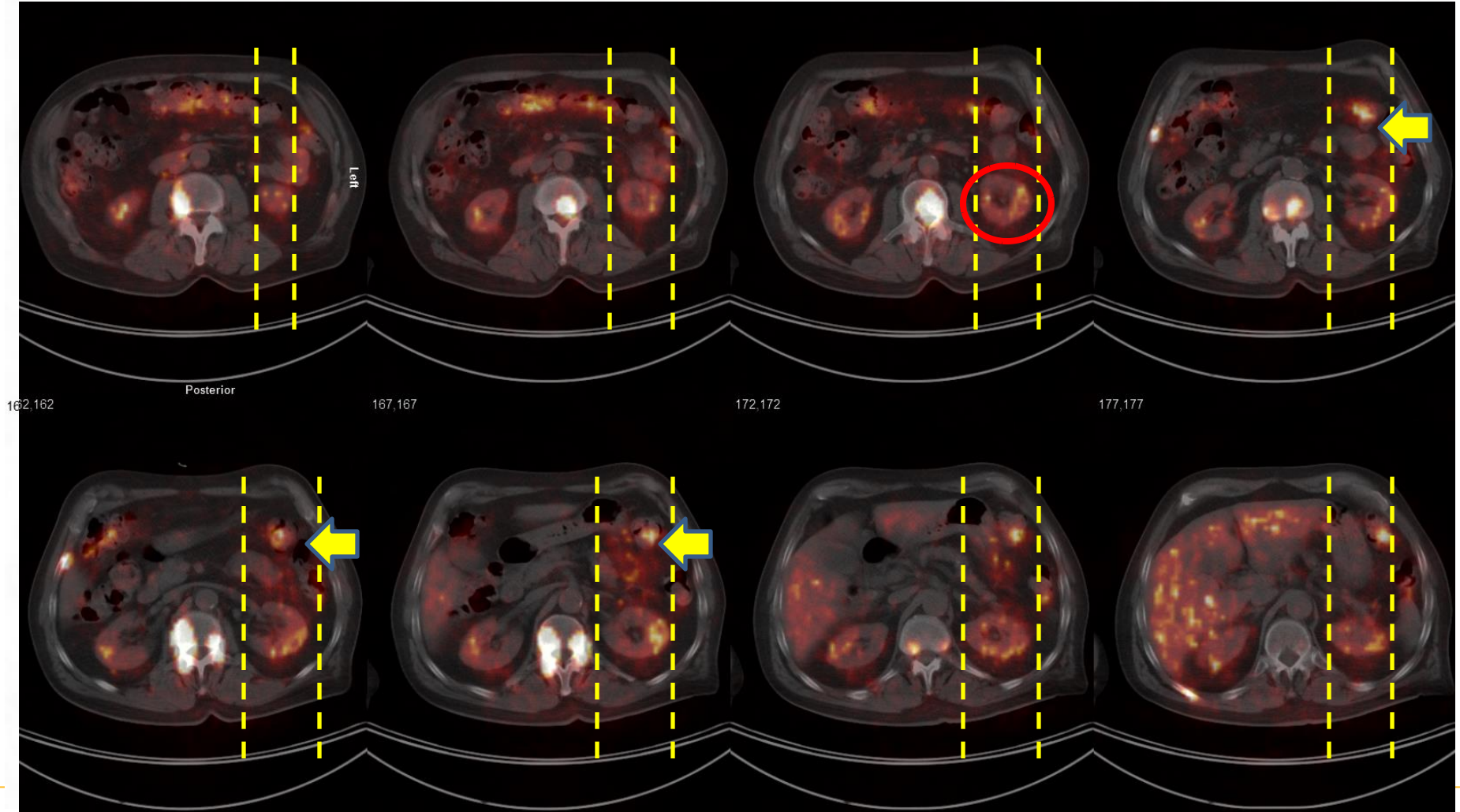


AUC Impact on Maximal Therapeutic Dose of ^{131}I -MIP-1095

- Maximum therapeutic dose using kidney as the limiting organ (23 Gy dose to kidneys*)
 - ^{123}I -MIP-1095 with 2D kidney ROIs
 - 5.4 GBq ^{131}I therapeutic dose
 - ^{124}I -MIP-1095 PET with 3D kidney VOIs
 - 20.2 GBq ^{131}I therapeutic dose
- 276% difference in maximum therapeutic dose estimates

*Emami et al, 1991 Int. J. Radiat. Oncol. Biol. Phys. 21: 109 –122

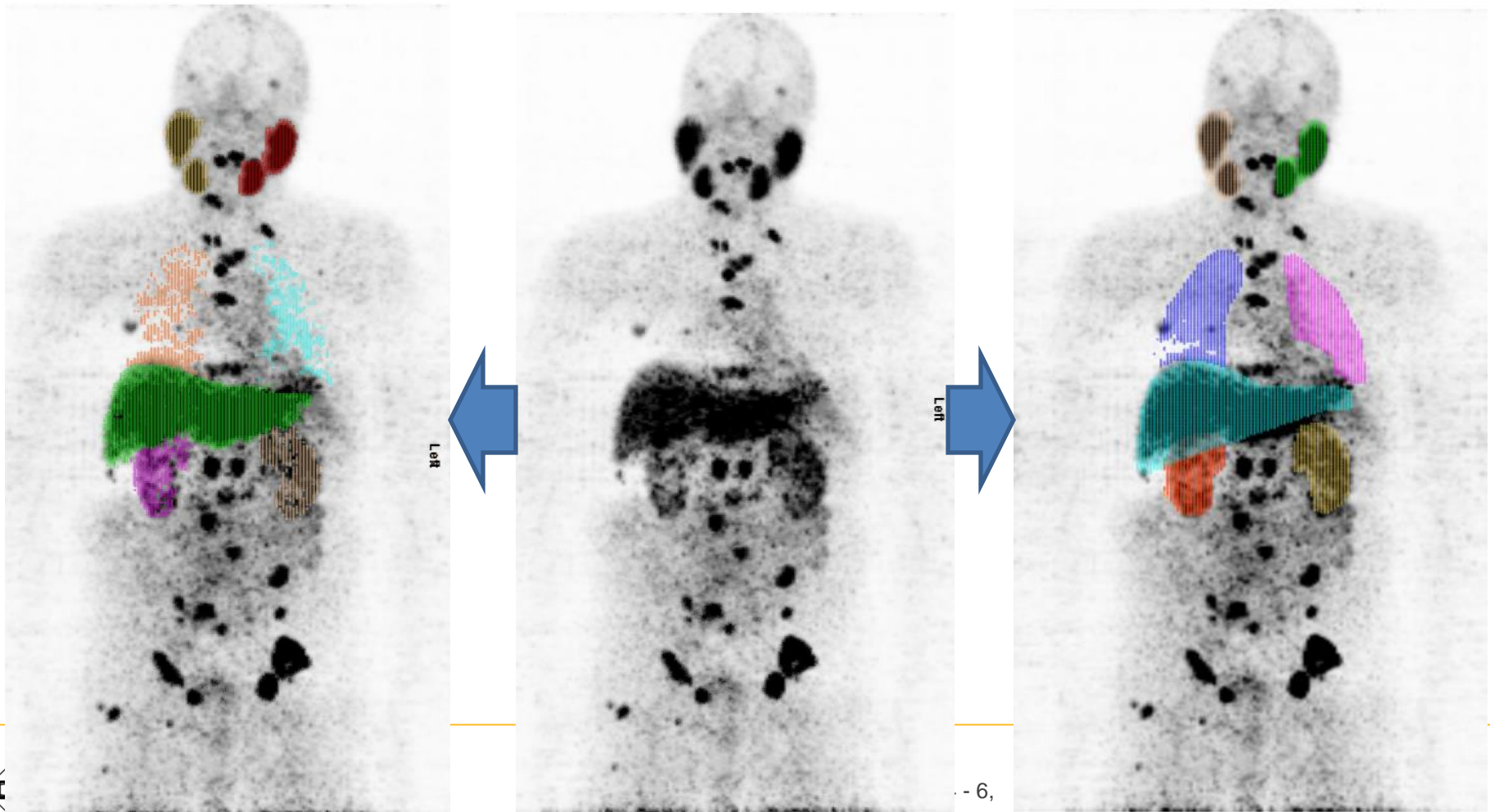
PSMA – a Theragnostic Approach



Coronal ^{124}I -MIP-1095 PET Slices Summed to Create 2D Planar Datasets

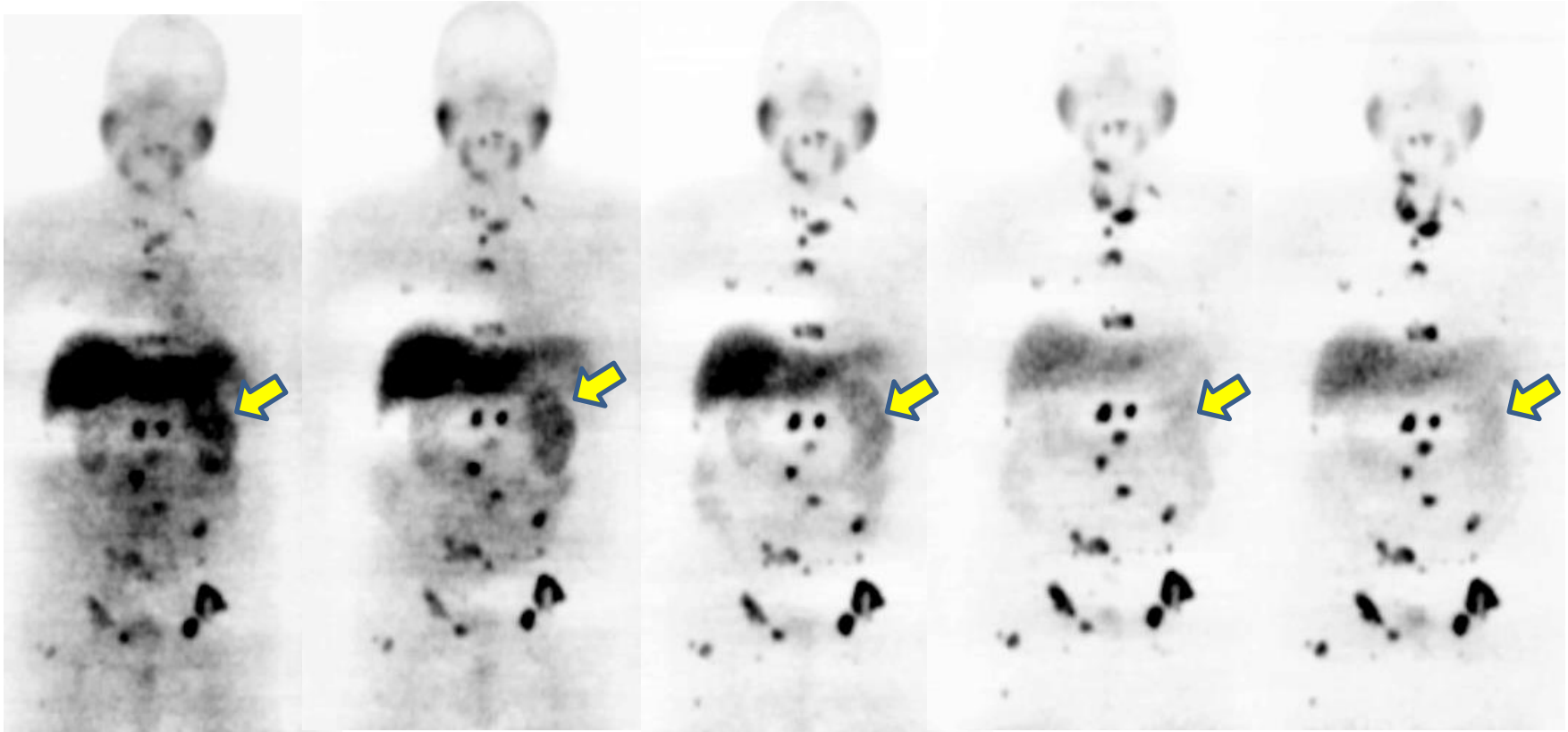
3D VOIs

2D ROIs



PSMA – a Theragnostic Approach

^{124}I -MIP1095



1.3 hr

3.9 hr

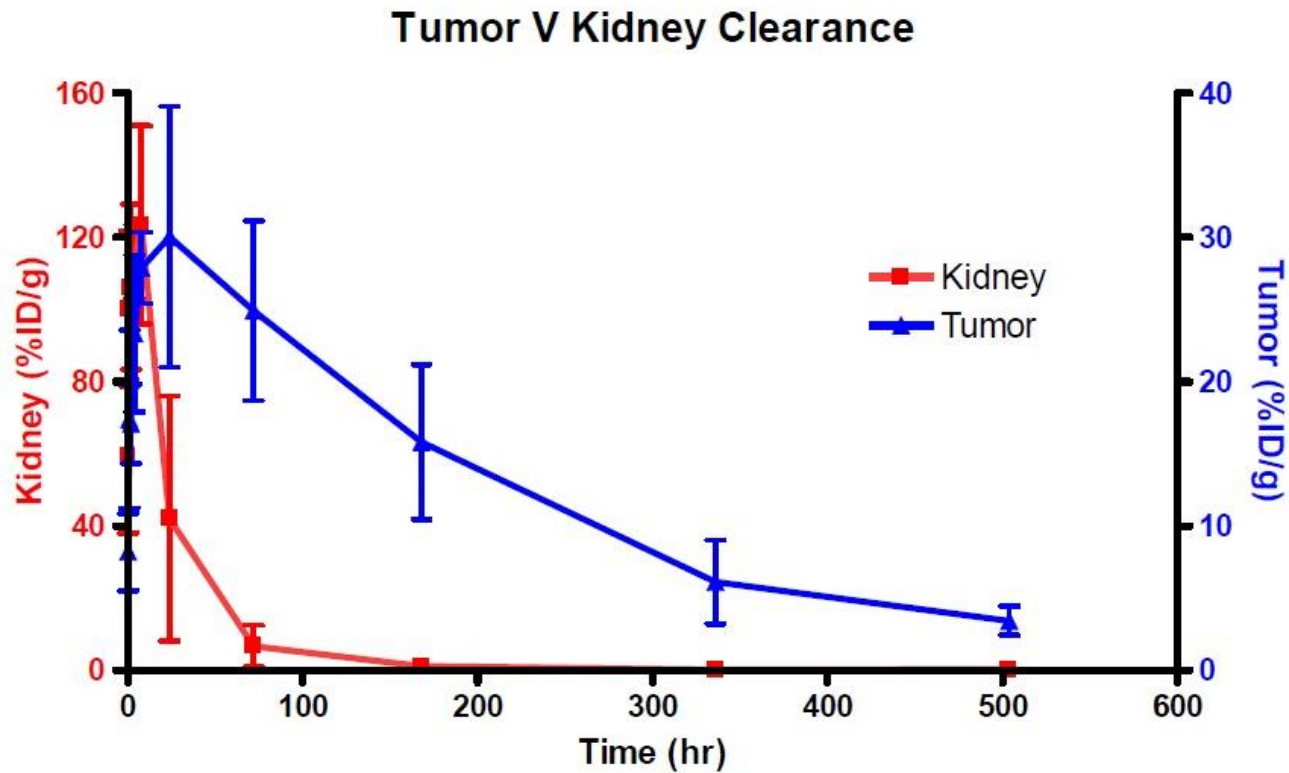
19.5 hr

72.3 hr

93.0 hr

Time post injection

^{124}I -MIP1095



PSMA – a Theragnostic Approach

^{131}I -MIP1095
Therapy

Sept 2011



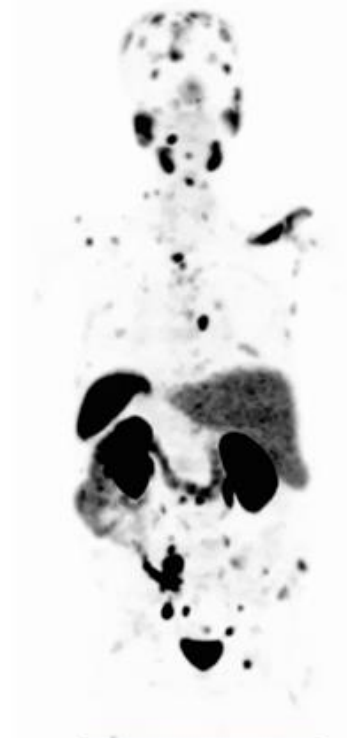
Pre therapy #1

Feb 2012



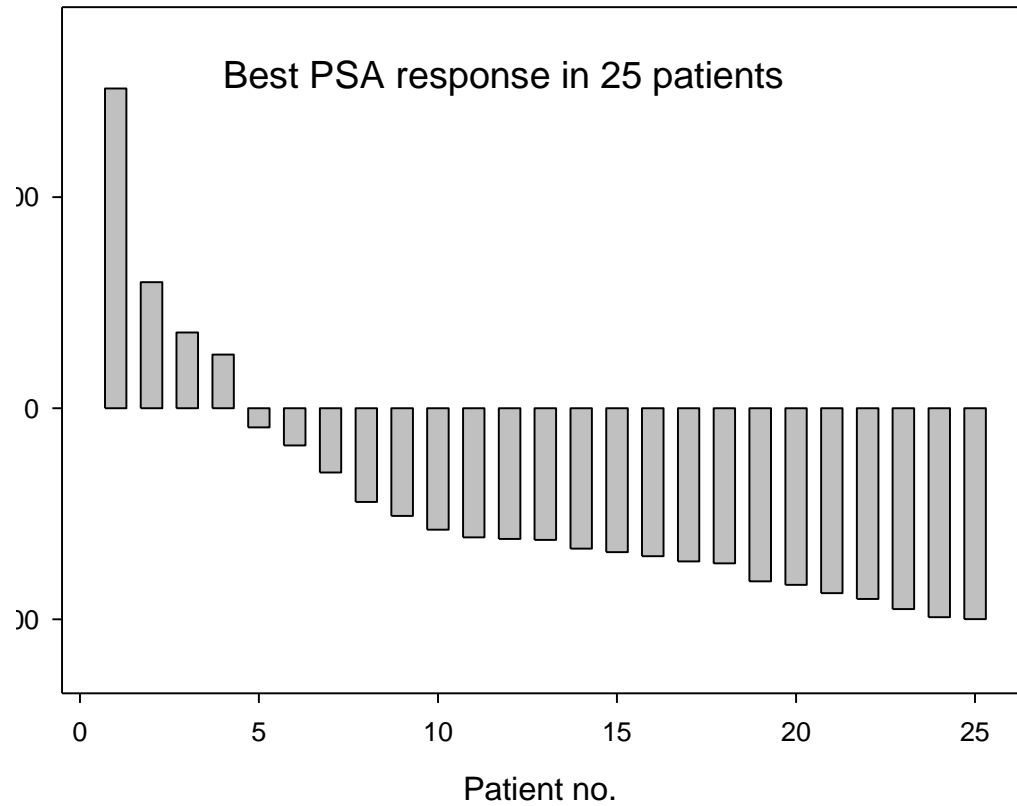
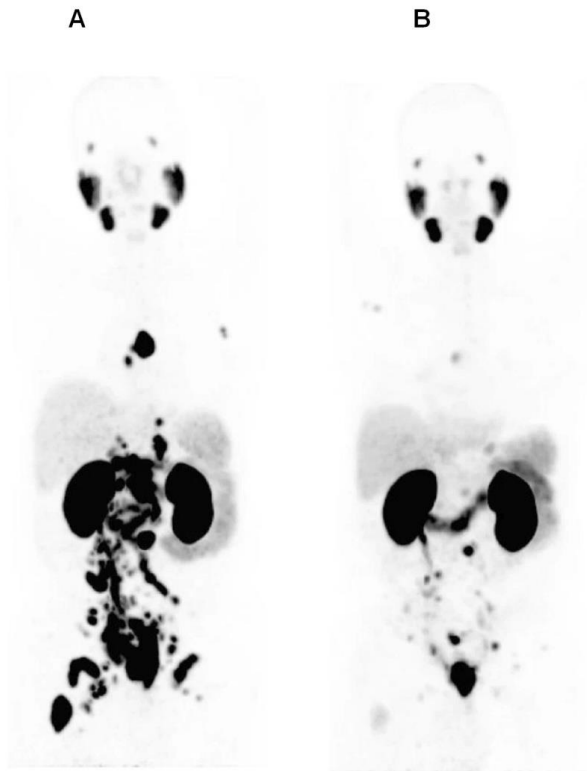
Post Rx #1

May 2012



Post Rx #2

¹³¹I-MIP1095 Therapy



^{131}I -MIP1095 Therapy

Gamma Energies:

- 364 keV (82% abundance)
- 637 keV (7% abundance)
- 284 keV (6% abundance)
- 723 keV (2% abundance)
- 80 keV (3% abundance)
- 29-34 keV (4.5% / x-rays)

Beta Energies: 606 keV (89% abundance)

Beta Range (Water): 2 mm

Physical half-life: 8.05 days

Disadvantages:

- Bone marrow toxicity: High probability for gamma emission
- Radiation protection from high energie gamma emission
Approx. 10d hospitalisation per cycle in Germany

^{177}Lu -DKFZ617 Therapy

Gamma Energies: **113 keV (3% abundance)**
 210 keV (11% abundance)

Beta Energies: **490 keV (100% abundance)**

Beta Range (Water): **1.5 mm**

Physical half-life: **6.7 days**

Advantages:

- Less bone marrow toxicity: Low probability for gamma emission. Tissue range of beta particle.
- No high energy gamma. Hospitalisation 48h per cycle in Germany
- Simultaneous imaging with favorably gamma energy.

^{225}Ac -DKFZ617 Therapy

Beta-emitters ($^{90}\text{Y}/^{177}\text{Lu}$):

Initial energy, MeV: 2.28/ 0.49

Tissue range, μm : 11000/ 1500

LET, keV/ μm : 0.015-0.4

Ion pairs per μm : 5-20

Half-life, d: 2.7/ 6.7

Alpha-emitter ($^{213}\text{Bi}/^{225}\text{Ac}$):

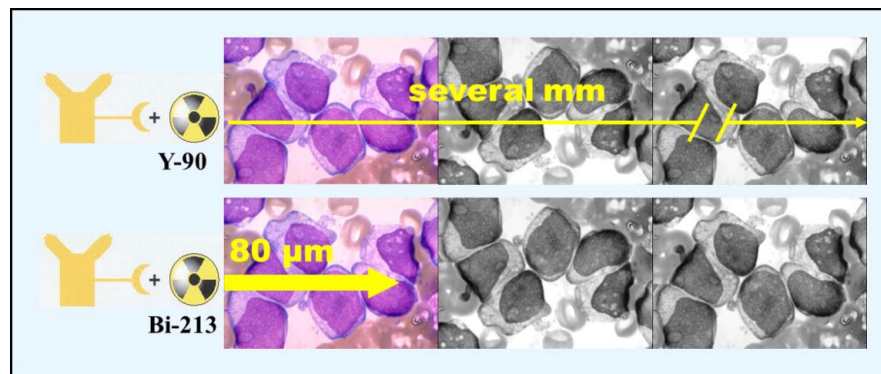
Initial energy, MeV: 8.4

Tissue range, μm : 85

LET, keV/ μm : 60-230

Ion pairs per μm : 2000-7000

Half-life, d: 0.03 / 10



^{225}Ac -DKFZ617 Therapy

Advantages:

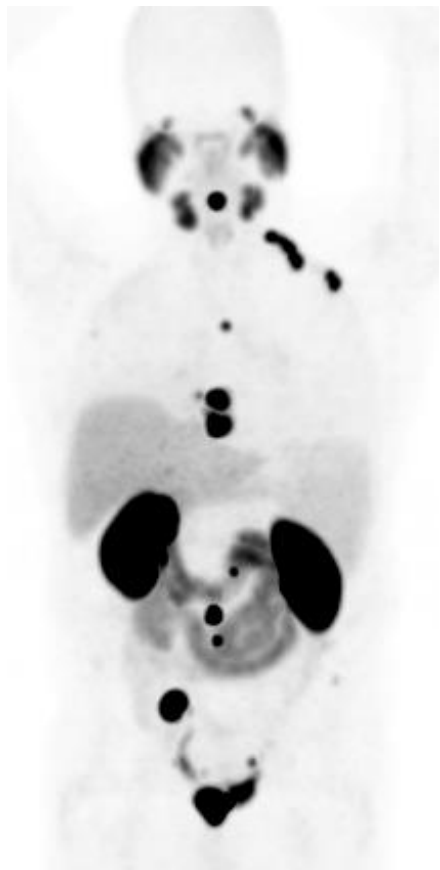
- **Selective cell kill even to micrometastases, due to short tissue range. While sparing surrounding tissue (bone marrow!).**
- **Nearly no gamma-emission. Hospitalisation 48h per cycle or even out-patient setting possible**
- **Overcome resistency to beta radiation, independent from cell cycle / oxigenation, ...**
- **PSMA-Tracers are predistinated for Ac-225 (half-life 10 d) due to cellular internalisation and long biological half-life**
- **>2 years of experiance with ^{225}Ac -DOTATOC in Heidelberg**

^{177}Lu -DKFZ617 Therapy

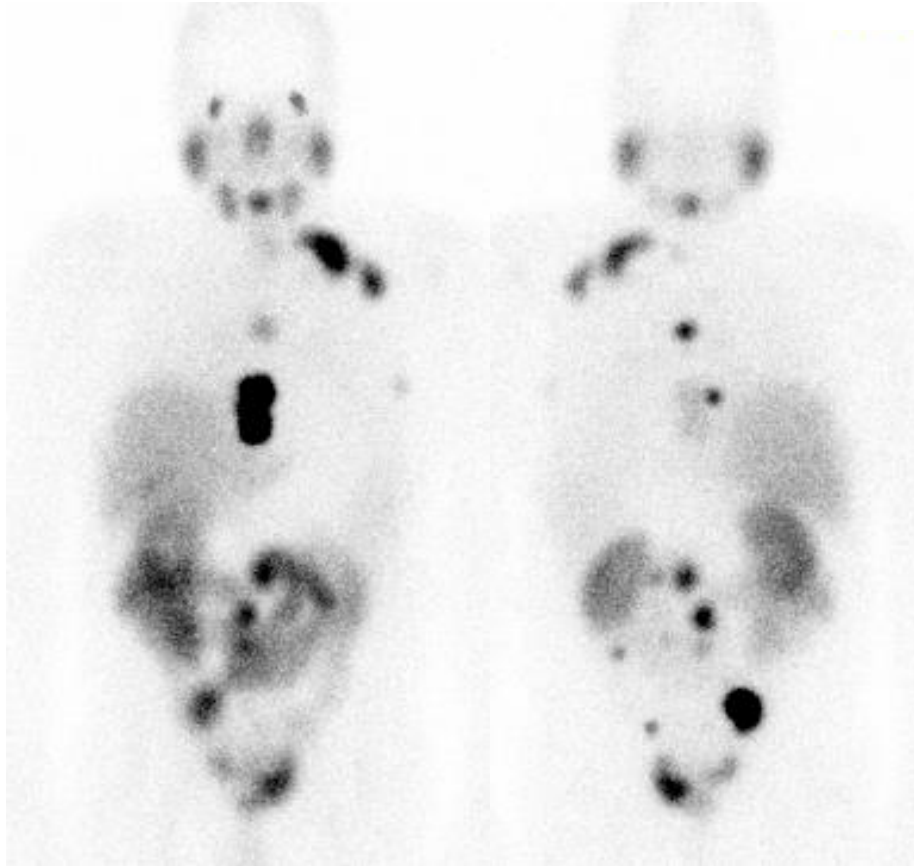


12/13

^{177}Lu -DKFZ617 Therapy

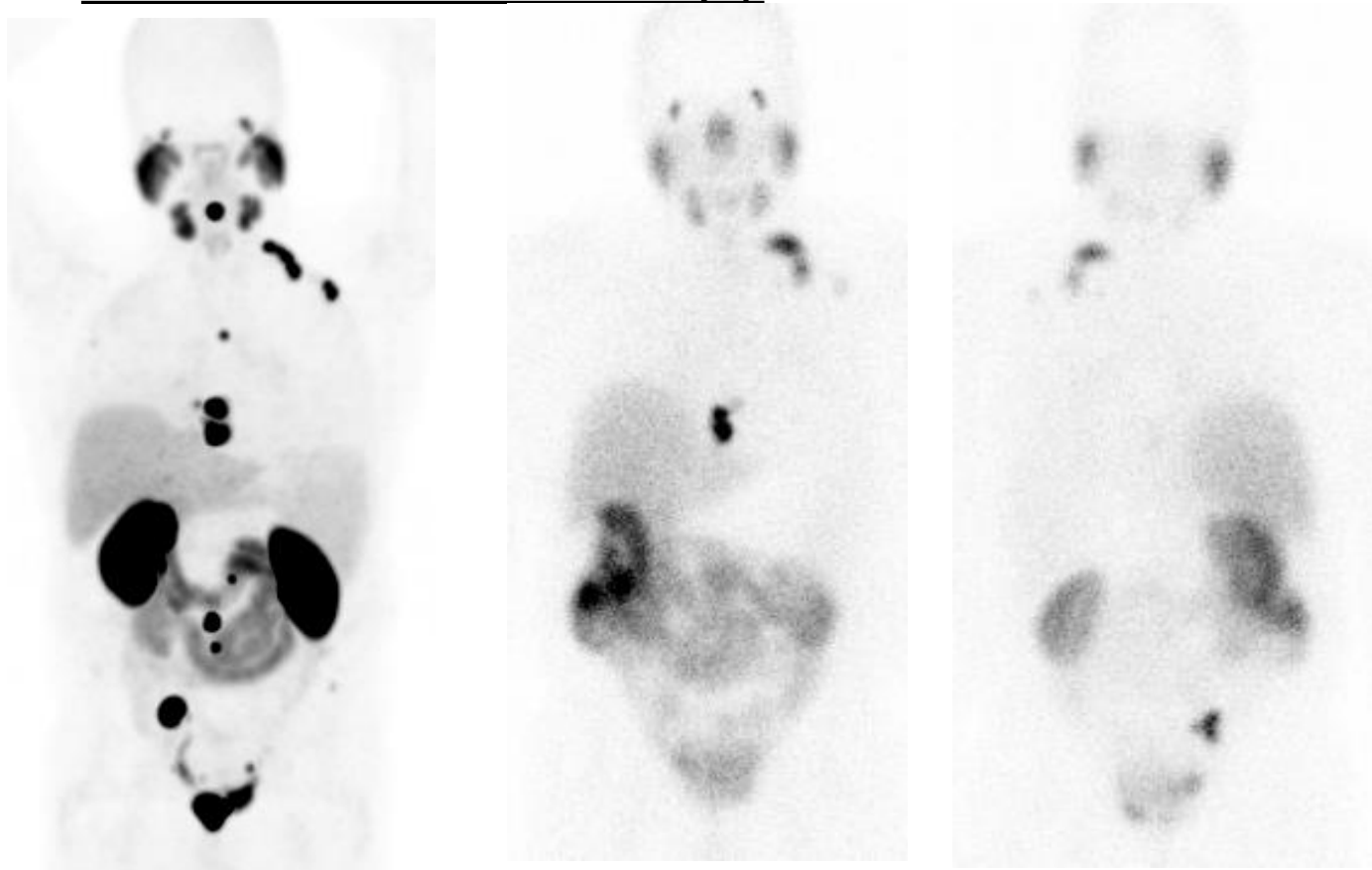


12/13



02/14

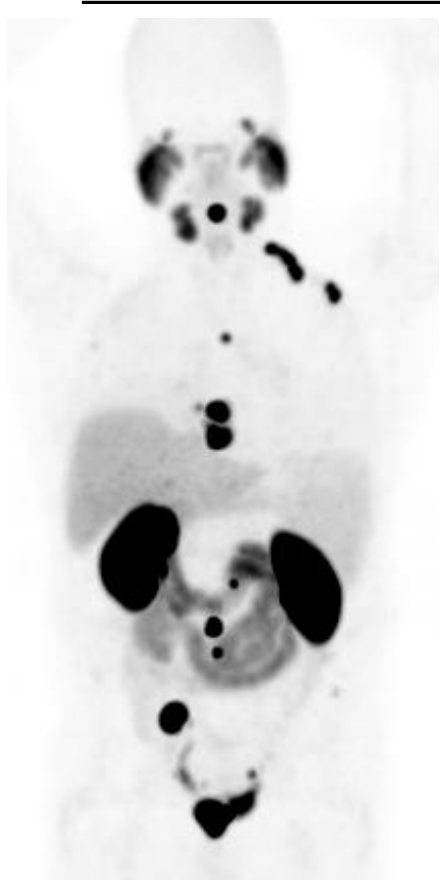
^{177}Lu -DKFZ617 Therapy



12/13

05/14

^{177}Lu -DKFZ617 Therapy



12/13

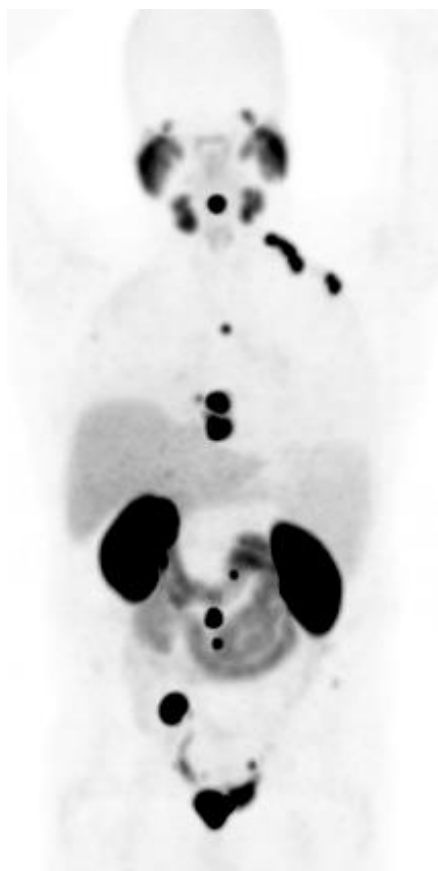


05/14

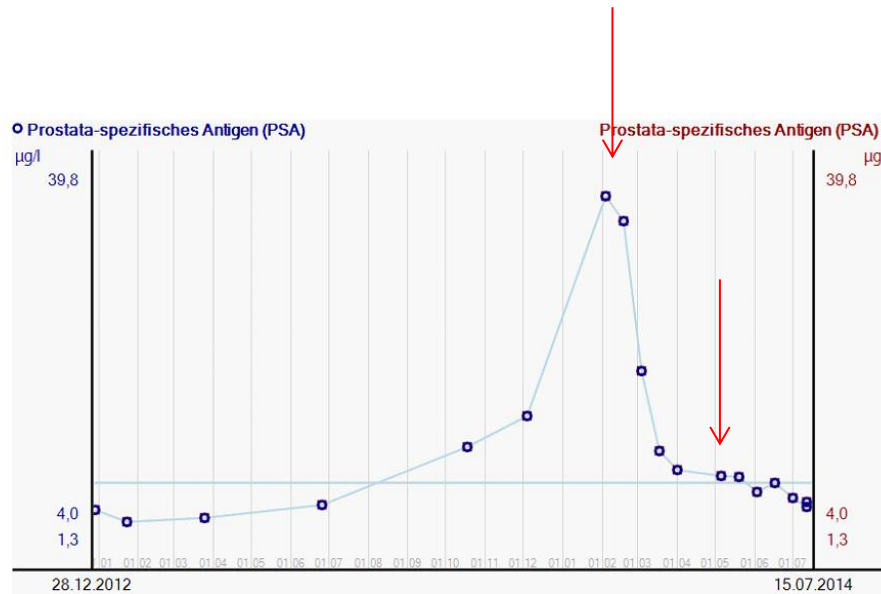


07/14

^{177}Lu -DKFZ617 Therapy

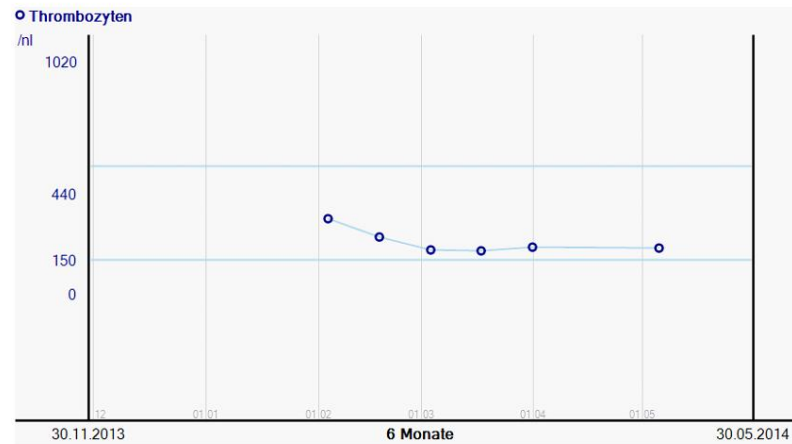
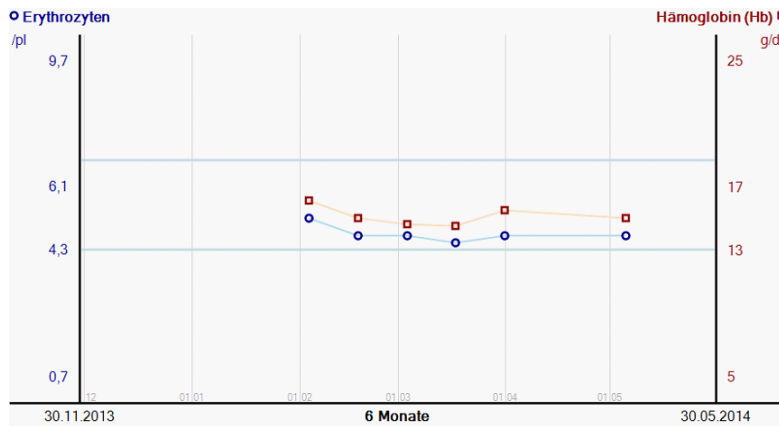
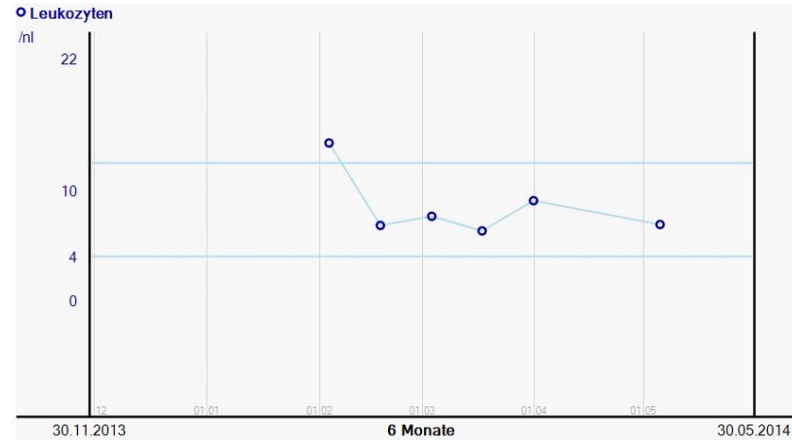
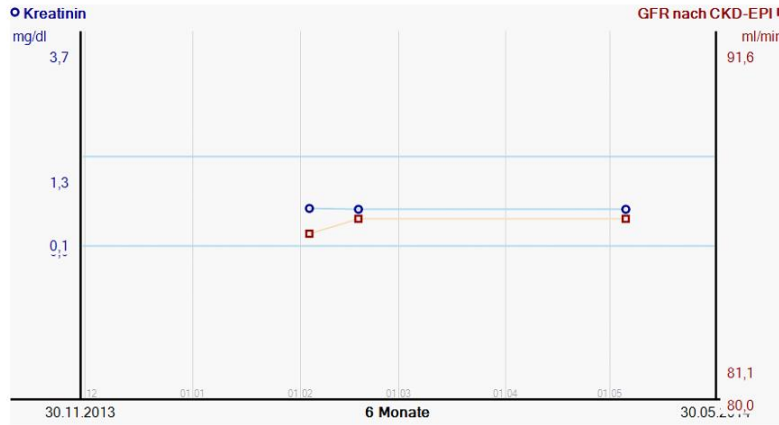


12/13

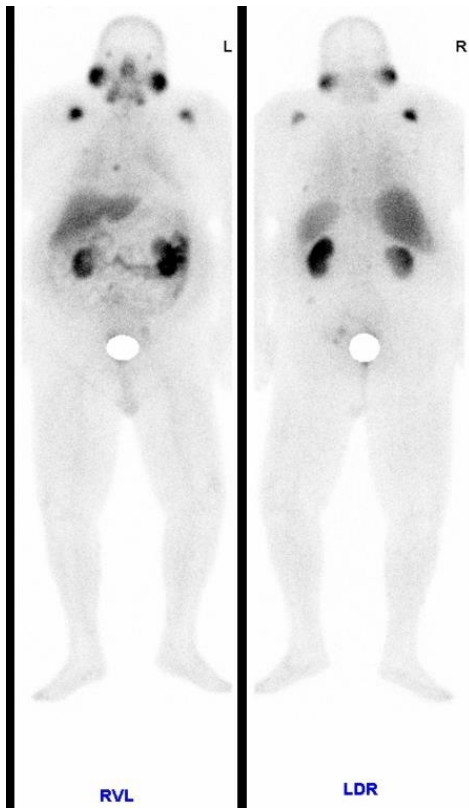


07/14

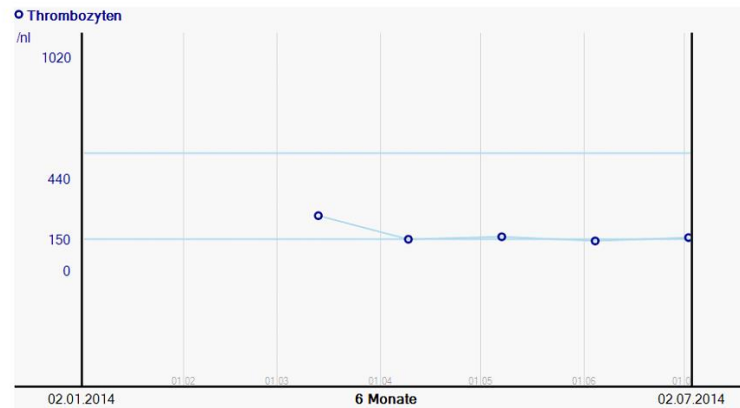
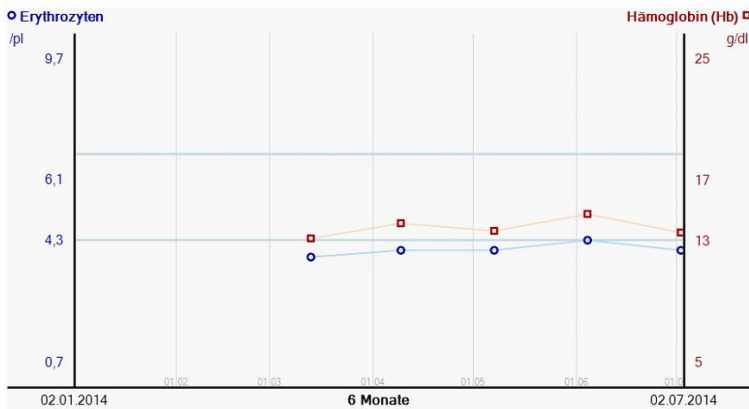
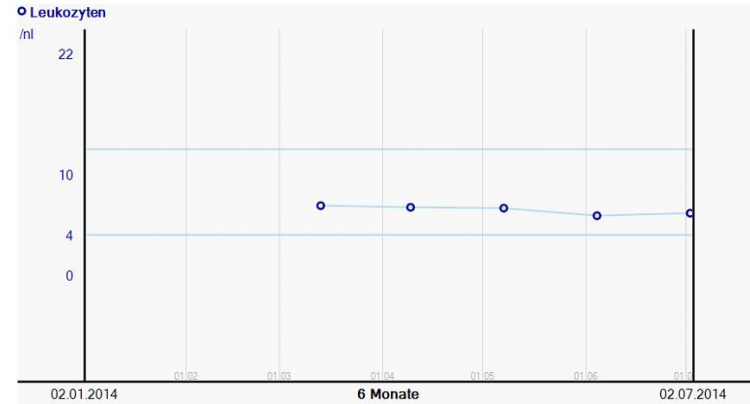
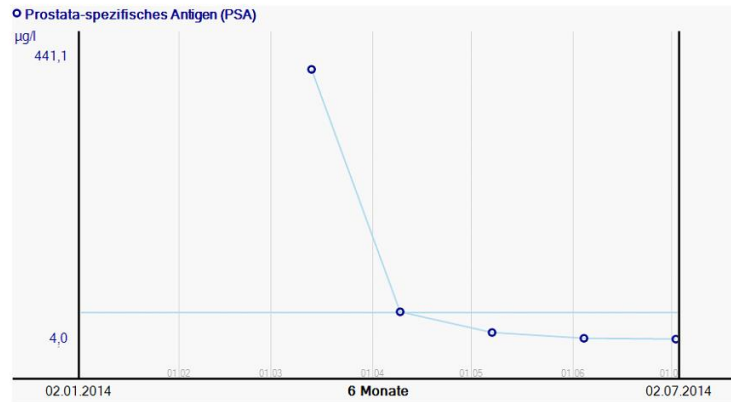
¹⁷⁷Lu-DKFZ617 Therapy



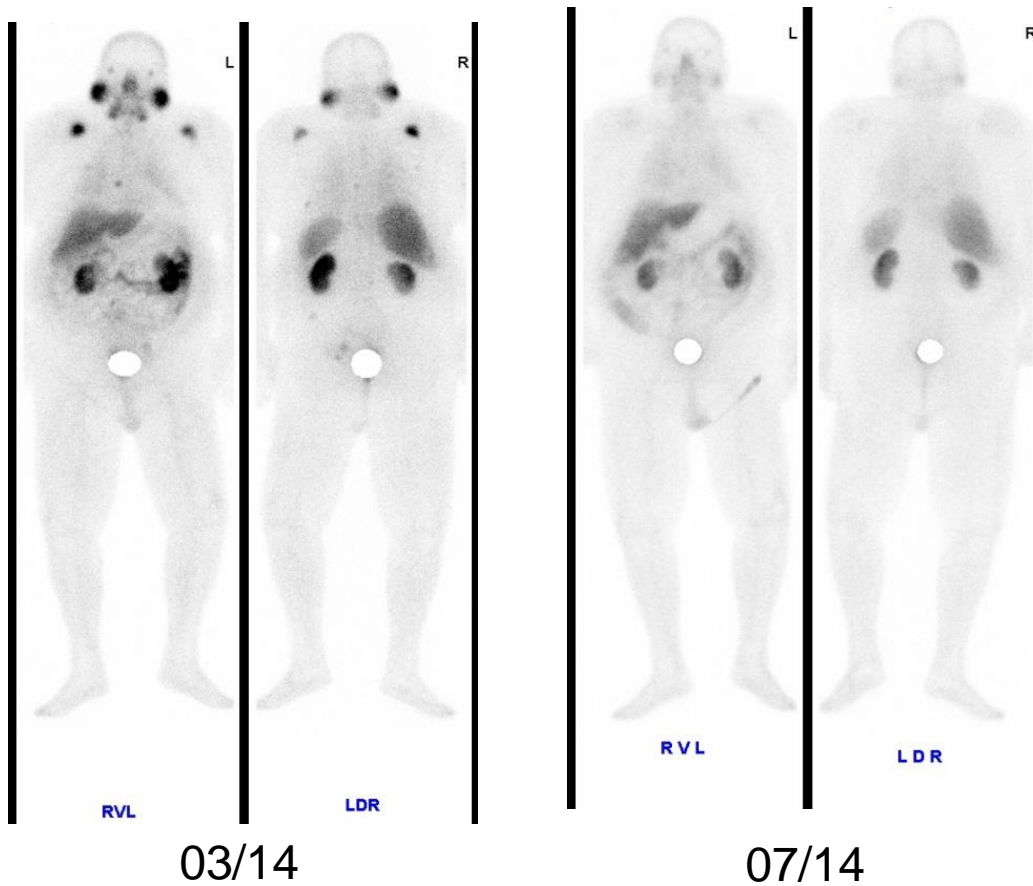
^{225}Ac -DKFZ617 Therapy



^{225}Ac -DKFZ617 Therapy



^{225}Ac -DKFZ617 Therapy

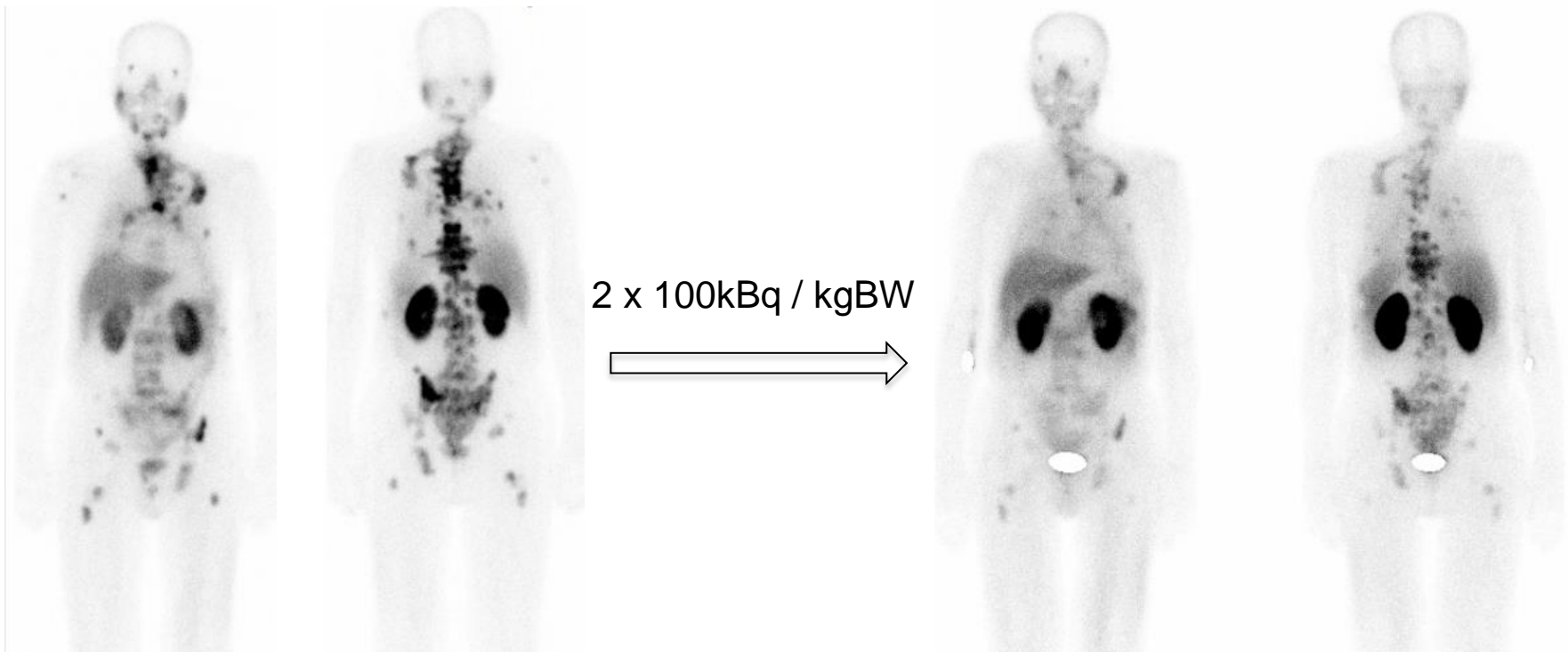


Pre-RTx: 6 cm



Post-RTx: 3 cm

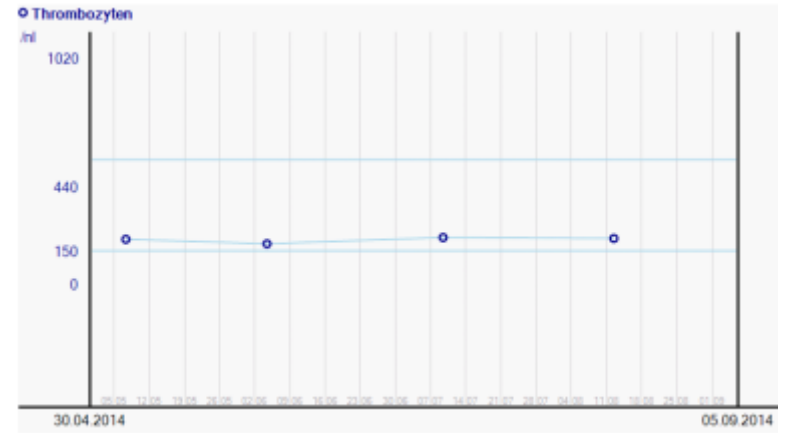
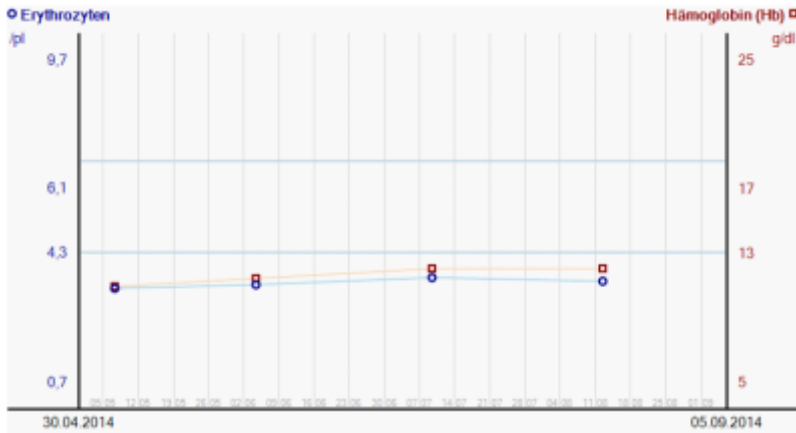
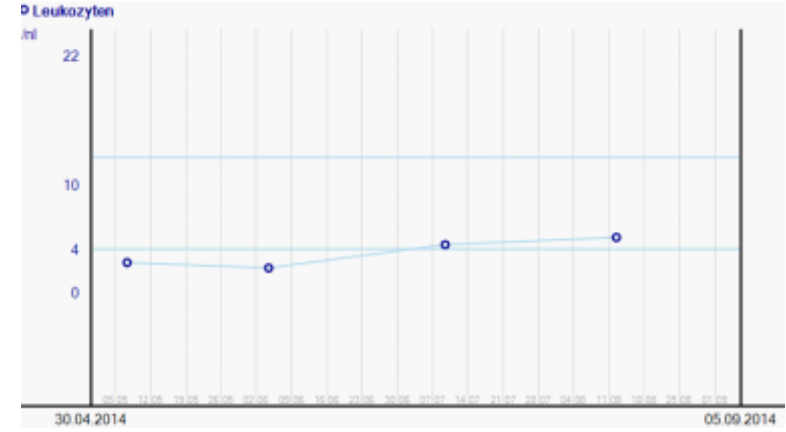
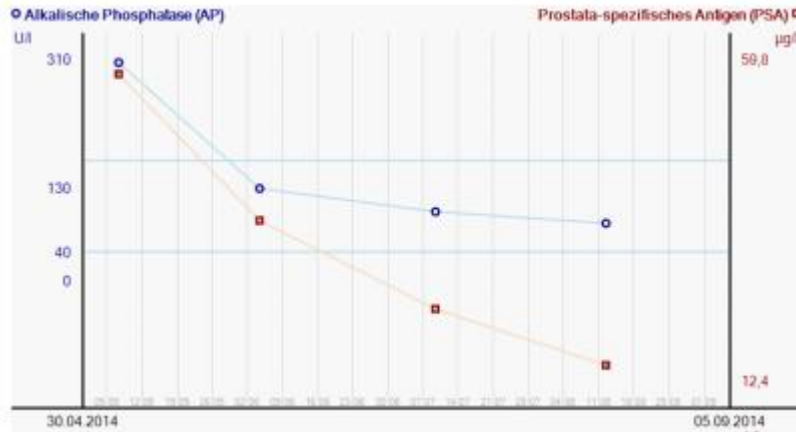
^{225}Ac -DKFZ617 Therapy



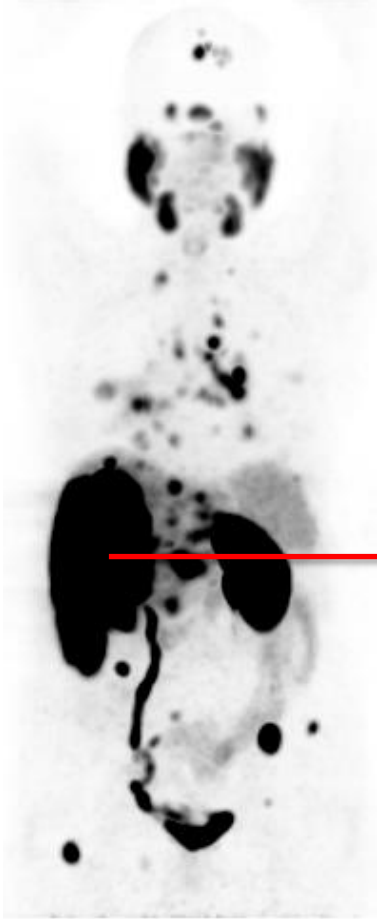
03/14

07/14

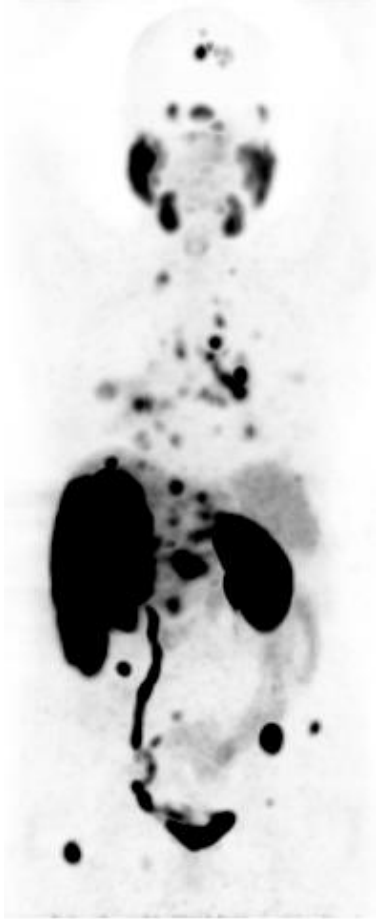
^{225}Ac -DKFZ617 Therapy



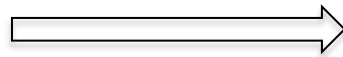
^{225}Ac -DKFZ617 Therapy



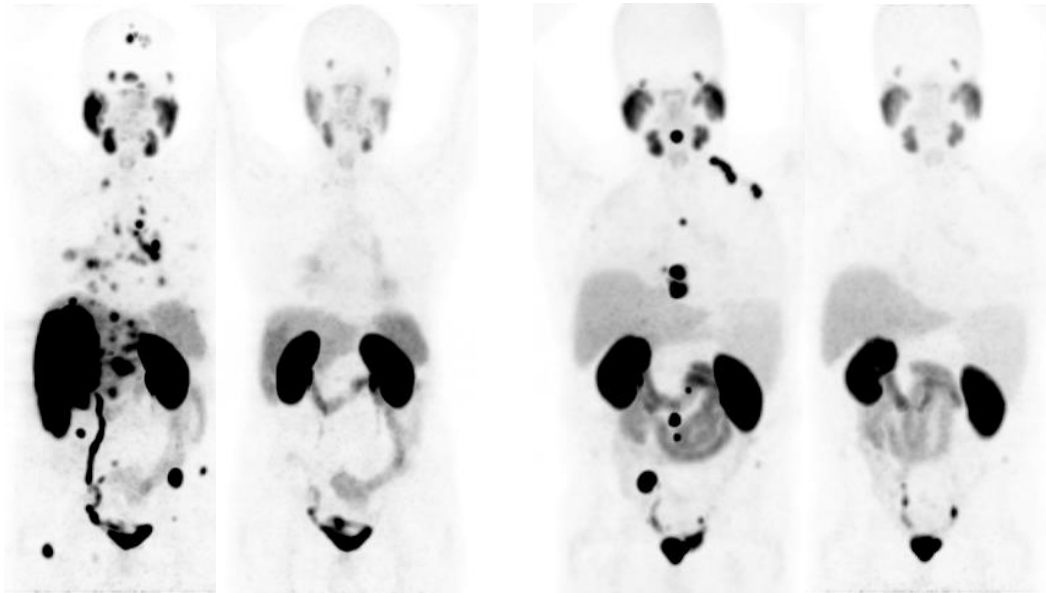
^{225}Ac -DKFZ617 Therapy



1 x 200kBq / kgBW



First Results PSMA Radionuclide Therapy - Summary:



^{225}Ac -DKFZ617 Therapy

^{177}Lu -DKFZ617 Therapy

^{177}Lu -DKFZ617:

7 / 10 Responses

4 / 10 Xerostomia

1 / 10 Nausea / Emesis

1 / 10 Fatigue

^{225}Ac -DKFZ617:

5 / 5 Responses

5 / 5 Severe Xerostomia

1 / 5 Nausea / Emesis

1 / 5 Severe Fatigue

Thanks to the Collaborators:

Molecular Insight Pharmaceuticals:

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ABX - advanced biochemical compounds

Thank you for listening