Peptide Radioligand Therapy (PRLT) in Castrate Resistant, Metastatic Prostate Cancer using Lu-177 PSMA

Harshad R. Kulkarni, Prof. Dr. Richard P. Baum
THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging (PET/CT)
ENETS Center of Excellence, Zentralklinik Bad Berka, Germany
Molecular Imaging of Prostate Cancer by PET

Radiolabelled PSMA Inhibitors

Ga-68, F-18-GRP-Binding Peptides

Zr-89-anti-PSMA MAb

C-11-AcOH

F-18-AcOH

C-11- and F-18-Cholines and Analogues

F-18-Amino Acids (GE148, FACBC)

F-18-Hormones

F-18-FDG

Ga-68 CXCR4-Binding Peptide

Cu-64 Small Molecule Inhibitors

Ga-68, F-18-αvβ3, EPCAM …

Ga-68-bone seekers

Zn-89-anti-PSMA MAb

Mabs against other Targets

OAA AcCoA LIPIDS

FAS

CIT ATP

Glycolysis

Ga-68, F-18-FLUORIDE

Ga-68-bone seekers

Radiolabelled PSMA Inhibitors, Bombesines

F-18-Fluoride

Courtesy Hans-Jürgen Wester, TUM
• A cell surface enzyme that’s continually internalized.
• Glutamate carboxypeptidase II (GCP-II) activity
• Folate hydrolase (FOLH1) activity
• Hydrolyses γ-peptide bonds between N-acetylaspartate and glutamate
• PSMA expression increases progressively in:
  – Higher grade tumors
  – Metastatic disease
  – Hormone-refractory prostate cancer
  – Present also in tumor neovasculature
• PSMA thought to play a role in tumor invasiveness
• Target validated with anti-PSMA antibodies (J591)
PSMA Expression is Prostate Cancer Specific and Increases with Tumor Grade

<table>
<thead>
<tr>
<th># Cases Studied</th>
<th>% Cases Reported to be PSMA Positive</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>251</td>
<td>94%</td>
<td>Wright et al</td>
</tr>
<tr>
<td>184</td>
<td>100%</td>
<td>Bostwick et al</td>
</tr>
<tr>
<td>51</td>
<td>84%</td>
<td>Mannweiler, et al</td>
</tr>
<tr>
<td>42</td>
<td>88%</td>
<td>Kusumi, et al</td>
</tr>
<tr>
<td>21</td>
<td>100%</td>
<td>Ananias, et al</td>
</tr>
<tr>
<td>905</td>
<td>99.9%</td>
<td>Loda, et al</td>
</tr>
</tbody>
</table>

PSMA Expression is Prostate Cancer Specific and Increases with Tumor Grade.
Correlation with pathology

Prostatectomy Specimen

20 X PSMA IHC

Courtesy: Steve Rowe and Steve Cho (UW)
Prostate Cancer - Management Options

• **Newly Diagnosed Local Disease**
  – Active surveillance
  – Surgery
  – Radiation
  – Multimodality for high-risk disease

• **Radiation plus androgen deprivation therapy**

• **Recurrent Disease**
  – Radiation, surgery, cryotherapy, HIFU for local recurrence
  – Androgen deprivation therapy for metastatic disease
  – **Radionuclide therapy** of bone metastases (Sm-153 EDTMP, Strontium, Alpharadin, Lu-177 labeled bisphosphonates)
  – In the EU alone, one man dies of hormone-refractory disease every 10-15 min
  – Peptide radioligand therapy (**PRLT**) using small molecules
<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Trial</th>
<th>Clinical Setting</th>
<th>Main Study Results</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Binds and stabilizes tubulin</td>
<td>TAX327</td>
<td>mCRCP</td>
<td>Improved OS 18.9 vs. 16.5 months (HR 0.76; 95% CI: 0.62-0.94)</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SWOG 9916</td>
<td>mCRPC</td>
<td>Improved OS 17.5 vs 15.6 months (HR 0.8; 95% CI: 0.67-0.97)</td>
<td></td>
</tr>
<tr>
<td>Cabazitaxel</td>
<td>Binds and stabilizes tubulin</td>
<td>TROPIC</td>
<td>mCRPC—post-docetaxel</td>
<td>Improved OS 15.1 months vs. 12.7 months (HR 0.70; 95% CI: 0.59-0.83)</td>
<td>2010</td>
</tr>
<tr>
<td>Sipuleucel-T</td>
<td>Immunotherapy; deiminase</td>
<td>IMPACT</td>
<td>mCRPC—symptomatic or minimally symptomatic</td>
<td>Improved OS 15.2 vs. 14.7 months (HR 0.79; 95% CI: 0.62-0.99)</td>
<td>2010</td>
</tr>
<tr>
<td>Enzalutamide</td>
<td>Androgen receptor blocker</td>
<td>COU-AA-302</td>
<td>mCRPC—chemotherapy-naïve</td>
<td>Improved PFS 16.5 vs. 8.3 months (HR: 0.53; 95% CI: 0.45-0.62)</td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AFFIRM</td>
<td>mCRPC—post-docetaxel</td>
<td>Improved OS 18.4 vs. 13.6 months (HR: 0.63; 95% CI: 0.53-0.75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PREVAIL</td>
<td>mCRPC—chemotherapy-naïve</td>
<td>Pending</td>
<td></td>
</tr>
<tr>
<td>Xofigo (radium-223)</td>
<td>Radio-pharmaceutical, alpha-emitter, and calcium mimetic</td>
<td>ALSYMPCA</td>
<td>mCRPC—patients ineligible for docetaxel or post-docetaxel with symptomatic bone metastases only</td>
<td>Improved OS 14.0 vs. 11.2 months (HR 0.70; 95% CI: 0.55-0.88)</td>
<td>2013</td>
</tr>
</tbody>
</table>

**Improvement by Docetaxel Chx: ~ 9 - 10 weeks**

**New drugs ~ 3 - 5 months**
Schematic Representation of a Drug for Imaging and Targeted Therapy

**Molecular Address**
- Antibodies, minibodies, Affibodies, SHALs, aptamers
- Regulatory peptides (agonists & antagonists)
- Amino Acids

**Targets**
- Antigens e.g. CD20, HER2
- GPCR e.g. SSTR
- Enzymes & inhibitors e.g. PSMA
- Transporters

**Reporting Unit**
- $^{99m}$Tc, $^{111}$In, $^{67}$Ga
- $^{64}$Cu, $^{68}$Ga
- Gd$^{3+}$

**Cytotoxic Unit**
- $^{90}$Y, $^{177}$Lu, $^{213}$Bi
- $^{105}$Rh, $^{67}$Cu, $^{186,188}$Re

**THERANOSTIC PAIRS**
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

- $^{68}$Ga, $^{90}$Y, $^{177}$Lu

Courtesy Helmut Mäcke (modified)
Thera(g)nostics

• Thera(n)nostics is the combination of a Diagnostic Tool that helps to define the right Therapeutic Tool for a specific disease – we see what we treat.

• Used first by John Funkhouser/pharma industry at the beginning of the 90’s at the same time the concept of Personalized Medicine appeared.

• Concerning radioisotopes, the term “THERAGNOSTICS” was created by Suresh Srivastava (Brookhaven National Laboratory).

• In NM, THERANOSTICS is easy to apply and to understand, because of an easy switch of the radionuclide from Dx to Rx on the same vector.

• The most prominent and oldest application is radioiodine.

Personalized Medicine

• The right treatment, for the right patient, at the right time, at the right dose. – first time », not anymore targeting the “disease” but the “specific tumor of a patient”.

• The concept of PM has now been extended to Personalized Health Care that includes all steps relevant for the cure of the patient at an individual level from the first sign of disease up to full recovery, including the physicians, the technologies, the drugs and of course all economic aspects, but also extended to the environment, relatives, nurses…

Molecular Nuclear Medicine and THERANOSTICS within MNM are definitely part of Personalized Health Care.
PET/CT – Prostate Cancer

- Elevated PSA without tumor detection by CI - potential indication for Ga-68 PSMA or bombesin antagonists (not for choline)
- Initial staging (LNM, distant metastases) - indication for Ga-68 PSMA or F-18 or C-11 FEC (or Ga-68 GRP) for detection of lymph node mets and in case of strongly elevated PSA levels (susp. distant mets)
- Detection of recurrence after initial therapy – proven indication for choline PET/CT (if PSA levels are above 1.5 ng/ml). Ga-68 PSMA in our experience is superior (at very low PSA levels in undifferentiated tumors)
- Molecular radiation therapy planning (MRTP) – excellent indication
- THERANOSTICS - selection of the most appropriate radiopharmaceutical for radionuclide therapy as well as monitoring therapy response - great future potential!
Strategy for targeting PSMA with small molecules

M = $^{99m}$Tc, $^{111}$In, $^{68}$Ga, $^{64}$Cu, $^{86}$Y

Chelator

Linker

PSMA Inhibitor

Banerjee *J Med Chem* 2008

M = $^{99m}$Tc, $^{111}$In, $^{68}$Ga, $^{64}$Cu, $^{86}$Y

Not listed, but most important: $^{177}$Lu (and in the future $^{188}$Re)
The DOTAGA PSMA small molecules (PSMA TUM-1, Technical University of Munich; and PSMA I&T, Imaging and Therapy) were labeled with Lu-177 at the Radiopharmacy of Zentralklinik Bad Berka and utilized after appropriate quality control (purity > 99 %)
First clinical experience of treating metastatic castrate-resistant prostate cancer using Lu-177 labeled DOTAGA prostate-specific membrane antigen (PSMA) ligand
Inclusion Criteria

- Histology: Adenocarcinoma of the prostate
- **Castration-resistant metastatic prostate cancer**
- Status post hormone deprivation therapy (LH-RH agonists / antagonists, orchidectomy)
- Testosterone level < 50 ng / dL (<2.0 nM)
- In asymptomatic or mildly symptomatic patients: s.p. therapy with Abiraterone or Enzalutamide
- Chemotherapy (a or b must be true):
  - a.) Taxane-based chemotherapy (paused for at least 4 weeks)
  - b.) Medically unsuitable for taxane-based chemotherapy
- Medically unsuitable for Alpharadin therapy
- **Tumor progression** (a or b must be true):
  - a.) PSA progression after PCWG2 criteria
  - b.) Radiographic progression according to RECIST
Checklist for Indication of $^{177}$Lu-PSMA Therapy (PRLT) 
Inclusion Criteria (...contd.)

- $^{68}$Ga-PSMA-PET uptake in the tumor foci
- Bone scintigraphy or better $^{18}$F-Fluoride PET/CT
- Life expectancy > 6 months
- ECOG performance status 0 or 1 / Karnofsky performance index > 60 %
- MAG-3 scintigraphy before 1$^{st}$ PRLT
- Creatinine clearance > 60 ml / min, normal serum creatinine
- PSA level (max. 2 weeks old)
- Hemoglobin ≥ 9 g / dl (> 6 mmol / l)
- Absolute neutrophils > 1.5 x $10^9$ / L , WBC > 4 x $10^9$ / L
- Platelets > 120 x $10^9$ / L
- GOT and GPT < 2.5 x ULN, bilirubin < 2 x ULN (upper limits of normal)
- Quality of life questionnaire EORTC QLQ-C30
- BPI-SF (Brief-Pain Index Short Form) questionnaire
- Signed informed consent
Total no. of patients: 30

- Bone metastases: 25
- Lymph node metastases: 18
- Lung metastases: 5
- Liver metastases: 2
- Residual primary tumor: 3
- Other: 1 patient with peritoneal and pleuropericardial metastases and one with testicular and adrenal metastases

Mean Age: 71.6 ± 7.3 years
Mean Gleason Score: 8 ± 1

Studies before therapy:
- Renal scintigraphy [\(^{99mTc}\) MAG3]
- Blood counts, renal / hepatic fn.
- \(^{68}\)Ga-PSMA PET/CT

**177\text{Lu}-PSMA Peptide Radioligand Therapy**

**Studies under / after therapy, dosimetry**
- Infusion of aminoacid solution (- 0.5 until 4 hrs) with/-without Gelofusine
- Blood counts, renal / hepatic fn.
- Renal scintigraphy [\(^{99mTc}\) MAG3]
- \(^{177}\text{Lu}\)-PSMA WB scan [planar scans for dosimetry]
- \(^{177}\text{Lu}\)-PSMA SPECT/CT of the tumor region
- Blood sampling
- Urine sampling
### Patients' Characteristics

Mean Age = 66.6 +/- 7.4 years  
Mean Gleason Score = 8 +/- 1

<table>
<thead>
<tr>
<th>Total no. of patients</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone metastases</td>
<td>37</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>30</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>6</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>2</td>
</tr>
<tr>
<td>Residual primary tumor</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>1 patient with peritoneal and pleuropericardial metastases and one with testicular and adrenal metastases</td>
</tr>
</tbody>
</table>
Patients‘ Characteristics

Mean Age = 66.6 +/- 7.4 years
Mean Gleason Score = 8 +/- 1

Previous Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>55</td>
</tr>
<tr>
<td>Antiandrogen therapy</td>
<td>55</td>
</tr>
<tr>
<td>Surgery</td>
<td>35</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>26</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>14</td>
</tr>
<tr>
<td>Other</td>
<td>1 (hyperthermia)</td>
</tr>
</tbody>
</table>

Disease status before PRLT: progressive disease in all patients
PRLT USING Lu-177 PSMA SMALL MOLECULES

- No. of patients treated: **55**
- No. of cycles administered: **122**
- Mean administered radioactivity per cycle: **5.7 GBq**
- Range of administered radioactivity per cycle: **3.4 – 8.6 GBq**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>No. of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

N = 55

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
77-y-o patient with progressive PROSTATE ADENOCARCINOMA

**Diagnosis established**: 07/1998
**Initial tumor stage**: pT3a (G3) pN0 M0 R0; Gleason 7 (3 + 4)

- **07/1998**: Retropubic radical prostatectomy
- **2004**: Percutaneous radiotherapy of prostate bed (PSA increase)
- **up to 2012**: Intermittent hormone therapy with LHRH analogues, bicalutamide
- **01-06 / 2012**: PSA increase from 6 to 28 ng / ml
- **10/2012**: Palliative chemotherapy with Taxotere (reduced dose), drop of PSA from 33 to 1 ng / ml
- **01/2014**: PSA rise to 7.3 ng / ml
Peptide Radio Ligand Therapy (PRLT)

Application of 3,600 MBq Lu-177 PSMA on 07/16/2014 (1\textsuperscript{st} course)
Application of 3,900 MBq Lu-177 PSMA on 09/23/2014 (2\textsuperscript{nd} course)
Application of 4,000 MBq Lu-177 PSMA on 09/12/2014 (3\textsuperscript{rd} course)
Application of 5,000 MBqLu-177 PSMA on 04/03/2015 (4\textsuperscript{th} course)

\textit{Cumulative administered activity 13.5 GBq Lu-177 PSMA}

Current Tumor Status
Partial remission of the disease (according to RECIST and PERCIST)
\textit{Excellent therapy response, no toxicity}
Ga-68 PSMA PET/CT Comparison

22.09.2014
Pre-PRLT No. 2

Extensive lymph node metastases

03.03.2015
Pre-PRLT No. 4

Resolution of extensive lymph node metastases after 2\textsuperscript{nd} & 3\textsuperscript{rd} PRLT

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
Lu-177 PSMA SPECT/CT obtained during PRLT–02

24.09.2014
20 h p.i.

High uptake in lymph node metastases

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
Ga-68 PSMA PET

Near complete regression of lymph node metastases post PRLT

Pre-PRLT - 02 - 22.09.2014

SUVmax = 205

Pre-PRLT - 04 - 03.03.2015

SUVmax = 15
Ga-68 PSMA PET MIP images comparison

Lateral view

Pre-PRLT - 02 - 22.09.2014
Pre-PRLT - 04 - 03.03.2015
Ga-68 PSMA PET/CT
Activity in port-a-cath mimicking supclavicular lymph node metastasis

1. Uptake (tracer retention) in Porta-cath reservoir
2. Uptake (tracer retention) at vascular entry of Porta-cath catheter
3. Uptake (tracer retention) in distal lumen of Port-cath catheter
4. Implantable cardiac Defibrillator
Ga-68 PSMA PET/CT
Activity in port-a-cath mimicking mediastinal lymph node metastasis

1. Uptake (tracer retention) in Porta-cath reservoir
2. Uptake (tracer retention) at vascular entry of Porta-cath catheter
3. Uptake (tracer retention) in distal lumen of Port-cath catheter
Lu-177 PSMA  post-RLT - 02
WB planar images

22h p.i.  45h p.i.

Excellent uptake in lymph node metastases

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
Lu-177 PSMA post-PRLT - 04
WB Planar images
PSA trends with RLT
Progressive drop of PSA after PRLT (biochemical response)

<table>
<thead>
<tr>
<th>Date</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>30.05.2014</td>
<td>35.89</td>
</tr>
<tr>
<td>13.07.2014</td>
<td>50.91</td>
</tr>
<tr>
<td>21.09.2014</td>
<td>30.39</td>
</tr>
<tr>
<td>08.12.2014</td>
<td>4.73</td>
</tr>
<tr>
<td>01.03.2015</td>
<td>0.95</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date</th>
<th>PRLT No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.07.2014</td>
<td>1</td>
</tr>
<tr>
<td>23.09.2014</td>
<td>2</td>
</tr>
<tr>
<td>09.12.2014</td>
<td>3</td>
</tr>
<tr>
<td>04.03.2015</td>
<td>4</td>
</tr>
</tbody>
</table>
Pre therapy: PET CT

Lu PSMA therapy

Post therapy: PET CT

serum PSA trend

PSA level (ng/ml)

Months after therapy
Pre therapy: PET CT

Lu PSMA therapy:
1st cycle

Post therapy: PET CT

Lu PSMA therapy:
2nd cycle

Persistent PSA response

1st Lu PSMA

2nd Lu PSMA
Best PSA response in 37 patients: represented as percentage change in the pre-therapy value.
Poorly differentiated adenocarcinoma of the prostate (acinar type), Gleason Score 4+5=9
Diagnosis by biopsy in October 2012
Initial Tumor Classification pT2c cN1 cM1(OSS); Stage IV (UICC)

Clinical course of disease

- **19-Sep-2012** Increased PSA (140 ng/ml), no symptoms (only occasional dysuria)
- **23-Oct-2012** UGS of prostate: volume 32 cc, 8 core needle biopsies showed prostatic adenocarcinoma of acinar type, involving between 30 and 97 % of the specimen, and a total Gleason’s score of 9
- **21-Dec-2012** CT scan: Thoracic and retroperitoneal lymphadenopathy and osteoblastic metastases in T-9 and T-12 vertebrae and in the left 10th rib posteriorly.
- **9-Jan-2013** Bone scan: multiple skeletal metastases
- **17-Jan-2013** Zoladex (first injection of the LHRH antagonist). Left hip pain since he had a fall; however the pain was thought to be secondary to bone metastasis.
- **01-Feb-2013** CT scan: mild mediastinal lymphadenopathy (including 12 mm prevascular lymph node) and multiple posterior retroperitoneal nodes (up to 1.6 cm), some showing slight improvement since 21-Dec-2012, multiple small sclerotic bony metastases through the ribs and thoracic spine (including T-5 / T-6 region, which also showed intense uptake on bone scan.
  - Grossly elevated PSA: 287.4 ng/ml
- **06-Feb-2013** External beam radiotherapy: 20 Gy at 5 cm depth in 5 fractions (5 x 4 Gy) to T-5 / T-6 region, to prevent progression of local disease and prevent cord compression, and 8 Gy (single session) to the sacroiliac region.
- **04/2013** Progressive Disease (Ga-68 PSMA PET/CT: lymph node and extensive bone metastases, local prostate cancer involving the seminal vesicles) Significant drop of PSA to 40.21 ng/ml under Zoladex therapy
  - Peptide Radioligand Therapy (PRLT)
- **13-AUG-2013**: RLT with 8600 MBq Lu-177 PSMA
Pretherapy Ga-68 PSMA PET/CT
Local prostate cancer involving the seminal vesicles with lymph node and extensive bone metastases.

3 months post Lu-177 PSMA Therapy
Excellent response to radioligand therapy. Most of the intense PSMA positive metastases are not discernible anymore.
Significant decrease in SUVmax of the target lesion (para-aortic lymph node metastasis) by 89% and of size on CT.

Fall in SUV max of the new target lesion in T-5 vertebra by 78%.

PSA dropped from 40.2 to 0.7 ng/ml 3 months later.
Partial Remission according to PERCIST: Reduction in SUVmax of the left broncho-hilar lymph node metastasis by 39% from 100 pre-therapy to 61 post-therapy.
Response to therapy of lung metastases as demonstrated by reduction in size of the lesion in S1/2 of the left lung.
Best molecular response: percentage change in the SUV\textsubscript{max} on $^{68}$Ga-PSMA PET/CT

Molecular Response:

- Progress
- Stable
- Partial Remission

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
**Bad Berka Dose Protocol**

**INPUT**
- 5 planar Whole body scans

**ROI Analysis**
- Hermes Whole Body Display
- ROI statistics

**Determination of activity**
- Excel sheet
- Time-activity graph
- Uptake

**Fit**
- ORIGIN PRO 8.1G
- Half-life
- Time-integrated (cumulated) activity

**Estimation of Mean Absorbed Dose**
- OLINDA/EXM 1.1
- Organ and Lesion
- Mean absorbed dose

**OUTPUT**

**DOCUMENTATION**
- Dosimetry Database:
  - Patient data
  - Therapy data
  - Dosimetric parameters
    - Uptake
    - Half-life
    - Residence time
  - Dosimetry results
    - Mean absorbed dose
Blood Sampling

<table>
<thead>
<tr>
<th></th>
<th>$T_{1/2,1}$ in h</th>
<th>$T_{1/2,2}$ in h</th>
<th>$T_{1/2,3}$ in h</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td></td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>P2</td>
<td>0.3</td>
<td>4</td>
<td>29</td>
</tr>
<tr>
<td>P3</td>
<td>0.2</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td>P5</td>
<td>0.1</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>P6</td>
<td>0.2</td>
<td>2</td>
<td>42</td>
</tr>
<tr>
<td>P8</td>
<td>0.2</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>

Mean absorbed dose in mGy/MBq

<table>
<thead>
<tr>
<th></th>
<th>Mean absorbed dose in mGy/MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.01</td>
</tr>
<tr>
<td>P2</td>
<td>0.02</td>
</tr>
<tr>
<td>P3</td>
<td>0.03</td>
</tr>
<tr>
<td>P5</td>
<td>0.03</td>
</tr>
<tr>
<td>P6</td>
<td>0.02</td>
</tr>
<tr>
<td>P8</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Biodistribution: $^{177}$Lu PSMA-TUM1

**Renal Uptake**

- 0.5h p.i.: 4%
- 3h p.i.: 2%
- 20h p.i.: 1%
- 45h p.i.: 0.5%
- 68h p.i.: 0.3%

**Methods**

- Biodistribution: $^{177}$Lu PSMA-TUM1

**C. Schuchardt**

Theranostics Center for Molecular Radiotherapy and Molecular Imaging
Lu PSMA-TUM1: Biodistribution and Dosimetry

Aim

Methods

Results

Conclusions

Whole body

Effective Half-life in h

Mean absorbed dose in mGy/MBq
Dosimetry

$^{177}$Lu PSMA: Prostate cancer

Metastatic lesions

Bone lesions:
Median $^{177}$Lu DOTATOC
(254 patients, 151 bone lesions)

Effective Half-life in h

Mean absorbed dose in mGy/MBq

140 Gy/treatment
35 Gy/treatment

39 Dosimetric Evaluations
**Dosimetry**

**177Lu PSMA: Prostate cancer**

- **Kinetics**
  - Median PSMA
  - Median DOTATOC
  - %IA vs. hours p.i.
  - Kidneys and Tumor lesions

- **Mean absorbed dose**
  - mGy/MBq
  - Kidneys and Tumor lesions
  - PSMA vs. DOTATOC

Shown are medium values

C. Schuchardt

Theranostics Center for Molecular Radiotherapy and Molecular Imaging
Effect on Renal Function

Mean Serum Creatinine (mmol/l)

No renal toxicity (p>0.05)

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
$^{177}$Lu PSMA: Prostate cancer

Mean absorbed dose to parotid glands higher than renal absorbed dose

- Parotid glands: 4-37 Gy per treatment
- Kidneys: 1-8 Gy per treatment
- Lesions (Bone and lymph node): 200 Gy per treatment (mean value)
Effect on Hematological Function

**Mean RBC Count**
- Pre-therapy: 6.5
- Post-therapy: 6.5

**Mean WBC Count**
- Pre-therapy: 4
- Post-therapy: 4

**Mean Platelet Count**
- Pre-therapy: 223
- Post-therapy: 220

No hematological toxicity ($p > 0.05$)
Survival after 1st PRLT

- Complete Remission
- Fortführung der Therapie
- Partialle Remission
- Stable Disease
- Progress
- Exitus letalis
Efficacy of PRLT (n=31 patients) with FU after 2-4 cycles

Number of patients treated: 55
Number of patients alive: 48
Number of therapy cycles: 122
Number of patients treated with multiple cycles (2-5): 40
Mean period of follow-up after first cycle of PRLT: 11 months (range 3 – 24)

Molecular complete Remission (2): 6 %
Partial Remission (12): 38 %
Stable Disease (7): 22 %
Progressive Disease after initial response (3): 9.6 %
Responders: 78 %
Non-responders: 22 %
(disease continued to progress)

7 patients died (median time to death 10 months after 1st PRLT)
Median time to progression after 1st PRLT in initial responders: 13 months (range 4 – 11)

Best PSA response: 100 % fall from 145.8 to 0 ng/ml, and 86 % (from 225 to 31.7 ng/ml)
Best quantitative molecular response: 89 % reduction in the SUVmax of target lymph node metastasis, followed by 78 % in bone metastasis

Improvement in quality of life and pain scores in all patients with symptomatic disease

THERANOSTICS Center for Molecular Radiotherapy and Molecular Radiotherapy, Zentralklinik Bad Berka
Conclusions

Peptide-based Radioligand Therapy (PRLT) of mCRPC using $^{177}\text{Lu}$ PSMA

- Effective in end-stage disease
  (killing tumor and not only improving symptoms)

- Excellent tolerability in all patients treated
  - no hematological or renal toxicity

- Selection of suitable patients as well as F/U after PRLT by Ga-68 PSMA PET/CT
  (Theranostics concept)

- **Future perspectives:**
  hyperfractionation, increase of treatment activity/dose,
  improved kidney protection by PMPA, radiosensitizers,
  different radionuclides, combination therapies
Acknowledgements
National and International Collaborators

• **Hans-Jürgen Wester, Munich**
  • Frank Rösch, Mainz
  • Helmut Mäcke, (Freiburg/ Basel)
  • Thea Maina-Nock, Athens
  • Jae Min Jeong, Seoul
  • Michael Schultz, Iowa

• Marion de Jong, Rotterdam
• Eric Krenning, Rotterdam
• Irvin Modlin, Yale
• Lisa Bodei, Milano

• Jean-Claude Reubi, Bern
• Stefan Schulz, Jena
• Amelie Lupp, Jena

• Gerd Binnig, Munich
• Maria Athelogou, Munich

• Matthias Blaickner, Seibersdorf
• Dale Bailey, Sydney
• Anna Celler, Vancouver

• Andrew Schally, Miami

• Rodney Balhorn, San Francisco

• THERANOSTICS Network, Germany
• THERANOSTICS Research Center

• Funds
  – Dinse-Stiftung, Hamburg
  – Keymar Foundation, Canada
WARMTH
WORLD ASSOCIATION OF RADIOPHARMACEUTICAL & MOLECULAR THERAPY
ICRT-2015, May 4-8th
10th INTERNATIONAL CONFERENCE ON RADIOPHARMACEUTICAL THERAPY

www.WARMTH.org
for more information
Targeted Radionuclide Therapy

We are small but very focused!

Thank you!