THERANOSTICS for Personalized Molecular Targeted Radiotherapy of Neuroendocrine Tumors and Prostate Cancer: Precision Oncology as fact, not as fiction

Professor Dr. Richard P. Baum
THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging
ENETS Center of Excellence, Zentralklinik Bad Berka, Germany

Chulalongkorn University, Faculty of Medicine
Bangkok, Thailand, 4th December 2018
Therapy Selection and Monitoring
Early Diagnosis, Risk Assessment
Epidemiology / Prevention

Patient History
Family hx / Demographics
Environmental Risk Factors / Treatments

Gen Expr Profile
Tissue arrays
Tumor Cell Genetics

Genetics
SNPs
NGSequencing

Proteomics
Metabolomics
Circulating Gene Transcripts (NETest)

Multimodal Imaging
PET/CT, PET/MR
Structure
Function
Molecular Biology

Precision Oncology
Personalised Medicine

Adapted from Markus Schwaiger
Theranostics

- Theranostics is the combination of a Diagnostic Tool that helps to define the right Therapeutic Tool for a specific disease – we see what we treat.
- Term coined first by PharmaNetics CEO John Funkhouser in 1998 (Herceptin test) at the same time the concept of Personalized Medicine appeared.
- Concerning radioisotopes, the term “THERAGNOSTICS” was created by Suresh Srivastava (Brookhaven National Laboratory).
- The most prominent and oldest application is radioiodine (switch of the radionuclide from diagnosis to radionuclide therapy).
- The first Theranostics World Congress (TWC) in NM was organized in 2011 at Zentralklinik Bad Berka (>400 participants from 56 countries).

Personalised Medicine

- The right treatment, for the right patient, at the right time, at the right dose
  – »not anymore targeting the “disease” but the “specific tumour 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.
PubMed-derived number of publications including the term theranostic or theragnostic during each year from Jan 2001 to Oct 2018 (search performed Oct 18, 2018).
Food & Drug Administration Approval (PI)
Approved January 26, 2018

Treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) including foregut, midgut, and hindgut neuroendocrine tumors in adults

Novartis acquired AAA for $ 3.9 B
Novartis to Acquire Endocyte for $2.1B, Expanding RLT Pipeline in Prostate Cancer

October 18, 2018
Increase in Therapeutic Nuclear Medicine Procedures

https://www.healthcare.siemens.com/molecular-imaging/theranostics
Targeted Molecular Imaging and Therapy

**Schematic Representation of a Drug for Imaging and Targeted Therapy**

**Pharmacokinetics/Biodistribution Modifier**

**Targeting**
- **Antigens**
  - e.g. CD20, HER2
- **GPCR**
  - e.g. SSTR
- **Enzymes & Inhibitors**
  - e.g. PSMA
- **Transporters**

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

**Reporting Unit**
- **99mTc**, **111In**
- **68Ga**, **44Sc**, **152Tb**, **64Cu**

**Cytotoxic Unit**
- **90Y**, **177Lu**
- **225Ac**, **213Bi**

*Courtesy Helmut Mäcke (modified)*
Targeted radionuclide therapy has unique promise for personalised and precise treatment of cancer, because both the targeting vehicle and the radionuclide can be tailored to the individual patient.
Ga-68 Generator System

TiO$_2$ based

Developed in close collaboration between
Radiopharmacy PET/CT Center,
Zentralklinik Bad Berka
and
Institute of Nuclear Chemistry
Johannes Gutenberg-Universität, Mainz,
Germany

Zhernosekov K, Filosofov DV, Baum RP, Rösch F
J Nucl Med 2007 (Oct); 48:1741-48

First clinical use in 2004, up to now over 15,000 studies done at ZKL Bad Berka

Simultaneous use of several generators

$^{68}$Ga-elucent, purification and synthesis module
Growing use of Ga-68

The Ga-68 generator was introduced in India at the Indo-German Symposium in Delhi in 2006 and was essential for Theranostics to become a viable clinical concept...

- Receptors
- Enzymes
- Transporters
- mRNA
- Antigens (pretargeting)
- Proliferation
- Hypoxia
- Glycolysis
- Angiogenesis
- Apoptosis
- Inflammation
- Transplantation
- Perfusion
- Lung ventilation

Dosimetry
- Staging, Selection, Planning,
- Monitoring the response to the therapy

Personalized medicine

EU approval for Ga-68 DOTATOC in Dec. 2016

following a positive opinion issued by the European Medicines Agency in October 2016, the European Commission has approved SomaKit TOC™ 40 μg, a kit for radiopharmaceutical preparation of gallium (Ga 68) edotreotide solution for injection, for Positron Emission Tomography (PET) imaging of somatostatin receptor overexpression...

NUCLEAR = UNCLEAR

From „unclear“ medicine to „new clear“ medicine to precision oncology

Ga-68 DOTATOC: liver metastasis, infiltration of stomach
Management Impact of SSTR PET/CT

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Ambrosini 2010</td>
<td>90</td>
<td>DOTA-NOC</td>
<td>50% Δ stage or therapy modification</td>
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<td>Srirajaskanthan R 2010</td>
<td>41</td>
<td>DOTA-TATE</td>
<td>Inter-modality Δ 71%</td>
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<tr>
<td>Frilling A 2010</td>
<td>52</td>
<td>DOTA-TOC</td>
<td>Δ treatment decision 60%</td>
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<td>Haswa N 2011</td>
<td>109</td>
<td>DOTA-NOC</td>
<td>Inter-modality Δ 19%</td>
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<tr>
<td>Ruf J 2011</td>
<td>64</td>
<td>DOTA-TOC</td>
<td>Inter-modality Δ 38%</td>
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<td>Hofman MS 2012</td>
<td>59</td>
<td>DOTA-TATE</td>
<td>Inter-modality Δ 47%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intra-modality Δ 10%</td>
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</table>

✔ High management impact similar in patients with negative or positive Octreotide SPECT/CT, suggesting redundancy of this technique

Hofman MS, J Med Imaging Rad Onc 2012;56(1)-40-7.
The world first **total body PET** has now been established at UC Davis (group of Simon Cherry) and first data were presented at the SNMMI Congress in Philadelphia in June 2018.
EXPLORER: First Human Images Oct. 2018

7.8 mCi FDG
65 kg subject
1 minute scan
1 bed position
90 mins post-injection
OSEM with PSF and TOF
20 subsets, 5 iterations
1x1x1.425 mm$^3$ voxels

bme.ucdavis.edu
Youtube - Explorer

Courtesy of
UC Davis
United Imaging
Zhongshan Hospital
1972 • somatostatin first isolated (Roger Guillemin)
1972 • octreotide synthesis
1987 • scintigraphy with $^{123}$I-octreotide
1991 • $^{111}$In-octreotide first employed
1991 • five G-protein coupled somatostatin receptors (sst1–5), identified and cloned
1991 • $^{111}$In-octreotide registered
1992 • First PRRT with high-dose $^{111}$In-octreotide
1994 • First $^{90}$Y-octreotide PRRT - Basel
1996 • First $^{177}$Lu-octreotate PRRT - Rotterdam
2000 • Phase III registration trial of $^{177}$Lu-octreotate
2012 • 2016 – Completion of NETTER-1 Trial
Zentralklinik Bad Berka - ENETS Center of Excellence since 2011

Molecular Radiotherapy & Imaging (PET/CT Center)
including a specialized nuclear medicine ward, medical physics

PASSION FOR PRECISION

- 1200 prostate cancer patients’ visits/year (no urology department!)
- 400 PSMA-mediated Radioligand Therapies (PRLT) per year
- 350 Peptide Receptor-mediated Radionuclide Therapies (PRRT) per year
- THERANOSTICS Research Center (Academy for Precision Oncology in statu nascendi)

PET/CT Center & NM Department since 1997
Nuclear Medicine Ward (22 beds for RN treatment) founded 1999
**Radiopeptide Therapy (ZKL Bad Berka)**

As of November 15, 2018

Patients treated \( n = 1577 \)
Therapy cycles \( n = 5856 \)

- **Lu-177** \( n = 4126 \)
- **Y-90** \( n = 1765 \)
- **Bi-213** \( n = 1 \)
- **Ac-225** \( n = 5 \)

Somatostatin receptor positive neuroendocrine tumors

<table>
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<tr>
<th></th>
<th>Y-90</th>
<th>Lu-177</th>
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<tbody>
<tr>
<td>Mean GBq</td>
<td>3.34</td>
<td>6.5</td>
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<tr>
<td>Max. GBq</td>
<td>9.50</td>
<td>12.6</td>
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</table>

**Age:** 4 – 86 years
**Median:** 59.8 years
Primary tumors of patients with metastatic NETs treated by PRRT (n=1570 patients)

- midgut: 505
- pancreas: 499
- others: 172
- CUP: 170
- lung: 109
- rectum: 61
- Thymus: 26
- stomach: 20
- colon: 8
Patient Selection for Personalised PRRT
The Bad Berka Score (BBS)

- SUV on receptor PET/CT (referrals: OctreoScan K.S.)
- Renal function (GFR and TER / creatinine & BUN)
- Hematological status (blood counts)
- Ki-67 index / tumor grade
- FDG status (glucose hypermetabolism of tumors/mets)
  - Liver involvement, extrahepatic tumor burden
  - Tumor dynamics (doubling time, new lesions)
  - Karnofsky performance score, ECOG status
- Weight loss
- Time since first diagnosis
- Functional activity of tumor
- Previous therapies
- Genetic data
Results and adverse events of personalized peptide receptor radionuclide therapy with $^{90}$Yttrium and $^{177}$Lutetium in 1048 patients with neuroendocrine neoplasms

Baum RP$^1$, Kulkarni HR$^1$, Singh A$^1$, Kaemmerer D$^2$, Mueller D$^1$, Prasad V$^3$, Hommann M$^2$, Robiller F$^4$, Niepsch K$^1$, Franz H$^5$, Jochems A$^6$, Lambin P$^{6,7}$ and Hörsch D$^8$

$^1$THERANOSTICS Center for Molecular Radiotherapy, Zentralklinik Bad Berka GmbH, Bad Berka, Germany
$^2$Department of General and Visceral Surgery, Zentralklinik Bad Berka GmbH, Bad Berka, Germany
$^3$Clinic for Nuclear Medicine, Charité, Berlin, Germany
$^4$Center of Molecular Imaging, Zentralklinik Bad Berka GmbH, Bad Berka, Germany
$^5$Lohmann and Birkner, Berlin, Germany
$^6$Department of Radiation Oncology (MAASTRO Clinic), Maastricht, The Netherlands
$^7$GROW - School for Oncology and Developmental Biology, Maastricht University, The Netherlands
$^8$Department of Gastroenterology/Endocrinology, all in Center for Neuroendocrine Tumors Bad Berka – ENETS Center of Excellence, Zentralklinik Bad Berka GmbH, Bad Berka, Germany
OVERALL SURVIVAL ACCORDING TO PRIMARY TUMORS

Patients with NENs of small intestinal origin (69 months 53.7-84.2 95% CI) had a better survival than those with other primary tumors.

Number at risk:
- Total: 1048
- Bronchial: 75
- Pancreas: 384
- Small bowel: 315
- CUP: 151
- Other: 123

Kaplan-Meier plot
71 y-o patient

Well-differentiated, non-functioning neuroendocrine neoplasm of the rectum: persistent remission of multiple liver metastases 5 years after 3 PRRT cycles

The primary tumor also responded to PRRT (decrease in size on CT and of uptake on PET).
Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors

Lisa Bodei · Mark Kidd · Giovanni Paganelli · Chiara M. Grana · Ignat Drozdov · Marta Cremonesi · Christopher Lepensky · Dik J. Kwekkeboom · Richard P. Baum · Eric P. Krenning · Irvin M. Modlin

Safety of PRRT: Kidney & Bone Marrow

Best Clinical Paper EJNMMI 2015
### Nephrotoxicity in 807 pts treated with PRRT

Grade according to CTCAE version 4.0

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>%</th>
<th>Y</th>
<th>%</th>
<th>Y+Lu</th>
<th>%</th>
<th>Lu</th>
<th>%</th>
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<tr>
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<td>526</td>
<td>65.2</td>
<td>200</td>
<td>55.9</td>
<td>109</td>
<td>69.4</td>
<td>216</td>
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<tr>
<td>G1</td>
<td>227</td>
<td>28.1</td>
<td>118</td>
<td>33.0</td>
<td>39</td>
<td>24.8</td>
<td>69</td>
<td>23.8</td>
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<tr>
<td>G2</td>
<td>40</td>
<td>5.0</td>
<td>29</td>
<td>8.1</td>
<td>6</td>
<td>3.8</td>
<td>5</td>
<td>1.7</td>
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<td>1</td>
<td>0.3</td>
<td>1</td>
<td>0.6</td>
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<tr>
<td>total</td>
<td>807</td>
<td>100</td>
<td>358</td>
<td>100</td>
<td>157</td>
<td>100</td>
<td>290</td>
<td>100</td>
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</table>

Lu-177 is **not** nephrotoxic!
Long-term Nephrotoxicity After PRRT: Fact or Fiction?

Jingjing Zhang, Harshad Kulkarni, Aviral Singh, Karin Niepsch, Christiane Schuchardt, Coline Lehmann, Richard P. Baum

Zentralklinik Bad Berka
THERANOSTICS Center for Molecular Radiotherapy & Precision Oncology
Zentralklinik Bad Berka, Germany
- **Treatment:** $^{177}\text{Lu}$- or $^{90}\text{Y}$ DOTATATE/-TOC PRRT (1–10 cycles)
- **Function:** prospectively documented in a structured database (comprising >250 items/patient)

### Conclusion:
This retrospective analysis with prospective documentation in a large cohort of 1361 NEN patients, receiving 4048 cycles of PRRT treated at a single institution over 20 years (with a median follow-up time of 91.8 months) did not reveal any evidence of significant long-term nephrotoxicity.

4048 cycles of PRRT were administered to 1361 NEN patients; in addition, 4052 records were available for restaging.
MDS/Leukemia after PRRT

- Kesavan and Turner reviewed sixteen key articles comprising a total of 2225 patients (2104 treated with PRRT monotherapy and 121 with PRRT combined with chemotherapy).
- **MDS/AL was a rare stochastic event occurring in 32 (1.4 %) patients.**
- Where bone marrow biopsy was performed, cases of MDS displayed cytogenetic abnormalities, consistent with secondary MDS.
- Factors associated with myelotoxicity included age >70 years, impaired renal function, baseline cytopenias, prior number of therapies, prior chemotherapy (alkylating agents), and prior radiotherapy.

- Myelodysplastic syndrome occurred in 2% and leukemia in 1.8% of PRRT patients, respectively
  
  *Bodei et al. 2016*


After initial PRRT (1048 cycles), grade 3 and 4 adverse events were rare. After 2633 follow-up cycles, G3 and G4 adverse events were present in less than 1% of all patients.

During follow-up, MDS (in 1.2%) or leukemia (0.8%) developed in 22 (2%) patients after a mean of 8 years from diagnosis of the neuroendocrine neoplasia.

Risk factors were previous chemotherapy and external beam radiation as well as high tumor load defined as involvement of more than 50% of the liver, or multiple (>10) bone and lymph node metastases.

Development of leukemia/MDS after PRRT was associated with a limited mean overall survival of 14.4 months.

Baum RP et al. Oncotarget 2018
A landmark publication in Theranostics

EMA Approval in September 2017
FDA Approval in January 2018

Phase 3 Trial of $^{177}$Lu-Dotatate for Midgut Neuroendocrine Tumors


N = 229 (ITT)
Number of events: 90

- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio: **0.21**
[0.129 – 0.338]
**p < 0.0001**

79% reduction in the risk of disease progression/death

Median PFS
Lu-DOTATATE arm
*06/16 reported: 28.4 mo

177Lu-Dotatate
Median PFS: not reached*

Octreotide LAR 60 mg
Median PFS: 8.5 months

All progressions centrally confirmed and independently reviewed for eligibility

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna
Overall Survival

HR: 0.536 (0.333, 0.864)  
P = 0.0094

mOS

Oct LAR 60 mg : 27.4 months

177 Lu-DOTATATE : NR
Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With $^{177}$Lu-Dotatate in the Phase III NETTER-1 Trial

Jonathan Strosberg, Edward Wolin, Beth Chasen, Matthew Kalke, David Bushnell, Martyn Caplin, Richard P. Batum, Pamela Kainz, Timothy Hobday, Andrew Hendifar, Kjell Oberg, Maribel Lopera Sierra, Thomas Thevenet, Ines Marguet, Philippe Ruszniewski, and Eric Krenning, on behalf of the NETTER-1 Study Group
Supplemental analysis of the NETTER-1 study, updated 12 months after primary analysis, continues to demonstrate statistically and clinically significant PFS benefit with $^{177}$Lu-DOTATATE.

Updated analysis continues to suggest survival benefit, to be confirmed at the protocol-specified OS analysis data cut-off (5 years after last patient was randomized, or after 185 deaths).

$^{177}$Lu-DOTATATE significantly delays time to deterioration in HRQoL in key domains related to overall quality of life (global health, physical functioning, role functioning), as well as symptom domains relevant to midgut NETs (diarrhea, pain, fatigue).
Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

John J. Zaknun • L. Bodei • J. Mueller-Brand • M. E. Pavel • R. P. Baum • D. Hörsch • M. S. O’Dorisio • T. M. O’Dorisio • J. R. Howe • M. Cremonesi • D. J. Kwekkeboom

The pdf of this guidance is available on our website www.prrtinfo.org

Included in 2013
S2k-Leitlinie Neuroendokrine Tumore
AWMF-Reg. 021-27

Practice guideline neuroendocrine tumors
AWMF-Reg. 021-27

Authors
Anja Rinke¹*, Bertram Wiedenmann²*, Christoph Auernhammer³, Peter Bartenstein⁴, Detlef K. Bartsch⁵, Nehara Begum⁶, Siegbert Faiss⁷, Christian Fottner⁸, Bernhard Gebauer⁹, Peter Goretzki¹⁰, Petra Lynen Jansen¹¹, Gabriele Pöpperl¹², Hans Schererbl¹³, Matthias M. Weber⁸, Thomas Mathias Gress¹⁴**, Marianne Pawel¹⁵**

Collaborators:

Federführende Fachgesellschaft:
Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (DGVS)
The COMPETE study

Trial started in 2017

Controlled, Open-label, Multicentre study of PRRT with $^{177}$Lu-Edotreotide compared to targeted molecular Therapy with Everolimus in neuroendocrine tumours of the pancreas (P-NET) and midgut

300 GEP-NET patients will be randomized 2:1 to receive either Targeted Radionuclide Therapy with $^{177}$Lu-Edotreotide consisting of a maximum of four cycles (7.5 GBq $^{177}$Lu-Edotreotide each), administered at 3-month-intervals for 9 months, or until diagnosis of progression (200 patients) or 10 mg Everolimus daily until diagnosis of progression (100 patients). Study duration per patient will be 24 months.
Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms: Safety and Survival Analysis in 69 Patients


INSTITUTION (ALL):

THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging, Zentralklinik Bad Berka, Bad Berka, 99437, Germany

*Contributed equally to this work
In G3 NEN patients median progression-free (PFS) and overall survival (OS) were 9.6 and 19.9 months, respectively, with a median follow-up time of 94.3 months (range 0.1-104.9 months).

Zhang et al. JNM Sept 2018
Intestinal NEN

NET G1
- Low tumor burden and/or stable
- High tumor burden and/or growth
  - W&W
  - SSA
  - PRRT

NET G2
- Ki67 < 10%
- Ki67 > 10%
  - SSA
  - SSA + locoregional therapy*
  - EVE
  - PRRT

NET G3
- Ki67 < 30%
  - FOLFOX
  - PRRT

NEC G3
- Cisplatin or Carboplatin + Etoposide

Nature Reviews in press

* If feasible; consider other therapies alternatively; EVE, Everolimus; W&W, watch and wait
Peptide Receptor Radiotherapy – what does the future hold?

- **Combination therapies – PRRT+**
  - PRCRT (PRRT + chemotherapy)
  - PRIT (PRRT + immunotherapy)
  - Surgery (neoadjuvant / adjuvant PRRT, use of intraoperative probes)
  - TACE (transarterial chemoembolization)
  - SIRT (selected internal radiation therapy)
  - RFA (radiofrequency ablation)
  - Kinase inhibitors
  - Radiosensitizers

- **Targeted alpha radiation therapy** (ART, e.g. Actinium-225, Bismuth-213)

- **Novel radioisotopes** for imaging and therapy (theranostic pairs like Sc-44/Sc-47, Cu-64/Cu-67, Tb-152/Tb-149, Tb-155/Tb-161)

- **Novel targets** (e.g. SSR antagonists, CXCR4, GLP, GIP)

- **Liquid biopsy** (circulating gene transscripts for better selection of patients for PRRT, prognostication of efficacy of therapy and of possible side effects), pCR of tissue samples

- **Radiomics** (selection of patients for PRRT, prognostication of therapy effects)

- **DUO-PRRT** i.e., using Y-90 and Lu-177 labeled SSA in sequence
- **TANDEM-PRRT** i.e., using Y-90 and Lu-177 or Ac-225 labeled SSA simultaneously
- Intra-arterial PRRT
- **Improvements in dosimetry** (personalized and predictive dosimetry)
PRCRT: marked improved PFS

<table>
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<tr>
<th>Study</th>
<th>Design</th>
<th>NET Patients</th>
<th>Treatment</th>
<th>Median PFS (months)</th>
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<td>Yao et al NEJM 2011</td>
<td>RCT</td>
<td>Pancreatic G1/G2</td>
<td>Everolimus</td>
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<tr>
<td>Raymond et al NEJM 2011</td>
<td>RCT</td>
<td>Pancreatic G1/G2</td>
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<td>Sun W JCO 2005</td>
<td>RCT</td>
<td>“Carcinoid”</td>
<td>FU/STZ, FU/DOX, dacarbazine</td>
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<tr>
<td>Strosberg et al Cancer 2011</td>
<td>RCT</td>
<td>Pancreatic</td>
<td>CAPTEM</td>
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<tr>
<td>Rinke et al JCO 2009</td>
<td>RCT</td>
<td>Midgut</td>
<td>SSA</td>
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<td>Kashyap et al EJNMMI 2015</td>
<td>Retrospective</td>
<td>FDG-avid NET</td>
<td>LuTate + 5-FU</td>
<td>48</td>
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Courtesy Rodney Hicks
Australia Leading the Way: RCT of PRCRT

Cohort A: **pancreatic NETs**: Lu-177 DOTATATE+CAPTEM vs. CAPTEM (control)

Cohort B: **small bowel NETs**: Lu-177 DOTATATE+CAPTEM vs. Lu-DOTATATE (control)

**CONTROL NETs Treatment Plan**

- **Cohort A**: pancreateic NETs: Lu-177 DOTATATE+CAPTEM vs. CAPTEM (control)
  - Lu-177 DOTATATE+CAPTEM vs. CAPTEM (control)

- **Cohort B**: small bowel NETs: Lu-177 DOTATATE+CAPTEM vs. Lu-DOTATATE (control)
  - Lu-177 DOTATATE+CAPTEM vs. Lu-DOTATATE (control)

**Note**: For CAPTEM alone one cycle is shown in this diagram. Each 8 week CAPTEM alone cycle includes 2 weeks CAPTEM followed by a 2 week break then another 2 weeks CAPTEM followed by a 2 week break.

**State | Site | Principal Investigator**
--- | --- | ---
NSW | Royal North Shore Hospital | A/Prof Nick Pavlakis
NSW | St George Hospital | Dr Katrin Sjoquist
WA | Fiona Stanley Hospital | Dr David Ransom
SA | The Queen Elizabeth Hospital | Dr Gabrielle Cehic
QLD | Royal Brisbane and Women’s Hospital | Dr David Wylde
VIC | Peter MacCallum Cancer Centre | Prof Rod Hicks
Identify PRRT efficacy prior to therapy

Individual assessment of therapy response after PRRT

Updated results of NETest analysis were presented at ASCO 2018
Nature Reviews in press
Somatostatin Receptor Antagonist

- Higher tumor uptake  
  Fani M. et al. JNM 2012
- Longer tumor retention time  
  Wild D. et al. JNM 2014
- Higher renal uptake  

Antagonist labels more sst\textsubscript{2} sites than agonist in human cancer tissues

Cescato R. et al. JNM 2011  
177\textsuperscript{Lu}-DOTA-TATE  
177\textsuperscript{Lu}-DOTA-BASS

Agonist  
Antagonist

Courtesy: Guillaume P. Nicolas
Extensive NET of pancreas with liver metastasis
PET/CT imaging with 4\textsuperscript{th} generation peptides

Antagonist labels more sst\textsubscript{2} sites than agonist in cancer patients leading to higher diagnostic sensitivity (TRC Bad Berka, first in human study)
Images of patient with ileal NET, showing bilobar liver metastases: Ga-68 OPS202 PET/CT (A and B), Ga-68 DOTATOC PET/CT (C and D), and MRI (E and F).

Patient with metastatic paraganglioma: higher tumor-to-background ratio (TBR) on Ga-68 NODAGA-LM3 PET/CT compared to Ga-68 DOTATOC PET/CT.

Detection of >140 osseous metastases
Targeted Alpha Radiation Therapy (ART)

- $\alpha$ mass is 7000 x that of $\beta$
- $\alpha$ 's energy is 30 x that of $\beta$ (typically 6 MeV versus 200 keV)
- Linear Energy Transfer (LET) ~100 times greater than $\beta$
- The effective range of $\alpha$ particles in tissue is approx 5 cell diameters (hundreds/thousands for $\beta$ particles)
Intra-arterial application of Bismuth-213 DOTATOC

Kratochwil et al. DKFZ Heidelberg, Germany

Intraarterial PRRT with cumulative 14 GBq Bi-213 DOTATOC

SNM 2012 Image of the Year

Fig. 4  Patient 3 with the acute danger of occlusion of both the liver veins and the lower caval vein due to a large lesion in the upper central liver (a, MR image) which was addressed by locoregional DOTATOC therapy administered into the proper hepatic artery (b, digital subtraction angiogram). Intense $^{68}$Ga-DOTATOC uptake and uptake of contrast medium for CT was present in the initial staging (c, fused PET/CT image). Only PET-negative, morphologically cystic residuals were found 6 months after therapy (d, fused PET/CT image)

Alpha Radiaton Therapy - the Coming Revolution
• PRRT is well tolerated and effective – even in very advanced NEN
• Median overall survival from start of treatment: > 46-59 (up to >90) months
• PRRT leads to significant improvement of clinical symptoms
• Cure is rarely possible - but excellent palliation can be achieved
• PRRT: part of the guidelines of major scientific & clinical societies

• Standardized treatments are usually applied - algorithms are available
• Significant kidney damage can be avoided (or reduced when using Y-90)
• PRRT should be performed at specialized centres as NET patients need highly individualized multidisciplinary treatment and long term care.

Future perspectives: personalized treatment based on precision oncology
  ➢ New peptides for diagnosis and therapy (antagonists, GLP, GIP)
  ➢ Combination therapies (PRCRT, PRIT), esp. in G3 NET
  ➢ Circulating biomarkers, gene cluster analysis, response assessment
  ➢ Personalized and predictive dosimetry
Prostate Cancer – Epidemiology

Of all cancers in males

- **PCa** has the highest incidence (most common malignancy)
- Lifetime risk of 1 in 6 men
- **PCa** ranks 3rd in mortality after lung and bowel cancer
- More than 300,000 deaths worldwide
- In the EU, every 12 minutes a man is dying from mCRPC

Incidence rate (per 100,000): 114.1
Mortality rate (per 100,000): 17
Prevalence (one year): 64,648
Prostate cancer: clinical state and treatment options

- **Castration Sensitive**
  - Hormonal Therapy
  - 2nd line Hormonal Therapy

- **Castration Resistant**
  - Docetaxel 2004
  - Abiraterone 2013
  - Enzalutamide 2014
  - Cabazitaxel 2010
  - Abiraterone 2011
  - Enzalutamide 2012
  - Radium-223

- **Local Therapy**
- **Non-Metastatic**
- **Metastatic**
- **Asymptomatic**
- **Symptoms**

- **Tumor volume**

- **Time**

- **Death**
<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</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18.9 vs. 16.5 months&lt;br&gt;(HR 0.76; 95% CI: 0.62-0.94)</td>
<td></td>
</tr>
<tr>
<td>Kongo (radium-223)</td>
<td>Radio-pharmaceutical, alpha-emitter, and calcium mimetic</td>
<td>ACS VMPCa (921 patients)</td>
<td>Placebo-controlled</td>
<td>Improved OS&lt;br&gt;14.0 vs. 11.2 months&lt;br&gt;(HR 0.70; 95% CI: 0.55-0.88)</td>
<td>2013</td>
</tr>
</tbody>
</table>

**Summary of data from J Clin Oncology:**

Survival benefit with chemotherapy ~ 9 - 12 weeks

2nd generation ADT ~ 3 - 5 months

Progression-free survival ranged from 16.5–18 mths, and overall survival from 14 to 32.4 months in early stages of disease.

**Urgent need for more effective therapies!**
CRPC M+ – what is known in 2018?

- Docetaxel-based therapy is the standard 1\textsuperscript{st} line chemotherapy in pts with mCRPC

- Poor prognosis, median overall survival with Chx 14 months
Docetaxel Adverse Events

- **Central nervous system**: Central nervous system toxicity (20% to 58%; severe: 6%; including neuropathy)
- **Dermatologic**: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: ≤5%), nail disease (11% to 41%)
- **Endocrine & metabolic**: Fluid retention (13% to 60%; severe: 7% to 9%)
- **Gastrointestinal**: Stomatitis (19% to 53%; severe 1% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)
- **Hematologic & oncologic**: Neutropenia (84% to 99%; grade 4: 75% to 86%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days; dose dependent), leukopenia (84% to 99%; grade 4: 32% to 44%), anemia (65% to 97%; dose dependent; grades 3/4: 8% to 9%), thrombocytopenia (8% to 14%; grade 4: 1%); febrile neutropenia (5% to 14%)
- **Hepatic**: Increased serum transaminases (4% to 19%)
- **Hypersensitivity**: Hypersensitivity (1% to 21%; with premedication 15%)
- **Infection**: Infection (1% to 34%; dose dependent)
- **Neuromuscular & skeletal**: Weakness (53% to 66%; severe 13% to 18%), myalgia (3% to 23%), neuromuscular reaction (16%)
- **Respiratory**: Pulmonary reaction (41%)
Cabazitaxel

Phase III TROPIC trial: OS\(^a\) versus mitoxantrone + prednisone

<table>
<thead>
<tr>
<th></th>
<th>cabazitaxel + prednisone</th>
<th>mitoxantrone + prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>378</td>
<td>377</td>
</tr>
<tr>
<td>Median OS (months) (95% CI)</td>
<td>15.1 (14.1–16.3)</td>
<td>12.7 (11.6–13.7)</td>
</tr>
<tr>
<td>Hazard Ratio (HR)(^b) (95% CI)</td>
<td>0.70 (0.59–0.83)</td>
<td></td>
</tr>
<tr>
<td>(P) value</td>
<td>&lt;.0001</td>
<td></td>
</tr>
<tr>
<td>Number of deaths</td>
<td>234 (62%)</td>
<td>279 (74%)</td>
</tr>
</tbody>
</table>

\(a\) Primary endpoint.

\(b\) HR estimated using COX model; an HR of <1 favors cabazitaxel

**Benefit of 2.4 months in overall survival**

*De Bono JS et al. Lancet 2010; 376(9747):1147-54.*
Cabazitaxel Adverse Events

- **Central nervous system**: Fatigue (37%), fever (12%)
- **Gastrointestinal**: Diarrhea (47%; grades 3/4: 6%), nausea (34%), vomiting (22%), constipation (20%), abdominal pain (17%), anorexia (16%), taste alteration (11%)
- **Hematologic**: Anemia (98%; grades 3/4: 11%), leukopenia (96%; grades 3/4: 69%), neutropenia (94%; grades 3/4: 82%; nadir: 12 days [range: 4-17 days]), thrombocytopenia (48%; grades 3/4: 4%)
- **Neuromuscular & skeletal**: Weakness (20%), back pain (16%), peripheral neuropathy (13%; grades 3/4: <1%), arthralgia (11%)
- **Renal**: Hematuria (17%)
- **Respiratory**: Dyspnea (12%), cough (11%)
Novel therapies

Current shortcomings:
- some are available only in US / Europe
- PSA useful for monitoring?
- therapy sequence????
- toxicity (also financial toxicity)
- very expensive (some over >200 000$)
**Cost of 2nd generation ADT in Germany for 12 months treatment:**

**XTANDI (Enzalutamide) ≥ 60,000 Euro (70,000 $)**

**Zytiga (Arbirarterone) ≥ 66,000 Euro (77,000 $)**

<table>
<thead>
<tr>
<th>Darreichungsform</th>
<th>Dosis pro Tag¹</th>
<th>Kosten pro Tag [€]²</th>
<th>Kosten für 6 Monate [€]²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tabletten</td>
<td>1000 mg³</td>
<td>181,50</td>
<td>33,124,54</td>
</tr>
<tr>
<td></td>
<td>+ Prednison/</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prednisolon 10 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Dosierung gemäß Produktinformation; ²Kostenberechnung nach Apothekenabgabepreis anhand des kostengünstigsten Präparates einschließlich Import (hier nur ein Präparat).
Cancers will be classified by gene analysis / molecular phenotypes
Organ site → secondary classification

Molecular phenotypes will be determined by molecular pathology and by molecular imaging (PET/CT, SPECT/CT, MRI, optical) using cancer type specific probes.

Treatment will be targeted against the individual tumor – Precision Oncology

Nuclear Medicine Physician will become the “PRECISION ONCOLOGIST”

Prostate cancer is a paradigm for this approach as molecular radiotherapy is applied based on the molecular phenotype (PSMA expression of metastases) as defined by PSMA PET/CT before starting the treatment.
PSMA for Targeting Prostate Cancer

- 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)

Henry N. Wagner: FDG – the molecule of the (last) century
PSMA – the target of this – and the next - decade
### 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>

*Courtesy of Dr. Neil Bander New York-Presbyterian Hospital*
Proposed mechanisms by which PSMA contributes to tumor growth and progression.

Poly-γ-glutamated folates released from dead and dying tumor cells are hydrolyzed to folate by PSMA and can then be taken up by nearby healthy tumor cells via proton-coupled folate transporter (PCFT), folate receptor (FR), or reduced folate carrier (RFC). Once inside the cell, folate is again polyglutamated and used for polyamine synthesis, methylation reactions, and the nucleotide synthesis required for cell proliferation. Free glutamate released by this reaction may be taken up by glutamate receptor, stimulating proliferative growth pathways.

PET/CT – Prostate Cancer

Key Points

- Elevated PSA without tumor detection by CI - potential indication for Ga-68 / F-18 PSMA or bombesin antagonists (not for choline)
- Initial staging (LNM, distant metastases) - indication for Ga-68 / F-18PSMA or choline (or Ga-68 GRP) for detection of lymph node mets
- Detection of recurrence after initial therapy - indication for choline PET/CT and in case of strongly elevated PSA levels (susp. distant mets)
- (if PSA levels are above 1.5 ng/ml). Ga-68 / F-18 PSMA is superior.
- Therapy monitoring - depending on the clinical question to be answered
- Molecular radiation therapy planning (MRTP) – excellent indication
- THERANOSTICS - selection of patients for radionuclide therapy and F/U
Prostate adenocarcinoma
Gleason = 9 (4 +5)
Prostatectomy with LN clearance (R1)
one month ago
Post-op PSA 0.37 ng/ml

What would be your decision?
Treating team wanted to know, if there are lesions outside the prostate region before planned EBRT of prostate bed.

\( ^{68}\text{Ga} \) (I & T) PSMA PET/CT shows….
RETROPERITONEAL NODES INVOLVEMENT & BONE METASTASES

THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging Zentralklinik Bad Berka

(~2 mm in size)

(~9 mm on CT)

NUCLEAR = UNCLEAR

From „unclear“ medicine to „new clear“ medicine to precision oncology

PSA 0.37 ng/ml !!
The first specific tracer for localizing PCA bone and bone marrow metastases is Ga-68 I & T PSMA PET/CT.
Our first experience with radioligand therapy using $^{177}$Lu-labeled PSMA inhibitor I&T in 56 patients with progressive metastatic castration-resistant prostate cancer demonstrated very promising results.

No G3 / G4 hemato- or nephrotoxicity observed.

**FIGURE 6.** 76-y-old patient after prostatectomy, external-beam radiation therapy to bone metastases, hormone therapy, and chemotherapy. (A–D) Patient had multiple PSMA-avid lymph node metastases, as revealed by $^{68}$Ga-PSMA PET/CT. (E–H) Excellent response to therapy (according to both RECIST 1.1 and EORTC criteria) after 2 cycles of $^{177}$Lu-PSMA RLT was demonstrated by $^{68}$Ga-PSMA PET/CT, with greater than 50% decrease in serum PSA level (from 15 to 6 ng/mL).
Widespread metastases, normal PSA (!) - excellent response to PRLT

3 x PRLT applications
16.3 GBq of Lu-177 PSMA

Before PRLT - 01

After PRLT - 03

Note! „low“ PSA does not mean „low tumor burden“!
Poorly differentiated PCa cells produce little/no PSA – however, strongly express PSMA!!

EXTENSIVE METASTASES
!!! PSA = 0.05 ng/ml !!!

Complete resolution of metastatic disease
mCR (PSA = 0.0 ng/ml)
Indication: Distant metastases with high PSMA expression confirmed on pre-therapy $^{68}$Ga-PSMA PET/CT, and progressive disease despite extensive previous treatments.

Recommendation: 3 cycles of $^{177}$Lu-PSMA-617 (6 GBq) every 8 weeks with laboratory examination every 4 weeks and restaging using $^{68}$Ga-PSMA PET/CT after the second cycle.
THE GERMAN MULTICENTER TRIAL

Preliminary Clinical Data of PSMA RLT


Reduces Serum PSA Levels

Improves Pain and QoL

Best Clinical Paper JNM 2017

**Diagnosis:**
- $^{68}$Ga-PSMA PET/CT
- $^{99m}$Tc-MAG3 renal scintigraphy
- Laboratory tests: bone marrow reserve, renal, hepatic function etc.

**Monitoring under therapy:**
- Clinical (symptoms)
- Biochemical (PSA)
- Molecular ($^{177}$Lu-PSMA whole-body scintigraphy and SPECT/CT)

**Assessment of side effects:** (questionnaire); laboratory evaluation of hematological, hepatic and renal function

**Restaging after PRLT**
- $^{68}$Ga-PSMA PET/CT: molecular and morphological response

**THERANOSTICS Center for Molecular Radiotherapy**
Ga-68 PSMA PET/CT – extensive hepatic metastases

Poorly differentiated prostate adenocarcinoma
Gleason score 8 (4 + 4), PSA 1462 ng/ml

- Extensive bilobar hepatic metastases
- Extensive abdominal lymph node metastases
- Multiple skeletal metastases
Ga-68 PSMA PET/CT – Restaging – EXCELLENT RESPONSE TO THERAPY

Significant regression of liver metastases following
3 cycles of Lu-177 PRLT (22.7 GBq) over 7 months
Best molecular response
Percentage change in the $SUV_{\text{max}}$ on $^{68}\text{Ga-PSMA PET/CT}$

Best molecular response: complete remission

Progress

Molecular Response

Stable

Partial Remission

THERANOSTICS Center for Molecular Radiotherapy, Zentralklinik Bad Berka
Individualized dosimetry: intrapatient variability due to tumor responses and varying tumor load between different therapy cycles.

Analysis for PSMA I&T and PSMA-617 revealed comparable results for both ligands.

Highest dose to normal organs: lacrimal glands (1 – 3.8 Gy/GBq), salivary glands (0.5 – 1.4 Gy/GBq) and kidneys (0.53 – 0.88 Gy/GBq).

Most favorable dosimetry (0.01 – 0.04 Gy/GBq) for red marrow.
Dosimetry PSMA RLT
9.2 GBq $^{177}$Lu PSMA-617

$^{68}$Ga PSMA PET/CT
MIP

$^{177}$Lu PSMA Post Therapy Scan - Anterior

68h p.i.  44h p.i.  20h p.i.  3h p.i.  0.5h p.i.
**Dosimetry PSMA RLT**

9.2 GBq $^{177}$Lu PSMA-617

**Regions of Interest**

- **M1** Bone metastasis
- **M2** Lymph node metastasis
- **M3** Bone metastasis
- **M4** Bone metastasis
- **M5** Lymph node metastasis

**Planar**

**SPECT**

**Uptake**

- **Whole body**
  - Half-life in h: 42
  - Dose in mGy/MBq: 0.04
  - Dose in Gy: 0.3
- **Kidneys**
  - Half-life in h: 30
  - Dose in mGy/MBq: 0.5
  - Dose in Gy: 4.6
- **Parotid glands**
  - Half-life in h: 25
  - Dose in mGy/MBq: 0.8
  - Dose in Gy: 7.1
- **M1 (bone)**
  - Half-life in h: 51
  - Dose in mGy/MBq: 32
  - Dose in Gy: 292
- **M2 (lymph node)**
  - Half-life in h: 52
  - Dose in mGy/MBq: 4
  - Dose in Gy: 38
- **M3 (bone)**
  - Half-life in h: 40
  - Dose in mGy/MBq: 22
  - Dose in Gy: 204
- **M4 (bone)**
  - Half-life in h: 46
  - Dose in mGy/MBq: 51
  - Dose in Gy: 467
- **M5 (lymph node)**
  - Half-life in h: 49
  - Dose in mGy/MBq: 6
  - Dose in Gy: 52

**Results**

- C. Schuchardt
- THERANOSTICS Center for Molecular Radiotherapy
PSMA radioligand therapy (PRLT) at Zentralklinik Bad Berka

Worldwide 1st PRLT with $^{177}$Lu-PSMA I&T was performed at ZBB in April 2013

Large number of cycles with $^{177}$Lu-PSMA (I&T / 617) until November 2018

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients treated</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Total number of cycles administered</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Mean administered radioactivity per cycle</td>
<td>6.8 GBq</td>
</tr>
</tbody>
</table>

---

**Graph:**
- x-axis: No. of Lu-177 / Bi213 PRLT cycles
- y-axis: No. of patients
- Data points:
  - No. of patients: 57, 74, 76, 35, 19, 15, 8, 6, 1
  - Counts: 1, 2, 3, 4, 5, 6, 7, 8, 11

---

**Table:**
- Total number of patients treated: >300
- Total number of cycles administered: >1000
- Mean administered radioactivity per cycle: 6.8 GBq

---

THERANOSTICS Center for Molecular Radiotherapy, Zentralklinik Bad Berka
### Lu-177 PRLT at Zentralklinik Bad Berka – n=274 patients

#### Distribution of metastases visualized on $^{68}$Ga PSMA PET/CT

<table>
<thead>
<tr>
<th>Site of metastases</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone/Bone Marrow</td>
<td>228</td>
</tr>
<tr>
<td>Lymph node</td>
<td>209</td>
</tr>
<tr>
<td>Lung</td>
<td>36</td>
</tr>
<tr>
<td>Liver</td>
<td>34</td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>- mediastinal</td>
<td></td>
</tr>
<tr>
<td>- peritoneal</td>
<td></td>
</tr>
<tr>
<td>- pleuropericardial</td>
<td></td>
</tr>
<tr>
<td>- testicular</td>
<td></td>
</tr>
<tr>
<td>- adrenal</td>
<td>85</td>
</tr>
</tbody>
</table>

#### Bone
- bone only: 41
- bone + LN: 75
- bone + LN + other: 112

#### LNM
- LN only: 30
- LN + other: 179

THERANOSTICS Center for Molecular Radiotherapy, Zentralklinik Bad Berka
Prostate adenocarcinoma

Extensive dissemination of disease post ADT and EBRT

Indication for Lu-177 PRLT
Nov 2015

PD on ADT and after EBRT to LNM

PSA 45 ng/ml

CR after 2 cycles Lu-177 PSMA RLT

Nov 2016

2 cycles of Lu-177 PRLT

PSA 0.00 ng/ml

Apr 2017

mCRPC, GS 8
Post Sx, pelvic RT

Oncologist recommenced ADT & EBRT to LNM

PSA 4.6 ng/ml

PD on ADT and after EBRT to LNM

CR after 2 cycles Lu-177 PSMA RLT
### Clinical course of disease – Lu-177 PRLT

<table>
<thead>
<tr>
<th></th>
<th>PRLT – 01 (Dec 2016)</th>
<th>PRLT – 02 (Feb 2017)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRLT 1</td>
<td>Excellent uptake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in disseminated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>skeletal metastases</td>
<td></td>
</tr>
<tr>
<td>PRLT 2</td>
<td>Complete resolution</td>
<td></td>
</tr>
<tr>
<td></td>
<td>of known skeletal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>metastases</td>
<td></td>
</tr>
</tbody>
</table>

**PRLT 1**
- Excellent uptake in disseminated skeletal metastases

**PRLT 2**
- Complete resolution of known skeletal metastases
Clinical course of disease – persistent biochemical response

PSA decrease by 100%

---|---|---|---|---
PSA (ng/ml) | 32.43 | 51.62 | 0.0 | 0.0
Time-point | Pre-PRLT-01 | Post-PRLT-01 | RST | Pre-PRLT-02 | Post-PRLT-02

PSA (ng/ml)

TRC

2017-HV-472593
Any PSA decline was observed in 146/208 (70%) patients, best response was biochemical complete remission (PSA=0.0 ng/ml).

Decrease in PSA by more than half was observed in 106 (53%) patients.
## Clinical course of disease – laboratory parameters

### No hematotoxicity

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood counts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>mmol/l</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
<td>8.3</td>
</tr>
<tr>
<td>WBC</td>
<td>Gpt/l</td>
<td>4.3</td>
<td>5.7</td>
<td>4.2</td>
<td>4.6</td>
</tr>
<tr>
<td>PLT</td>
<td>Gpt/l</td>
<td>232</td>
<td>223</td>
<td>227</td>
<td>225</td>
</tr>
</tbody>
</table>

| **Renal function test** |       |            |            |            |            |
| Urea        | mmol/l| 5.3        | 5.1        | 7          | 6.6        |
| Creatinine  | μmol/l| 58.4       | 64         | 71.9       | 67         |
| eGFR        | ml/min/1.73m² | >60       | >60        | >60        | >60        |

### No nephrotoxicity

---

2017-HV-472593
Safety of $^{177}\text{Lu-PSMA-617}$ radioligand therapy in metastatic castration-resistant prostate cancer patients with a single functioning kidney
Creatinidine at baseline and after each therapy - no CTCAE-3 or 4 was observed.
Lu-177 PRLT- Safety

- $^{177}$Lu-PSMA radioligand therapy was *tolerated very well* by the patients with no severe acute or long-term adverse events.
- Short-lasting mild fatigue is the most common immediate side effect.
- Long-term side effects are relatively mild with *xerostomia* <3 % of the patients (transient in in about 5 – 10 %)
- G3-4 hematological toxicities were reported in 2 – 5 % of the patients undergoing PRLT.

*Baum et al., Okamoto et al., Kulkarni et al., Kabasakal et al., Delker et al., Kratochwil et al., Hohberg et al., Scarpa et al., von Eyben et al.*
Safety analysis - Hematological effects of PRLT (n = 223)

**ANEMIA**

<table>
<thead>
<tr>
<th>(CTCAE v4.03)</th>
<th>G0*</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-PRLT</strong></td>
<td>44</td>
<td>144</td>
<td>32</td>
<td>3</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Post-PRLT</strong></td>
<td>19</td>
<td>143</td>
<td>54</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

G0*, Normal reference range; NA, Not applicable
Safety analysis - Hematological effects of PRLT (n = 223)

LEUKOCYTOPENIA

No. of patients (n)

<table>
<thead>
<tr>
<th>G0*</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PRLT</td>
<td>184</td>
<td>19</td>
<td>7</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Post-PRLT</td>
<td>174</td>
<td>29</td>
<td>10</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

G0*, Normal reference range; NA, Not applicable

(CTCAE v4.03)
Safety analysis - Hematological effects of PRLT (n = 223)

**THROMBOCYTOPENIA**

<table>
<thead>
<tr>
<th>(CTCAE v4.03)</th>
<th>G0*</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
<th>G4</th>
<th>G5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PRLT</td>
<td>190</td>
<td>20</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td>Post-PRLT</td>
<td>160</td>
<td>45</td>
<td>12</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

G0*, Normal reference range; NA, Not applicable
Survival benefit from currently recommended chemotherapy, hormonal therapy and alpharadin therapy

- Docetaxel: 2.5 Mo
- Cabazitaxel: 2.4 Mo
- Abiraterone: 3.9 Mo
- Enzalutamide: 4.8 Mo
- Radium 223: 3.6 Mo
Kaplan–Meier curves for progression-free survival (PFS) months from start of PRLT (n=254)

PFS for all patients

Median progression-free survival 9.8 months

# censored subjects 99
# deaths/events 155

Median survival 9.8 m
Kaplan–Meier curves for overall survival (OS) months from start of PRLT (n=254)

OS for all patients

Median overall survival: 31 months

# deaths/events 96

Median survival 30.8667

96/254 (37.8%) patients died (median follow-up 22.3 months)
Survival data from $^{177}$Lu-PRLT at 55 months

Influence of previous chemotherapy (CTx)

- Median OS without previous CTx: 38 months, $n = 114$
- Median OS after previous CTx: 19 months, $n = 110$

Cumulative survival

- No CTx: $n = 114$
- CTx: $n = 110$

$\text{p} \leq 0.05$

Early initiation of $^{177}$Lu-PSMA radioligand therapy is effective in mCRPC and may offer a significant survival benefit.

Randomized controlled studies are required to best determine the place of PRLT.
• 62 year old internist
• Partially neuroendocrine differentiated, hormone-refractory adenocarcinoma of the prostate
• Presented in Feb. 2016 with severe pain, had to give up his practice, refused Chx
• Locally recurrent disease, pelvic lymph node & disseminated bone metastases

**Persistent CR 30 months after start of PRLT**

Feb. 2016
PSA 356 ng/ml

PRLT-1

PRLT-2

PRLT-3

July 2018
PSA 0.00 ng/ml

Quality of Life (QoL): Restarted his practice as a doctor and is doing regular sports
De novo Radioligand Therapy using $^{177}$Lu-labeled PSMA Small Molecules in Patients with Metastatic Prostate Cancer

No. 529
11:00 AM
Early initiation of Lu-177 PSMA radioligand therapy prolongs overall survival in metastatic prostate cancer
(http://www.abstractsonline.com/pp8/#!/4627/presentation/2212)
https://webmobile.experimentengage.com/~SNM181/?navItemNumber=13272#/?eventItem/62220 2/4


Harshad R. Kulkarni, MD, Christiane Schuchardt, AVIRAL SINGH, MD, MSc, Thomas Langbein, Richard P. Baum, MD, PhD. THERANOSTICS Center for Molecular Radiotherapy, Zentralklinik Bad Berka, Bad Berka, Germany.
Gleason 8 mPC with PSMA-avid primary and multiple LN as well as peritoneal metastases (no prior therapy)

Partial remission of primary tumor and metastases after 1st line (de novo) Lu-177 PSMA Radioligand Therapy
225 Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study

Mike Sathekge¹ • Frank Bruchertseifer² • Otto Knoesen³ • Florette Reyneke¹ • Ismaheel Lawal¹ • Thabo Lengana¹ • Cindy Davis¹ • Johncy Mahapane¹ • Cecelia Corbett¹ • Mariza Vorster¹ • Alfred Morgenstern¹,²
Targeted Alpha Therapy for Prostate Cancer

April 2017
PSA = 1300.69 ng/ml

September 2017
PSA <0.05 ng/ml

Excellent Response
Soft tissue Mets

2 x
\(^{225}\text{Ac-PSMA}\)

No Photoshop used!

Courtesy: Mike Sathekge, Pretoria
Targeted Alpha Radiation Therapy (ART)

- α mass is 7000 x that of β
- α 's energy is 30 x that of β (typically 6 MeV versus 200 keV)
- Linear Energy Transfer (LET) ~100 times greater than β
- The effective range of α particles in tissue is approx 5 cell diameters (hundreds/thousands for β particles)
In hormone-responsive cancers, appropriate endocrine modification results in catastrophic effects on cancers of several kinds in man and animals, even in those in the terminal stages of the disease. Of course, there ensues pari passu improvements in the host’s condition.

The results are often spectacular.

The benefit can be evident within a few hours after the intervention...

The first revolution in the treatment of prostate cancer
Andrew Schally *1926  (Nobel Prize for the detection of neuropeptides in 1977) at his home in Miami, June 2012.
CR of liver mets under ADT with Bicalutamide & Degarelix – GnRh-Antagonist
The second revolution in the treatment of prostate cancer!

- 12/2014
  PSA = 2,923 ng/mL

- 7/2015
  PSA = 0.26 ng/mL

- 9/2015
  PSA < 0.1 ng/mL
Figure 6: Swimmer-Plot: Duration of tumor control in months (A), and relative to the duration of previous treatment lines (B).
Translation to Theranostic using PSMA-Radioligands

Suppressing SG metabolism to achieve lower uptake:

- high safety and feasibility
- commonly used to treat severe sialorrhea (even in children)

Multifocal ultrasound-guided injections of 80 units of botulinum toxin A to the right parotid gland of a 63-year-old patient with mCRPC:

Dynamic salivary gland scintigraphy - Baseline

Injection of Botulinum Toxin for Preventing Salivary Gland Toxicity after PSMA Radioligand Therapy: an Empirical Proof of a Promising Concept

Richard P. Baum 1 · Thomas Langbein 1 · Aviral Singh 1 · Mostafa Shahinfar 1 · Christiane Schuchardt 1 · Gerd Fabian Volk 2 · Harshad Kulkarni 1

Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s13139-017-0508-3
mCRPC GS 9, s.p. Docetaxel, Cabazitaxel and Enzalutamide

Progression under Lu-177 PSMA radioligand therapy

TANDEM PRLT (Lu-177 + Ac-225)

THERANOSTICS Center for Molecular Radiotherapy, Zentralklinik Bad Berka

Remission after TANDEM PRLT (4.5 GBq $^{177}$Lu plus 5 MBq $^{225}$Ac)
PSMA-based Radioligand Therapy (PRLT)

- Effective in end-stage disease (tumor regression, even achieving CR as last line in some patients)
- Significant improvement of clinical symptoms and Karnofsky Performance Status
- Prolongs progression-free survival (PFS)


- Very likely to provide a substantial survival benefit for patients after all conventional therapy options


- Excellent tolerability in nearly all patients treated
  - No or minimal hematotoxicity in chemotherapy-naive patients
  - No nephrotoxicity, low rate (<3%) of persistent salivary gland toxicity
- Patient selection and response to therapy assessment after PRLT using Ga-68 PSMA PET/CT (Theranostics Concept)

**Future perspectives:**
- Combination of Lu-177 + Ac-225 – TANDEM Alpha Radiation Therapy (ART)
- New diagnostic probes (F-18 rhPSMA)
- New therapeutic radionuclides and combination with other treatments
- Prospective clinical trials have started in 2018 (TheraP Study/Australia, Vision Trial / Endocyte)
High activity, pain reduction and low toxicity with $^{177}$Lu-PSMA-617 theranostics in metastatic castrate-resistant prostate cancer (mCRPC): results of a phase II prospective trial

Uro-oncology Tumour Multidisciplinary Team,
Peter MacCallum Cancer Centre, Melbourne, Australia

Waterfall plot of PSA response

- Red: <30%
- Orange: ≥30%
- Blue: ≥50%

= 62%
(95% CI 47-75)

8 pt with PSA decline ≥ 99%. PSMA PET baseline and post $^{177}$Lu-PSMA617

Hofman MS, Violet J … Sandhu S, Lancet Oncology 2018
Hofman MS, et al, SNMMI 2018
TheraP Study

A randomised phase 2 trial of $^{177}$Lu-PSMA$_{617}$ theranostic versus cabazitaxel in progressive metastatic castration resistant prostate cancer
THERANOSTICS AND PRECISION MEDICINE SPECIAL FEATURE: REVIEW ARTICLE

Theranostics of prostate cancer: from molecular imaging to precision molecular radiotherapy targeting the prostate specific membrane antigen

HARSHAD R KULKARNI, MD, AVIRAL SINGH, MD, THOMAS LANGBEIN, MD, CHRISTIANE SCHUCHARDT, Dipl.-Ing., DIRK MUELLER, PhD, JINGJING ZHANG, MD PhD, COLINE LEHMANN, MD and RICHARD P BAUM, MD PhD

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• Marion de Jong, Rotterdam
• Eric Krenning, Rotterdam

• Jean-Claude Reubi, Bern
• Stefan Schulz, Jena
• Amelie Lupp, Jena
• Andrew Schally, Miami
• Gerd Binnig, Munich
• Philippe Lambin, Maastricht
• Anthony Chang, Grand Rapids

• Ralph Wirtz, Cologne
• Matthias Blaickner, Seibersdorf
• Lisa Bodei, Milano / New York
• Irvin Modlin, Yale University

• Martin Pomper, Baltimore
• Richard Wahl, St. Louis

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• Christiane Schuchardt
• Karin Niepsch
• Daniel Kämmerer
• Dieter Hörsch
• Merten Hommann

• Dinse-Foundation, Hamburg
• Patients (esp. Josh Mailman) and many others...
Thank you for your attention!
“Anyone who stops learning is old, whether at 20 or 80. Anyone who keeps learning stays young. The greatest thing in life is to keep your mind young.”

*Henry Ford* (1863 – 1947)