PSMA Targeted radionuclide therapy in Prostate Cancer

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Radionuclide therapy

* cell size ~20 µm
Radionuclide therapy

* cell size ~20 µm

**Diagram:**

- **Prostate cancer cell**
  - **PSMA**
  - **Ligand** on tumor cell
  - **Antibody**
  - **Inhibitor**

*PSMA* on tumor cell

*PSMA* on tumor cell
Radionuclide therapy

- Radionuclide therapy
- Radionuclide

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Particle</th>
<th>Mean beta energy (keV)</th>
<th>Max tissue penetration (~number of cells)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yttrium-90</td>
<td>Beta</td>
<td>935</td>
<td>12 mm (~600)</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>Beta, Gamma</td>
<td>190</td>
<td>2 mm (~100)</td>
</tr>
<tr>
<td>Lutetium-177</td>
<td>Beta, Gamma</td>
<td>130</td>
<td>2 mm (~100)</td>
</tr>
<tr>
<td>Actinium-225</td>
<td>Alpha</td>
<td></td>
<td>50-100 µm (2-3 cells)</td>
</tr>
</tbody>
</table>

* cell size ~20 µm
PSMA-targeted radionuclide therapy

- 90Y J591 phase I trial, New York, USA
  - 29 patients: 2 ↓PSA, 6 stabilized

- 177Lu J591 phase II study, New York, USA
  (Clin Cancer Res. 2013;19:5182–5191)
  - 47 patients: 60% ↓PSA
PSMA-targeted radionuclide therapy

- I-131 MIP-1095
  - Zechmann CM, et al. (2014), Heidelberg, Germany
  - 28 pts mCRPC, 1 dose administration
    - 75% any ↓ PSA
    - 61% > 50% ↓ PSA

PSMA-targeted radionuclide therapy

- 177Lu PSMA617
  - Ahmadzadehfar H, et al. (2016), Bonn, Germany
  - 24 pts with hormone and chemotherapy refractory
  - Median PSA = 522 ng/ml

Oncotarget. 2016;7:12477–12488
PSMA-targeted radionuclide therapy

PSA change from baseline at 8 weeks after the first cycle

79.1 %: any PSA decline
41.6 %: >50% PSA decline
PSMA-targeted radionuclide therapy

Ga68 PSMA

PSMA-targeted radionuclide therapy

Before Rx

After 2 doses

Ga68 PSMA
PSMA-targeted radionuclide therapy

Hematotoxicity

Nephrotoxicity

Hepatotoxicity

PSMA-targeted radionuclide therapy

- **177Lu PSMA617**
  - Rahbar K, et al. (2016), Münster, Germany
  - 28 pt with conventional therapy refractory
  - Total 50 treatment
  - After 2\textsuperscript{nd} dose
    - 75\% ↓ PSA
    - 50\% ↓ PSA >50%
  - Median survival 29.4 wk better than historical best supportive care of 19.7 wk

PSMA-targeted radionuclide therapy

PSMA-targeted radionuclide therapy

WBC: white blood cell, Hb: haemoglobin, Tx: Therapy, n.s.: not significant,
PSMA-targeted radionuclide therapy

- **177Lu PSMA617**
  - Baum RP, et al. (2016), Bad Berka, Germany
  - 56 patients
  - up to 5 treatments
  - Median PFS 13.7 months.
  - Survival after 28 months was 78.6%.
PSMA-targeted radionuclide therapy

- 70 yrs. mCRPC with l.n. metastasis

Before Rx 1st Lu-177 2nd Lu-177
PSMA-targeted radionuclide therapy

- 76 yrs. mCRPC with bone and l.n. metastasis
PSMA-targeted radionuclide therapy

• 177Lu PSMA617, Münster, Germany
  • 59 pt with end-stage mCRPC
  • Total 159 treatments (median 3, range 1-7)
    • 91% ↓ PSA
    • 53% ↓ PSA > 50%

• Median PSA progression-free survival 18 wk.
• Median overall survival 32 wk.
PSMA-targeted radionuclide therapy

- Predictor of longer OS
- PSA decline after 1st treatment (56 vs 29 wk. p=0.04)
- Baseline ALP < 220 U/L (56 vs 28 wk. p<0.01)
Predictors of Response: 177Lu PSMA-617

Ferdinandus J, et al. (2017), Bonn, Germany

40 patients

Parameters effect PSA response 2 mo after RLT

univariate analysis: parameter with negative impact
  - younger age (<65 yr)
  - regular need for pain medication
  - high GSC, high GGT, high CRP, high LDH,

multivariate analysis:
  - number of platelets
  - Regular need for pain medication
PSMA-targeted radionuclide therapy

- 78 yrs. with mCRPC

Before Rx  
After 2 cycles
PSMA-targeted radionuclide therapy

- 177Lu PSMA617
  - Hofman MS, et al. (2018), Melbourne, Australia
  - 1st prospective study, phase II, single-arm, single-centre
  - 30 pt with metastatic castration resistant who progressed after standard treatments

PSMA-targeted radionuclide therapy

- **177Lu PSMA617**
  - Hofman MS, et al. (2018), Melbourne, Australia
  - Up to 4 cycles of treatment
  - best PSA response:
    - 97% ↓ PSA
    - 70% ↓ PSA ≥ 30%
    - 57% ↓ PSA ≥ 50%
    - 37% > 10 points improve in health score (EORTC-Q30) after 2nd cycle
PSMA-targeted radionuclide therapy

PSA response after 12 wk.

Best PSA response from baseline
PSMA-targeted radionuclide therapy

- 3 months after last treatment

<table>
<thead>
<tr>
<th></th>
<th>Bone scintigraphy</th>
<th>Soft-tissue lesions (nodal and visceral; n=17)</th>
<th>PSMA PET</th>
<th>FDG PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>n/a</td>
<td>5 (29%)</td>
<td>3 (10%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>n/a</td>
<td>9 (53%)</td>
<td>9 (30%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11 (37%)†</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>9 (30%)</td>
<td>2 (12%)</td>
<td>8 (27%)</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>Not performed (clinical progression or death)</td>
<td>9 (30%)</td>
<td>0</td>
<td>9 (30%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Not performed (death from other cause)</td>
<td>1 (3%)</td>
<td>1 (6%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>

Data are n (%). The FDG PET refers to metabolic responses. PSMA = prostate-specific membrane antigen. *As assessed by Response Evaluation Criteria in Solid Tumors (version 1.1) with Prostate Cancer Clinical Trials Working Group 2 caveats. †Non-progressive disease on bone scintigraphy includes patients with complete or partial response or stable disease.

*Table 2: Imaging response at 3 months after last cycle of LuPSMA received*
PSMA-targeted radionuclide therapy

- 177Lu PSMA617
  - Hofman MS, et al. (2018), Australia
  - Up to 4 cycles of treatment:
    - PSA progression-free survival of 7 months
    - Median overall survival was 13.5 months
### PSMA-targeted radionuclide therapy

**Table 3: Treatment-emergent adverse events**

<table>
<thead>
<tr>
<th>Grade 1-2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 4 attributed to LuPSMA*</th>
<th>Grade 3 attributed to LuPSMA*</th>
<th>Grade 4 attributed to LuPSMA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>26 (87%)</td>
<td>0</td>
<td>0</td>
<td>26 (87%)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>12 (40%)</td>
<td>13 (43%)</td>
<td>0</td>
<td>11 (37%)</td>
<td>11 (37%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (40%)</td>
<td>5 (17%)</td>
<td>3 (10%)</td>
<td>8 (27%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16 (53%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>15 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (50%)</td>
<td>0</td>
<td>0</td>
<td>15 (50%)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>7 (23%)</td>
<td>7 (73%)</td>
<td>0</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12 (40%)</td>
<td>2 (7%)</td>
<td>0</td>
<td>8 (27%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Pain</td>
<td>8 (27%)</td>
<td>3 (10%)</td>
<td>0</td>
<td>5 (17%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (33%)</td>
<td>0</td>
<td>0</td>
<td>10 (33%)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>8 (27%)</td>
<td>0</td>
<td>0</td>
<td>7 (23%)</td>
<td>0</td>
</tr>
<tr>
<td>Dry eyes</td>
<td>5 (17%)</td>
<td>0</td>
<td>0</td>
<td>5 (17%)</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>3 (10%)</td>
<td>0</td>
<td>0</td>
<td>3 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oculomotor nerve disorder</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Spinal fracture</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n (%). Grade 1-2 adverse events occurring in ≥10% of the cohort and all grade ≥3 adverse events are presented. There were two grade 5 adverse events not attributed to LuPSMA: pneumonia (n=1), hepatic failure (n=1). LuPSMA=Lu isotopically labelled prostate-specific membrane antigen-617. *Possibly, probably, or definitely according to Common Terminology Criteria for Adverse Events.
Chula case: Lu-177 PSMA

1st dose
PSA (before) 117 -> 83 (7 wk after)

2nd dose
PSA (before) 83 -> 177 (8 wk after)
Chula case: Lu-177 PSMA

1st dose
PSA (before) 545->946 (8 wk after)

2nd dose
Conclusion for 177Lu-PSMA-617

- Convincing therapeutic response, both PSA level and radiologic findings.
  - 60-90% ↓ PSA
  - 30-50% ↓ PSA ≥ 50%
  - PFS 15-30 wks
  - OS 30-60 wks
- ~30% short / non-responders
- dose escalation was limited by hematological toxicity
Radiation

• β-beta particle
  • mass = electron
  • e.g. Lu-177
  • low LET (linear energy transfer)

• α-alpha particle
  • mass = 2 neutrons + 2 protons
  • e.g. Ac-225, Bi-213
  • high LET
PSMA-targeted radionuclide therapy

- 225Ac-PSMA617: Heidelberg, Germany
• 225Ac-PSMA617
• Kratochwil et al., Heidelberg, Germany
PSMA-targeted radionuclide therapy

- 225Ac-PSMA617
- Results:
  - 40 pts.
    - 2 died before 8 wk after 1st treatment
    - Of 38 pts.
      - Only 1 dose in 9: 5 non-response, 4 severe xerostomia
      - 33 (87%) ↓ PSA
      - 24 (63%) ↓ PSA > 50%
PSMA-targeted radionuclide therapy

• 225Ac-PSMA617
  • “Duration of Tumor Control” (not “time to PSA progression”)
    • 225Ac PSMA: “new clinical tumor-related symptoms” or “PSA relapse to baseline”
    • Other medication: first administration of a drug to initiation of the next treatment line
PSMA-targeted radionuclide therapy

• 225Ac-PSMA617

• Results:
  • 40 pts.
  • Of 38 pts.
    • median time tumor control 9.0 mo (5 pts. > 2 yrs.)
    • 1st-line: 8 mo. Abiraterone: 10.0 mo
    • 2nd-line: 7 mo. Docetaxel: 6.5 mo
    • 3rd-line: 6 mo. Enzalutamide: 6.5 mo
    • 4th-line: 4 mo. Cabazitaxel: 6.0 mo
PSMA-targeted radionuclide therapy

Abiraterone
Docetaxel
$^{225}$Ra
Enzalutamide
Cabazitaxel
$^{177}$Lu-PSMA617

$^{225}$Ac-PSMA617
Ongoing response at data analysis
Other (Estramustine, Mitomycin, Ketokonazole, Cabozantinib)
PSMA-targeted radionuclide therapy
PSMA-targeted radionuclide therapy

- 225Ac-PSMA617
- Pretoria, South Africa & Karlsruhe, Germany
- 17 advanced metastatic CA prostate (>10 metastatic foci), chemotherapy-naïve
  - 8 bone-only metastases
  - 3 l.n.-only metastases
  - 6 l.n. + bone metastases
  - 2 visceral metastases; 1 lung metastases, 1 brain + liver metastases.
PSMA-targeted radionuclide therapy

• Treatment was repeated every 8 weeks
  • 3/17 received only 2 cycles due to excellent response
    • Negative PSA and Ga-68 PSMA
  • 9/17 received 3 cycles
  • 5/17 received > 3 cycles
• at least 1 year follow up
PSMA-targeted radionuclide therapy

- PSA response after 1st cycle
  - 12/17 ≥80%
  - 1/17 ≥50%
  - 1/17 <50%
  - 3/17 increased
    - 2/3 ↓ at end of treatment
    - 1/3 not response after 3rd cycle

Eur J Nucl Med Mol Imaging. 2018 Sep 19
PSMA-targeted radionuclide therapy

• At the end of treatment
  • 14/17 PSA ↓ ≥90%
  • 11/17 complete resolution by 68Ga-PSMA11
  • treatment-naïve tend to respond better

• Follow-up
  • median follow-up period of 13 months
  • 14/17 alive at the time of the analysis
    • 7/14 remission (undetectable serum PSA)
    • 7/14 stable disease (serum PSA and 68Ga-PSMA11 PET/CT)
PSMA-targeted radionuclide therapy

progressed while on Zoladex

symptom-free on 11-month follow-up
PSMA-targeted radionuclide therapy

July 2017
PSA = 782 ng/ml

Sep 2017
PSA = 71 ng/ml

Nov 2017
PSA = 0.64 ng/ml

Jan 2018
PSA = 0.07 ng/ml

May 2018
PSA = 0.04 ng/ml

treatment-naïve

Decreased pain

symptom-free on 10-month follow-up
PSMA-targeted radionuclide therapy

April 2017
PSA = 33.84 ng/ml
Sx, EBT, ADT

August 2017
PSA = 68 ng/ml
improve

September 2017
PSA = 81 ng/ml
But new lesions

-> Chemo then die after 4 mo.
PSMA-targeted radionuclide therapy

**Graph a:**
- **Leucocyte count:**
  - Before treatment: 6.82
  - After treatment: 5.74

- **Haemoglobin:**
  - Before treatment: 12.05
  - After treatment: 11.3

**Graph b:**
- **Serum creatinine level:**
  - Before treatment: 104.35
  - After treatment: 116.29

- **Serum albumin level:**
  - Before treatment: 36.69
  - After treatment: 37.44
PSMA-targeted radionuclide therapy

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Review Article
Targeted α-therapy of prostate cancer using radiolabeled PSMA inhibitors: a game changer in nuclear medicine

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EDITORIAL

Why Targeting of PSMA Is a Valuable Addition to the Management of Castration-Resistant Prostate Cancer:
The Urologist’s Point of View

Boris A. Hadaschik¹ and Martin Boegemann²

¹Department of Urology, University Hospital Essen, Essen, Germany; and ²Department of Urology, University Hospital Münster, Münster, Germany
Currently, radioligand therapy using PSMA ligands is limited to the treatment of metastatic CRPC patients with progressive disease despite prior treatment with at least 2 lines of approved and endorsed strategies, according to multidisciplinary guidelines and/or objective exclusion criteria against the use of (as of yet not given) remaining options. However, because of the excellent toxicity profile of this new and promising therapeutic option, it is the clear desire of PC patients and patient organizations that it be made available now to patients with earlier stages of the disease; in these stages, patients might receive a superior benefit, a longer progression-free survival, and an improved quality of life, as they exhibit a better performance status and lower tumor burden. On the basis of existing observations and experiences, prospective multicenter studies with more homogeneous groups of metastatic CRPC patients are currently being planned in Germany.
PSMA-targeted radionuclide therapy

- Essential inclusion criteria (German Society of Nuclear Medicine)
  - non-resectable metastases
  - progression under guidelines therapy
  - detected PSMA expression of the tumor
  - reasonable hematological function
    - Leukocyte count > 2000/mm³
    - thrombocyte > 75,000/mm³
  - creatinine < 2 x upper standard limit
  - AST or ALT < 5 x upper standard limit
  - six-week interval with myelosuppressive therapy
Thank You
for
Your Attention