PEPTIDE RECEPTOR RADIONUCLIDE THERAPY IN NEUROENDOCRINE TUMOURS

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NEUROENDOCRINE TUMOURS (NETs)

Rare type of tumours (incidence 0.2/100,000)
Most frequently originated from gastrointestinal tract, pancreas and lungs
Can produce hormones (e.g. carcinoid syndrome)
 Majority of patients present with metastatic disease
5-year survival of approximately 50%

Dutch Guideline on Neuroendocrine Tumours Version 1.0 (Oncoline)
Somatostatin Receptor

- 5 subtypes (SSTR1-SSTR5)
- membrane bound
- via coupling with G-protein
- internalisation
- expression variable in tumours

- High sensitivity (>70%): GEP tumours, SCLC, paragangliomas, lymphomas, NBL, pheochromocytoma, granulomatous disease
- Intermediate sensitivity (50-70%): Breast cancer, thyroid cancer
THERAPY IN NET PATIENTS

Surgery is the only curative treatment!

Tsoli M, et al. Ther Adv Endocrinol Metab 2019, Vol 10:1-18. Reproduced under the terms of the Creative Commons Attribution, Attribution 4.0 International licence (CC BY 4.0; available at: https://creativecommons.org/licenses/by/4.0/; accessed Jul 2021).
PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

EMA approval for GEP NETs

Progressive disease after somatostatin analogues

Off-label use for other types of SSTR-positive tumours

Treatment goals:
- Improvement quality of life
- Tumour response
- Increase PFS/OS
NETTER-1: STUDY DESIGN

Multicentre, randomised phase III study, in patients with advanced SSTR-positive midgut NETs

Primary endpoint: Progression-free survival (PFS)

Secondary endpoints: Objective response rate (ORR), overall survival (OS), safety

NETTER-1 STUDY

Progression-free survival

79% lower risk of disease progression or death in the $^{177}$Lu-DOTATATE group than in the control group

Overall survival (interim analysis)

60% lower estimated risk of death in the $^{177}$Lu-DOTATATE group than in the control group (HR: 0.40; P=.004)

1/10 Ph 3 NETTER-1: 177Lu-DOTATATE vs. high-dose octreotide in patients with midgut NET, final OS data

→ mOS 48.0 vs. 36.3 mo (HR 0.84; p=0.30)

! This time, a Phase 3 trial does not show increased OS in NET

But...

! Crossover rate: 36%

Strosberg J, et al. abstract ASCO 2021. With permission from Prof J. Strosberg
NETTER-1

Safety data

Short-term toxicity: nausea (59%) and vomiting (47%), probably related to amino acid infusions

Low rates of grade 3 or 4 haematologic toxic effects

No evidence of renal toxicity

One patient (0.9%) was considered to have histologic changes consistent with myelodysplastic syndrome

<table>
<thead>
<tr>
<th>Lab abnormality*</th>
<th>All grades, %</th>
<th>Grades 3–4, %</th>
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<th>Grades 3–4, %</th>
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</thead>
<tbody>
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<td>¹⁷⁷Lu-DOTATATE + octreotide LAR 30 mg (n=111)</td>
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<tr>
<td>Lymphopenia</td>
<td>18</td>
<td>9</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Anaemia</td>
<td>14</td>
<td>0</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Leukopenia</td>
<td>10</td>
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<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<td>Octreotide LAR 60 mg (n=110)</td>
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<tr>
<td>Lymphopenia</td>
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PRRT AT ERASMUS MC

1992  $^{111}$In-octreotide therapy
1997  $^{90}$Y-DOTATOC and amino acids
2000  $^{177}$Lu-DOTATATE

2018  >1500 patients treated with $^{177}$Lu-DOTATATE
Median survival

In-111 Octreotide: 12 mo
(31 dead, 1 [3%] alive)

Y-90 OctreoTher: 36 mo
(34 dead, 24 [41%] alive)
P<0.001 vs In-111 Octreotide

Lu-177 Octreotate: >48 mo (?)
(55 dead, 319 [85%] alive)

Preliminary, many patients censored with short follow-up: not yet reliable!
INCLUSION CRITERIA

Pathology proven, inoperable tumour

Tumour uptake on $^{111}$In-DTPA-octreotide scintigraphy $\geq$ normal liver

No prior therapy with radiolabelled SSAs

Hb $\geq$ 6 mmol/L; WBC count $\geq$ 2 x $10^9$/L; platelet count; $\geq$ 75 x $10^9$/L; serum creatinine $\leq$ 150 umol/L

24-hr urine: clearance $>$ 50 mL/min

Karnofsky performance status $\geq$ 50

PATIENT SELECTION

Unpublished data from Erasmus MC.

Tumour Uptake on $^{111}$In-DTPA-Octreotide Scintigraphy
IMAGING WITH $^{68}$Ga-SSA PET/CT

$^{68}$Ga-SSA

PET-tracer

Higher affinity for the SSTR

1-day protocol

Uptake > liver

Images courtesy Jeroen Musch.
THE ROTTERDAM PROTOCOL

Granisetron or Ondansetron

4 cycles; 8-week interval
Hospitalisation 1 night

200 mCi

\(^{177}\)Lu-DOTATATE

2.5% arginine / 2.5% lysine

4 hours
(for renal protection)
CLINICAL PRACTICE

200 mCi $^{177}$Lu-DOTATATE in 100 mL

Images courtesy of Erasmus MC.
One venous access with two lines

\[ \text{\(^{177}\text{Lu-DOTATATE}\)} \text{ in 100 mL} \]

\[ \text{Pump for} \text{ \(^{177}\text{Lu-DOTATATE}\)} 200 \text{ mL/h} \]

\[ \text{Pump for amino acids 250 mL/h} \]

Amino acids

Images courtesy of Erasmus MC.
SUBACUTE HAEMATOXICITY

Haematotoxicity:¹

- Acute/reversible Any grade 3/4 in 9.5%
  - Risk: Age >70 years
  - Renal clearance <60 mL/min

In NETTER-1:²

- Grade 3–4 haematological toxicity occurred in <10% of patients receiving \(^{177}\text{Lu-DOTATATE + octreotide LAR 30 mg}\)

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HAEMATOXOTOXICITY

Grade 3 or 4 toxicity in 34 out of 320 patients\(^1\)

No relation with bone marrow dose\(^2\)

1. Bergsma H, et al. Eur J Nucl Med Mol Imaging 2016;43:453-463. Reproduced under the terms of the Creative Commons Attribution, Attribution 4.0 International licence (CC BY 4.0; available at: https://creativecommons.org/licenses/by/4.0; accessed Jul 2021);

LONG-TERM HAEMATOTOXICITY

Haematotoxicity MDS/acute leukaemia

- Sabet A, et al. 2013 n=203 3 x MDS/acute leukaemia¹
- Brabander T, et al. 2017 n=610 13 x MDS/acute leukaemia²

- Total 16/813 (2%)
RENAL AND LIVER FAILURE

Renal failure in 6 patients (1%) → probably not related to PRRT

- 1 patient hypotension after bleeding
- 1 patient hydronephrosis
- 4 patients dehydration

In NETTER-1, no evidence of renal toxic effects

No liver failure

Loss of renal function


Creatinine clearance in 323 patients after PRRT

Annual loss of renal function in 208 patients
HORMONAL CRISIS

Hormonal crisis 1% overall (6 out of 479 patients)\(^1\)

9% of functional pancreatic NETs\(^2\) and 10% of bronchial NETs

7% of PGL/PCC\(^3\)

Very rare in midgut NETs (0.4%)\(^1\)

Occurs up to 2 days after treatment

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### TUMOUR RESPONSE RATE

**Tumour Type** | **CR** | **PR** | **SD** | **PD** | **NE** | **Total**
---|---|---|---|---|---|---
Midgut | 2 (1%) | 55 (30%) | 99 (55%) | 16 (9%) | 9 (5%) | 181
Hindgut | 0 (0%) | 4 (33%) | 6 (50%) | 1 (8%) | 1 (8%) | 12
Pancreatic | 6 (5%) | 66 (50%) | 40 (30%) | 17 (13%) | 4 (3%) | 133
Bronchial | 0 (0%) | 7 (30%) | 7 (30%) | 6 (26%) | 3 (13%) | 23
Other foregut | 1 (8%) | 4 (33%) | 5 (42%) | 2 (17%) | 0 (0%) | 12
Unknown | 0 (0%) | 29 (35%) | 35 (43%) | 11 (13%) | 7 (9%) | 82
**Total** | 9 (2%) | 165 (37%) | 192 (43%) | 53 (12%) | 24 (5%) | 443

Best responses are listed, outcome according to RECIST 1.1
**SURVIVAL DATA**

<table>
<thead>
<tr>
<th>Tumour type</th>
<th>No of patients</th>
<th>PFS (months)</th>
<th>TTP (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midgut</td>
<td>181</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Hindgut</td>
<td>12</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>133</td>
<td>30</td>
<td>31</td>
</tr>
<tr>
<td>Bronchial</td>
<td>23</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>Other foregut</td>
<td>12</td>
<td>25</td>
<td>Not defined</td>
</tr>
<tr>
<td>Unknown</td>
<td>82</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td><strong>443</strong></td>
<td><strong>29</strong></td>
<td><strong>36</strong></td>
</tr>
</tbody>
</table>

**Cumulative survival (%)**

- Bronchus: 52 months (95% CI 49-55)
- Pancreas: 71 months (95% CI 56-86)
- Midgut: 60 months (95% CI 52-68)
- Unknown: 53 months (95% CI 44-62)
FACTORS PREDICTING MEDIAN OVERALL SURVIVAL

Liver metastases

- Median overall survival: 57 months
- No liver metastases: 119 months
- Hazard ratio 0.46 95% CI 0.34 to 0.62, p<0.001

Bone metastases

- Median overall survival: 47 months
- No bone metastases: 89 months
- Hazard ratio 0.56 95% CI 0.38 to 0.83, p<0.01

KPS

- Median overall survival:
  - <70: 27 months
  - 70: 50 months
  - 80: 65 months
  - 90: 81 months
  - 100: 91 months
  - p<0.01

Alkaline phosphatase

- Median overall survival:
  - ALP <120: 83 months
  - ALP >120: 47 months
  - Hazard ratio 0.45 95% CI 0.35 to 0.59, p<0.001

TTD in HRQoL was significantly longer in the $^{177}$Lu-DOTATATE group compared with the high octreotide arm (60 mg) in the following domains: global health, physical functioning, role functioning, diarrhoea, pain, body image, disease-related worries, and fatigue.

<table>
<thead>
<tr>
<th>Domain</th>
<th>HR (95% CI)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Global health status</td>
<td>0.41 (0.24-0.69)</td>
<td>0.001</td>
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<tr>
<td>Body image</td>
<td>0.43 (0.23-0.80)</td>
<td>0.006</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0.47 (0.26-0.85)</td>
<td>0.011</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>0.52 (0.30-0.89)</td>
<td>0.015</td>
</tr>
<tr>
<td>Disease-related worries</td>
<td>0.57 (0.36-0.91)</td>
<td>0.018</td>
</tr>
<tr>
<td>Pain</td>
<td>0.57 (0.34-0.94)</td>
<td>0.025</td>
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<tr>
<td>Role functioning</td>
<td>0.58 (0.35-0.96)</td>
<td>0.030</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.62 (0.40-0.96)</td>
<td>0.030</td>
</tr>
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</table>

ESMO GUIDELINE LUNG AND THYMIC CARCINOIDS

Metastatic lung or thymic carcinoid

TC
or slowly progressive carcinoids

Observation
SSAs [IV, C]
Locoregional therapies including surgery [IV, B]

AC
or significantly progressive carcinoids
or post-SSA therapy

Everolimus* [II, B]
Temozolomide-based ChT [IV, C]*

PPRT* [IV, B]
IFN-α* [IV, B]
Platinum-based ChT* [IV, C]

Baudin E, et al. Annals of Oncology 2021. © 2021 European Society for Medical Oncology. Published by Elsevier Ltd. All rights reserved.
OPTIMISING PRRT

- Superior radionuclides
- Improved SST2 ligands
- Increased SST2 levels
- Combination with immunotherapy
- Combination with targeted therapy
- Combination with DNA modulating agents

Brabander T, et al. ERC 2019. Used with permission of Bioscientifica Limited, from Endocrine-related cancer, Brabander T, et al. 26(8); 2019. permission conveyed through Copyright Clearance Center, Inc.
Only if PFS $\geq 18.0$ months from start of initial PRRT
2 extra cycles of $7.4$ GBq $^{177}$Lu-DOTATATE

Objective response in 16%
Stable disease in 60%

Median PFS 15 months from start retreatment
Overall survival 81 months (after first treatment)
No additional toxicity

OPTIMISING PRRT

Superior radionuclides

Improved SST2 ligands

Increased SST2 levels

Combination with targeted therapy

Combination with DNA modulating agents

Combination with immunotherapy

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PEPTIDE RECEPTOR RADIONUCLIDE THERAPY (PRRT)

Neuroendocrine tumour cell

Somatostatin receptor

DNA damage

Cell death

177Lu-DOTA-TATE

Healthy cell

No damage

Survival

Images courtesy of Dr Julie Nonnekens
COMBINATION THERAPY

PRRT

DNA damage

90%

Single strand breaks

Easily repaired

Not cytotoxic

10%

Double strand breaks

Not easily repaired

Cell death

Images courtesy of Dr Julie Nonnekens
COMBINATION THERAPY

PRRT

DNA damage

90%

10%

Replication

Single strand breaks

90%

10%

Double strand breaks

Easily repaired

Not easily repaired

Not cytotoxic

Cell death

PARP inhibition

Images courtesy of Dr. Julie Nonnekens
RESULTS

Cellular survival

![Graph showing cellular survival after PRRT and PRRT + PARPi treatment.](image)

- PRRT
- PRRT + PARPi

Level of DNA damage

![Graph showing level of DNA damage over time after PRRT and PRRT + PARPi treatment.](image)

- PRRT
- PRRT + PARPi

Figures adapted from: Nonnekens J, et al. Theranostics 2016;6(11):1821–32. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (CC-BY; available at: https://creativecommons.org/licenses/by/4.0/; accessed Sep 2021).
Optimising PRRT

Superior radionuclides

Improved SST2 ligands

Increased SST2 levels

Combination with targeted therapy

Combination with immunotherapy

Combination with DNA modulating agents

177Lu-DOTA-Octreotate

Hsp90

mTOR

PD-L1

PARP

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RADIONUCLIDES

Alpha and beta radiation for therapy

Alpha emission:
High ionising power
Short range
Stopped by paper

Beta emission:
Moderate ionising power
Moderate range
Stopped by 5 cm aluminium

RADIONUCLIDES

Bismuth-213:
- $^{213}$Bi-DOTATOC (Kratochwil C, et al. EJNMMI 2014)
- 7 patients with a response and favourable acute and mid-term toxicity

Lead-212:
- $^{212}$Pb-DOTAMTATE (Stallons T, et al. Mol Can Ther 2019)
- 79% of animals were tumour free after 31 weeks
- Phase 1 trial in patients is running

Erasmus MC will start with phase 1 dose escalation study $^{225}$Ac-DOTATATE in 2022

OPTIMISING PRRT

177Lu-DOTA-Octreotate

Superior radionuclides

Increased SST2 levels

Combination with targeted therapy

Improved SST2 ligands

Combination with immunotherapy

Combination with DNA modulating agents

Hsp90 mTOR PARP

Brabander T, et al. ERC 2019. Used with permission of Bioscientifica Limited, from Endocrine-related cancer, Brabander T, et al. 26(8); 2019. permission conveyed through Copyright Clearance Center, Inc.
ANTAGONIST

No internalisation

Higher tumour uptake

ANTAGONIST

$^{177}\text{Lu-DOTA-JR11}$ vs. $^{177}\text{Lu-DOTA-octreotad}$

4.4 higher radiation dose

Delay in tumour growth and longer median survival

Dalm SU, et al. JNM 2016. This research was originally published in JNM. Dalm SU, et al.. Comparison of the Therapeutic Response to Treatment with a $^{177}\text{Lu}$-Labeled Somatostatin Receptor Agonist and Antagonist in Preclinical Models. J Nucl Med. 2016, 57(2) 260-265. © SNMMI.
OPTIMISING PRRT

Superior radionuclides

Improved SST2 ligands

Increased SST2 levels

Combination with targeted therapy

Combination with immunotherapy

Combination with DNA modulating agents

Brabander T, et al. ERC 2019. Used with permission of Bioscientifica Limited, from Endocrine-related cancer, Brabander T, et al. 26(8); 2019. Permission conveyed through Copyright Clearance Center, Inc.
Epigenetic regulation is a mechanism of cells to regulate gene expression.

Epidrugs can induce epigenetic modification resulting in upregulation of the SSTR
- 5-aza-2'-deoxycytidine (5-aza-dC)
- Valproic acid (VPA)

In vitro uptake increased 3820% and 300% in different cell lines.

Clinical trial is running at EMC.

Veenstra MJ, et al. Oncotarget 2016;9(19):14791-14802. Reproduced under the terms of the Creative Commons Attribution, Attribution 4.0 International licence (CC BY 4.0; available at: https://creativecommons.org/licenses/by/4.0/; accessed Aug 2021).
RADIOEMBOLISATION

90Y-Microspheres

Radioembolisation
- Hepatocellular carcinoma
- Liver metastases of colorectal carcinoma

Glass spheres 20-30 μm / resin spheres 20-60 μm

90Y T1/2 64 hr, 3-11 mm tissue penetration
>150 Gy possible

**Y-MICROSPHERES**

**90Y-Microspheres**

Patient selection

- Good liver reserve
- Good bili, albumin, INR
- Patent function ampulla Vateri (abscess)
- No significant hepatopulmonary shunt
  - \(^{99m}\)Tc-MAA
- Portal vein thrombosis is no contraindication
HOLMIUM MICROSPHERES

$^{166}\text{Ho}}$-Microspheres

After $^{177}\text{Lu}}$-DOTATATE additional $^{166}\text{Ho}}$-spheres in NET patients

Objective response in 43% of patients

One patient with radioembolisation induced liver disease (fatal)


Images courtesy of Dr T Brabander, Erasmus MC.
Radiotherapists
Oncologist
Endocrinologist
Surgeons
Pathologists
Radiotherapists
Nuclear Medicine Physicians
Radiologists

TUMOURBOARD

Therapy
PRRT with $^{177}$Lu-DOTATATE has good results in terms of PFS and OS

Long term toxicity is limited and mostly haematological

All patients should be evaluated by an MDT, PRRT is always a multidisciplinary treatment

New developments in radioligands, receptor expression and combination therapy are expected
THANK YOU FOR YOUR ATTENTION