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First-in-human study of novel SSTR antagonist ^{177}Lu-DOTA-LM3 for peptide receptor radionuclide therapy in patients with metastatic neuroendocrine neoplasms: dosimetry, safety and efficacy

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ABSTRACT

The objective of this study was to assess the safety, dosimetry, and efficacy of the ^{177}Lu-labeled somatostatin receptor (SSTR) antagonist DOTA-p-Cl-Phe-cyclo (D-Cys-Tyr-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)D-Tyr-NH2 (^{177}Lu-DOTA-LM3) in patients with metastatic neuroendocrine neoplasms (NENs). **Methods:** Fifty-one patients (age 27–76, mean 51.6±13.9 years) with metastatic NENs underwent peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTA-LM3 between August 2017 and December 2019. The median administered activity per cycle was 6.1±0.88 GBq (range 2.8–7.4 GBq). ^{68}Ga-NODAGA-LM3 PET/CT was used for patient selection and follow-up after ^{177}Lu-DOTA-LM3 PRRT. Morphologic and molecular responses were evaluated in accordance with RECIST 1.1 and European Organization for Research and Treatment of Cancer (EORTC) criteria. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Dosimetry was performed in 11 patients and compared with the SSTR agonist ^{177}Lu-DOTATOC in 247 patients undergoing PRRT on the same dosimetry protocol. **Results:** Higher uptake and a longer effective half-life of ^{177}Lu-DOTA-LM3 was found for whole-body as well as kidneys, spleen, and metastases, resulting in higher mean absorbed organ and tumor doses as compared to the agonist ^{177}Lu-DOTA-TOC. All patients tolerated therapy without any serious acute adverse effects. Mild nausea without vomiting was observed in 5 (9.8%) patients; no other symptoms were reported. The most severe delayed adverse event was CTC-3 thrombocytopenia in 3 (5.9%) patients. Neither CTC-4 thrombocytopenia nor CTC-3-4 anemia or leukopenia was observed after treatment. No significant decline in renal function was observed, nor was hepatotoxicity. According to RECIST

1.1, disease control could be reached in 40 patients (disease control rate, 85.1%) of 47 patients monitored after ^{177}Lu-DOTA-LM3 PRRT, with a partial response in 17 (36.2%) and stable disease in 23 (48.9%), whereas 7 (14.9%) patients had progressive disease, and by EORTC criteria, complete remission in 2 (4.3%), partial remission in 21 (44.7%), stable disease in 18 (38.3%), and progressive disease in 6 (12.8%) patients. **Conclusion:** "Antagonist PRRT" with ^{177}Lu-DOTA-LM3 could be administered without severe adverse effects and was well tolerated by the majority of patients, with thrombocytopenia occurring only in a few patients. No other severe adverse effects were observed, particularly no nephrotoxicity. The SSTR antagonist ^{177}Lu-DOTA-LM3 appears to be very promising for PRRT, provides favorable biodistribution and higher tumor radiation doses than SSTR agonists, and was very effective in treating advanced metastatic NENs, especially in patients with low or no SSTR agonist binding, even achieving complete remission in some patients.

Key Words: Peptide receptor radionuclide therapy (PRRT); SSTR antagonist; ^{177}Lu-DOTA-LM3; first-in-human; neuroendocrine neoplasms (NENs)

INTRODUCTION

Neuroendocrine neoplasms (NENs) comprise a heterogeneous group of neoplasms arising from diffuse neuroendocrine system cells, and are most commonly found in the gastrointestinal tract, pancreas, and lung (*1-3*). Neuroendocrine neoplasms have been regarded as fairly rare diseases, but their incidence and prevalence have increased substantially in recent decades, partially because of improved diagnostic evaluation (*3-6*). The majority of NENs overexpress somatostatin receptors (SSTRs), making them accessible for radiodiagnostic and therapeutic approaches of NENs.

Over the past two decades, SSTR-targeted imaging (i.e., octreotide scintigraphy or SSTR PET) using radiolabeled somatostatin analogs followed by peptide receptor radionuclide therapy (PRRT) with these analogs labeled with β-emitters (e.g., ^{177}Lu or ^{90}Y) or, more recently, α-emitters (e.g., ^{213}Bi or ^{225}Ac) has demonstrated remarkable success in the management of neuroendocrine neoplasms (*7-10*). SSTR-targeted imaging particularly with ^{68}Ga-labeled somatostatin analogs for PET/CT plays an important role in the detection of the primary tumor, staging, restaging, assessment of treatment response of NENs (*11*), and furthermore, in the selection of patients who will qualify for and benefit from PRRT (theranostics). PRRT with therapeutic radioisotopes such as ^{90}Y or ^{177}Lu-labeled somatostatin analogs (DOTATATE or DOTATOC) has become an established treatment approach for patients with unresectable or metastatic, progressive, well-differentiated, SSTR-positive NENs (*12-15*). The significant benefit of PRRT over cold somatostatin analog therapy demonstrated by the randomized, controlled NETTER-1 trial (*16*) led to the approval of ^{177}Lu-DOTATATE (Lutathera) by both the European Medicines Agency and the U.S. Food and Drug Administration for the treatment of SSTR-positive gastroenteropancreatic neuroendocrine tumors in adults.

All SSTR-targeting radiopharmaceuticals described above and currently in clinical use are SSTR agonists, such as DOTATOC, DOTANOC, and DOTATATE. Agonists readily internalize into tumor cells, allowing tracer accumulation in the target cells. For a long time, it was believed that the process of internalization and subsequent accumulation of the radioligands in tumor cells was

essential for efficient SSTR-targeted imaging and therapy. However, recent developments have indicated that potent somatostatin receptor antagonists, known to poorly internalize into tumor cells, may be as good as, or even superior to, agonists for such purposes (*17-19*). Despite the fact that SSTR antagonists show no internalization, in vitro and in vivo data demonstrated higher tumor uptake with a higher tumor-to-background ratio and longer tumor retention time compared to the agonists, likely because a larger number of binding sites (receptor activation state) can be recognized by the antagonists than the SSTR agonists (*17*). This finding was confirmed by ex vivo autoradiography of patient-derived tumor samples, which demonstrated a more than four-fold increase on average in the tumor binding of the SSTR antagonist ^{177}Lu-DOTA-BASS as compared to the SSTR agonist ^{177}Lu-DOTA-TATE (*20*), suggesting that this binding may increase localization accuracy for tumors, but also increase the efficacy of radionuclide therapy with SSTR antagonists. The first clinical evaluation of SSTR antagonists confirmed the preclinical data, as it showed higher tumor uptake of the antagonist ^{111}In-DOTA-BASS and improved tumor-to-background ratios as compared to the agonist ^{111}In-DTPA-octreotide (*21*).

Among the recently developed somatostatin antagonists, several analogues, such as JR10 (DOTA-p-NO_2-Phe-c[D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2), JR11 (DOTA-p-Cl-Phe-c[D-Cys-Aph(Hor)-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2), and LM3 (DOTA-p-Cl-Phe-c[D-Cys-Tyr-D-Aph(Cbm)-Lys-Thr-Cys]-D-Tyr-NH_2) proved to have outstanding affinity, also using different macrocyclic chelating systems (e.g., DOTA and NODAGA) and various radiometals (e.g., ^{90}Y, ^{177}Lu, ^{64}Cu, and ^{68}Ga) (*22-24*). PET/CT with the somatostatin antagonist ^{68}Ga-NODAGA-JR11 detected significantly more metastases with higher tumor-to-background ratios than the SSTR agonist ^{68}Ga-DOTATOC (*25*). In a pilot study in 4 patients with advanced neuroendocrine tumors, the SSTR antagonist ^{177}Lu-DOTA-JR11 demonstrated a favorable biodistribution profile and increased tumor dose compared with the agonist ^{177}Lu-DOTATATE (*26*).

The aim of this first-in-human study was to explore the safety, dosimetry, and preliminary

efficacy of the novel ^{177}Lu-labeled SSTR antagonist ^{177}Lu-DOTA-LM3 in patients with metastatic neuroendocrine neoplasms. The kinetics and dosimetry of the antagonist ^{177}Lu-DOTA-LM3 was also compared with the SSTR agonist ^{177}Lu-DOTATOC in patients undergoing PRRT on the same dosimetry protocol.

MATERIALS AND METHODS

Patients

From August 2017 to December 2019, 51 patients (33 men and 18 women; age 27–76; mean age 51.6±13.9 years) with metastatic NENs met the eligibility criteria (histopathologically confirmed metastatic NENs with tumor uptake greater than normal liver parenchyma uptake on ^{68}Ga-1,4,7-triazacyclononane,1-glutaric acid-4,7-acetic acid-LM3 (^{68}Ga-NODAGA-LM3) PET/CT imaging, disease progression within 3–6 months prior to ^{177}Lu-DOTA-LM3 PRRT) for the study. Of these 51 patients, 26 (51%) had functioning tumors. In 37 patients, there was no or low SSTR2 agonist binding on baseline ^{68}Ga-DOTATOC or DOTATATE PET/CT, i.e., insufficient for agonist PRRT with DOTATOC or DOTATATE. ^{177}Lu-DOTA-LM3 was administered in compliance with the German Medicinal Products Act (section 13, subsection 2b), the 1964 Declaration of Helsinki, and the responsible regulatory body (Government of Thuringia). The study was performed in accordance with German regulations (Federal Agency for Radiation Protection) concerning radiation safety and was approved by the institutional review board. Written informed consent was obtained from all patients. The demographics of the patients at baseline are given in **Table 1**.

^{68}Ga-NODAGA-LM3 PET/CT Imaging

^{68}Ga-NODAGA-LM3 PET/CT was used for patient selection and follow-up after ^{177}Lu-DOTA-LM3 PRRT. PET/CT (Biograph mCT Flow 64; Siemens Medical Solutions AG) was performed 45–60 min after intravenous administration of ^{68}Ga-NODAGA-LM3 (mean activity = 285 MBq). All patients received 20 mg of furosemide intravenously to accelerate renal tracer excretion.

Contrast-enhanced CT (spiral CT using a Biograph mCT Flow 64) was acquired after intravenous administration of 60–100 mL of nonionic iodinated contrast agent.

Treatment regimen

^{177}Lu labeling of the DOTA-conjugated SSTR antagonists [DOTA-LM3] was performed in our radiopharmacy in accordance with good manufacturing practice (GMP) regulations. In brief, the DOTA-LM3 peptide was incubated with the required radioactivity of ^{177}Lu-Cl_3 at 90°C for 30 min in sodium acetate buffer (0.4 M, pH 5.5). To this buffer, 5–10 mg of gentisic acid was added to prevent radiolysis. Quality control parameters were monitored (radiochemical purity, radiochemical identity, pH value, ethanol content, endotoxin content, and proof of sterility). High-performance liquid chromatography was used for quality control. Radiochemical purity was more than 99% in all cases.

An in-house produced amino acid infusion (1600 mL of 5% lysine HCl and 10% L-arginine HCl) was administered for nephroprotection during each PRRT cycle at least 30 minutes pre-tracer administration and lasted for 4 hours. The radiopharmaceutical was co-administered by slow intravenous injection over 10–15 minutes with a dedicated second infusion pump system for radionuclide therapy. ^{177}Lu-DOTA-LM3 administered activity was individually calculated based on Bad Berka Score, tumor uptake on ^{68}Ga-NODAGA-LM3 PET/CT, renal function, hematologic status, previous treatments, and Karnofsky Performance Score (*13,27-29*). The interval between the treatment cycles was 10 weeks.

Post-therapy whole-body scintigraphy was performed with a SPIRIT DH-V dual-head gamma-camera (Mediso Medical Imaging Systems) using medium-energy general-purpose collimator, a 15% energy window with a peak at 208 keV, and a scan speed of 15 cm/min at 5 time points from 0.5 to 118 hours after injection. SPECT/CT imaging was obtained approximately 24 hours after injection.

Dosimetry

Dosimetry was performed in 11 patients in accordance with our protocol established from more than 1,000 patients with NENs undergoing PRRT (*13,30*) and compared with the SSTR agonist ^{177}Lu-DOTATOC in 247 patients undergoing PRRT on the same dosimetry protocol. Biodistribution was determined based on planar whole-body scans and SPECT/CT, and dosimetric calculations were performed using OLINDA software (MIRD Scheme). To analyze kinetics, we used the following parameters: effective half-life (in hours) and uptake (% IA, fraction of injected activity), which were calculated using the fit of the time-dependent activity curve to a mono- or bi-exponential function.

Safety

All patients were clinically monitored during therapy and for at least 2–4 days thereafter as inpatients for possible side effects (such as nausea, vomiting, breathlessness, and fatigue). Vital parameters were recorded during therapy and a structured questionnaire documented any delayed complication. Laboratory analysis including hematologic status, renal function, and liver function was performed before and after ^{177}Lu-DOTA-LM3 PRRT as well as during follow-up (restaging was performed regularly until death). Details were prospectively documented in a structured database (comprising over 250 items per patient). Renal function was further quantified by measuring the tubular extraction rate (TER) using ^{99m}Tc-MAG3 renal scintigraphy. Treatment-related adverse events were recorded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Response Assessment

Molecular and morphologic responses were evaluated in accordance with European Organization for Research and Treatment of Cancer (EORTC) criteria (*31-34*) and Response Evaluation Criteria in Solid Tumors (RECIST 1.1) (*35*), respectively. Imaging was performed before each PRRT cycle

and at restaging. The disease control rate (DCR) was defined as complete remission, partial remission, and stable disease.

Statistical Analysis

Continuous variables were denoted as mean ± standard deviation. The rates of adverse events at baseline and at the end of treatment were compared. Differences between paired samples before and after treatment were determined by Student t-tests. For all variables that were proven with the Kolmogorov-Smirnov test to follow the skewed distribution, quantitative data were described in terms of median and range, and nonparametric sign tests were used to determine the significance of differences between parameters before and after treatment. Fisher's exact test was performed to compare treatment response rates. All statistical tests were two-tailed, and a P value of less than 0.05 was considered statistically significant.

RESULTS

^{177}Lu-DOTA-LM3 Scintigraphy After Therapy

A total of 92 PRRT cycles of ^{177}Lu-DOTA-LM3 were administered. The median administered activity per cycle was 6.1±0.8 GBq (range 2.8–7.4 GBq). The peptide mass administered per cycle was 218±80 μg. At the time of analysis, follow-up for a median of 17.0 months (range, 1–29 months) after 2 or more therapy cycles was available for 26 patients. All PRRT-naïve patients received at least 2 cycles of ^{177}Lu-DOTA-LM3 treatment. Treatment cycles and cumulative radioactivity are summarized in **Table 2**.

Excellent uptake of ^{177}Lu-DOTA-LM3 in the tumor lesions as well as significant uptake in the kidneys, spleen, and liver was observed on post-therapy planar and SPECT/CT images (**Fig. 1**). The radiopharmaceutical was predominantly excreted through the kidneys.

Dosimetry

Whole-body clearance of the tracer was rapid, with an effective half-life of 56–93 hours. The maximum renal uptake at 20 h p.i. was 15% IA (mean 7% IA) and showed a wash-out with an effective half-life of 47–159 hours. The highest uptake in the spleen was observed at 3 h p.i. with 5% IA, exhibiting an exponential decline with an effective half-life of 74–156 h. The liver also demonstrated moderate uptake at 20 h p.i., up to 7% IA and a half-life of 67–75 hours. Concerning the radiation dose delivery of ^{177}Lu-DOTA-LM3 to NEN lesions, the maximum uptake at 20 h p.i. was 11.9% IA for liver metastases and 1.3% IA for bone metastases. All tumor lesions followed an exponential decline with a long mean effective half-life of 111 hours.

Dosimetry results from 11 patients treated with 5.9±1.2 GBq ^{177}Lu-DOTA-LM3 were analyzed. The whole-body absorbed doses were 0.12±0.03 Gy/GBq (0.07–0.18 Gy/GBq). Calculated radiation-absorbed doses of normal organs were 2.3±0.9 Gy/GBq (0.5–3.6 Gy/GBq) for kidneys, 0.39±0.05 Gy/GBq (0.35–0.44 Gy/GBq) for the liver, and 3.4±1.6 Gy/GBq (1.2–5.4 Gy/GBq) for the spleen. Mean absorbed doses to bone lesions were 1–57 Gy/GBq, and 15–81 Gy/GBq for liver lesions (**Fig. 2**).

The kinetics and dosimetry of ^{177}Lu-DOTA-LM3 were also compared with 247 NEN patients receiving 7±1 GBq ^{177}Lu-DOTATOC in our center applying the same dosimetry protocol. ^{177}Lu-DOTA-LM3 showed a longer whole-body effective half-life (76 h) compared to ^{177}Lu-DOTATOC (54 h) and the same was true for kidneys (LM3 92 h, TOC 67 h) and spleen (LM3 97 h, TOC 79 h), as well as for metastases (LM3 111 h, TOC 81 h). Due to the longer effective half-life and higher uptake, mean absorbed organ and tumor doses were higher for ^{177}Lu-DOTA-LM3—whole body: TOC 0.04 Gy/GBq, LM3 0.12 Gy/GBq; kidneys: TOC 0.6 Gy/GBq, LM3 2.3 Gy/GBq; spleen: TOC 0.8 Gy/GBq, LM3 3.4 Gy/GBq; and tumor: TOC 10 Gy/GBq, LM3 51 Gy/GBq. Hepatic metastases, as compared to osseous lesions, demonstrated the highest uptake and longest effective half-life for ^{177}Lu-DOTA-LM3 therapy (0.14%IA/ml and 110 h). The highest tumor dose was therefore estimated for liver metastases in the case of ^{177}Lu-DOTA-LM3 (TOC 12 Gy/GBq,

LM3 93 Gy/GBq) (**Fig. 3**).

Safety

All patients tolerated the therapy without any serious acute adverse effects. Mild nausea without vomiting was observed in 5 patients (9.8%); no other symptoms or clinically significant adverse effects were noticed or reported by any patient during hospitalization for therapy or follow-up for 29 months.

The most severe delayed adverse event was CTC-3 thrombocytopenia in 3 (5.9%) patients; however, no bleeding occurred and no thrombocyte infusions were necessary. CTC-3 lymphopenia was reported in 1 (2.0%) and 4 (7.8%) of patients before and after ^{177}Lu-DOTA-LM3 treatment, respectively. No CTC-4 thrombocytopenia or lymphopenia was observed. No CTC 3-4 anemia, neutropenia or leukopenia was observed after treatment (**Table 3**). There was a statistically significant reduction in leukocyte counts (before therapy: 7.04±2.18, median (IQR) of 6.3 (5.4, 8.4); after therapy: 5.81±2.21 Gpt/l, median (IQR) 5.1 (4.5, 6.5) Gpt/l; $P<0.05$), neutrophil counts (before therapy: 4.67±1.93, median (IQR) of 4.2 (3.2, 5.7); after therapy: 4.08±1.95 Gpt/l, median (IQR) 3.2 (2.7, 4.0) Gpt/l; $P<0.05$), lymphocyte counts (before therapy: 1.16±0.64, median (IQR) of 1.2 (0.9, 1.6); after therapy: 0.87±0.46 Gpt/l, median (IQR) 0.9 (0.7, 1.1) Gpt/l; $P<0.05$), and platelet counts (before therapy: 232±104 Gpt/l, median (IQR) of 225 (178, 250); after therapy: 192±70 Gpt/l, median (IQR) 182 (144, 225) Gpt/l; $P<0.05$). A statistically significant reduction occurred in hemoglobin level (7.74±0.99 vs. 7.46±1.00 mmol/l, $P<0.05$), although the absolute differences were minimal and clinically insignificant (**Fig. 4**).

There was no evidence of any nephrotoxicity during the observed time frame (median follow-up time, 17 months). No statistically significant change in serum creatinine levels was observed (from 88.17±37.2 to 87.11±37.9 μmol/l, $P>0.05$). We further compared the change in TER for renal function evaluation before and after treatment. Slightly decreased TER values were noted in 21/46 (45.7%) of patients treated with ^{177}Lu-DOTA-LM3, whereas 25/46 (54.3%) of

patients showed improvement after treatment. No statistically significant change occurred in TER (before therapy: 168±65; after therapy: 171±56; P>0.05) (**Fig. 4**). No hepatotoxicity was observed.

Efficacy of ^{177}Lu-DOTA-LM3 PRRT

Of the 55 patients recruited, response evaluation was possible in 47 patients. The majority were evaluated after two cycles of treatments. Among those patients who were evaluated after one cycle of treatment, 6 patients received only one cycle of ^{177}Lu-DOTA-LM3 treatment due to the progression of disease, 15 patients were either previously treated with agonist PRRT and planned at restaging after one cycle of ^{177}Lu-DOTA-LM3 PRRT or switched to other treatment modalities. After ^{177}Lu-DOTA-LM3 PRRT, a morphologic response assessment (RECIST 1.1) was documented by contrast-enhanced CT or MRI: partial remission in 17 (36.2%), stable disease in 23 (48.9%), and progressive disease in 7 (14.9%) patients, and by molecular response evaluation based on EORTC criteria: complete remission in 2 (4.3%), partial remission in 21 (44.7%), stable disease in 18 (38.3%), and progressive disease in 6 (12.8%) patients. An example is shown in **Fig. 5**. The disease control rate at 3–6 months after PRRT was 85.1% according to RECIST 1.1, and 87.2% based on EORTC criteria. The treatment responses are shown in **Table 4**.

DISCUSSION

To our knowledge, to date, this is the first study to evaluate the ^{177}Lu-labeled SSTR antagonist DOTA-LM3, and represents the largest cohort of patients with metastatic NENs treated with PRRT using an SSTR antagonist. This study comprised patients with progressive, heavily pretreated disease—in particular, 68.6% were previously treated with the ^{177}Lu-DOTATOC/TATE agonist PRRT—with any grade of NENs. Antagonist ^{177}Lu-DOTA-LM3 PRRT resulted in excellent tumor response with a disease control rate of 85.1%.

The renal absorbed dose of ^{177}Lu-DOTA-LM3 was noticeably higher than that of the patient cohort receiving ^{177}Lu-DOTATOC in our center under the same dosimetry protocol. Our results

were also consistent with the SSTR antagonist exhibiting higher renal uptake and a higher absorbed renal dose than the SSTR agonist, as reported by Wild et al. (^{177}Lu-DOTA-JR11 vs. ^{177}Lu-DOTA-TATE, 1.8 vs. 1.2 Gy/GBq) (*26*) and by Nicolas et al. in a preclinical model (*36*).

Kidney was considered one of the main organs at risk and the dose-limiting organ in PRRT using SSTR agonists. Accordingly, potential renal adverse effects could be expected in patients treated by SSTR antagonists. However, in this study, despite the longer effective half-life and higher uptake of ^{177}Lu-DOTA-LM3, no nephrotoxicity was observed during any cycle of ^{177}Lu-DOTA-LM3 or on follow-up. No grade 3/4 renal insufficiency occurred. Four patients with previous grade 2 renal insufficiency did not experience worsening of renal function, and two even showed an improvement in renal function after treatment (one grade, one with normal index), which was likely explained by ending other treatment modalities. These results are consistent with those obtained for ^{177}Lu-labeled JR11 (*37*).

Contrary to previous JR11 studies, hematotoxicity of ^{177}Lu-DOTA-LM3 was low. While the reasons are unclear, the different molecular structure and peptide amounts may help explain this. A recently published phase I trial of the radiolabeled somatostatin antagonist ^{177}Lu-satoreotide tetraxetan (^{177}Lu-DOTA-JR11) in 20 patients with advanced well-differentiated NENs showed an unexpectedly high rate of hematologic toxicity grade 4 in 57% (4 of 7) patients after the second cycle (*37*). In the present study, no grade 4 hematologic toxicity was reported in any of the patients after 1–4 cycles of ^{177}Lu-DOTA-LM3 therapy. Severe adverse events (grade 3) occurred in less than 10% of patients, including grade 3 thrombocytopenia in 3 (5.9%) patients, grade 3 lymphopenia in 4 (7.8%) patients, which had been reported in 1 (2.0%) patient before treatment, and 1 was also reported with grade 3 thrombocytopenia. Among the three patients with grade 3 thrombocytopenia occurred, two of them were previously treated with six cycles of ^{177}Lu-DOTATOC/TATE PRRT followed by two cycles of ^{177}Lu-DOTA-LM3 (6.4 GBq and 6.0 GBq) and seven cycles of ^{177}Lu-DOTATOC/TATE PRRT, followed by one cycle of ^{177}Lu-DOTA-LM3 (6.9 GBq), respectively, and one patient was PRRT-naïve, receiving two cycles of ^{177}Lu-DOTA-LM3

(5.9 GBq and 6.8 GBq). The cumulative radioactivity in these three patients was among the average level of all patients. No special baseline characteristics or significantly different intervention was found for these three patients who exhibited grade 3 hematologic toxicity when compared to other patients in the cohort. The rates of additional any grade lymphopenia (11.8%) and grade 3 or 4 lymphopenia (6%) after ^{177}Lu-DOTA-LM3 treatment were slightly lower than that of the agonist ^{177}Lu-DOTATATE reported as 18% and 9% in the NETTER-1 trial, respectively (*16*).

The adverse event rate of severe (grade 3 or 4) hematologic toxicity was higher than that of personalized PRRT with ^{90}Y and ^{177}Lu-labeled SSTR agonist in 1,048 patients with NENs treated in our center (13)—less than 1% of patients of grade 3 and 4 adverse events after the initial PRRT of 1,048 cycles and 2,633 follow-up cycles. However, 68.6% of the patients in the present study were re-treated with PRRT. In a highly selected cohort of 168 patients who had previously received PRRT (*38*), grade 3-4 hematotoxicity occurred in 6.6% and 7.7% of patients after retreatment and re-retreatment with ^{177}Lu-DOTATATE PRRT, respectively. This overall rate of grade 3 and 4 adverse events, with the exception of lymphopenia which was not reported, was close to the results of the present study using ^{177}Lu-DOTA-LM3 of 5.7% in patients previously treated with ^{177}Lu-DOTATOC/TATE PRRT.

The excellent treatment response to ^{177}Lu-DOTA-LM3 was attributable to the high doses delivered to the metastases. Antagonist ^{177}Lu-DOTA-LM3 demonstrated higher uptake and a longer effective half-life in tumor lesions, resulting in higher tumor radiation doses than ^{177}Lu-DOTATOC. These results are consistent with the findings of molecular imaging (PET/CT) using the SSTR antagonist as well as PRRT in preclinical studies comparing the SSTR antagonist ^{177}Lu-DOTA-JR11 with ^{177}Lu-DOTA-TATE; in a clinical pilot study by Wild et al. in four patients with progressive NENs, the SSTR antagonist ^{177}Lu-DOTA-JR11 demonstrated a 1.7–10.6 times higher tumor dose than the agonist ^{177}Lu-DOTATATE (*26*).

With regard to substantial tumor accumulation, liver metastases, compared to bone metastases, demonstrated the highest uptake and longest effective half-life for therapy using ^{177}Lu-

DOTA-LM3. The highest tumor radiation dose among all metastatic sites between ^{177}Lu-DOTA-LM3 and ^{177}Lu-DOTA-TOC was estimated to be to liver metastases using ^{177}Lu-DOTA-LM3. These results potentially indicate the applicability of predominant liver metastatic NENs treated with an SSTR antagonist, and are also promising for intra-arterial PRRT with ^{177}Lu-DOTA-LM3 to treat liver metastases of NENs.

This study suffers from a few limitations. No strict pretest criteria for the selection of patients were applied, and the patient group was heterogeneous. The number of PRRT-naïve patients is relatively small for accurate assessment of efficacy. Follow-up was not long enough to evaluate the longer-term safety profile and outcomes. Despite these shortcomings, we were able to demonstrate for the first time that PRRT with the SSTR antagonist ^{177}Lu-DOTA-LM3 is feasible and may lead to improved outcomes in patients with NENs. Further analysis in a larger group of patients, with longer follow-up duration, is warranted.

CONCLUSION

This study indicates the significant efficiency of a new type of SSTR antagonist ^{177}Lu-DOTA-LM3 in advanced metastatic NENs. It provides favorable biodistribution and higher tumor radiation doses than SSTR agonists, even achieving complete remission in some patients. “Antagonist PRRT” could be administered without severe adverse effects and was well tolerated by the majority of patients, with thrombocytopenia occurring only in a few patients. No other severe adverse effects were observed, especially no renal toxicity.

DISCLOSURE

Helmut Maecke is a co-inventor of somatostatin receptor–based antagonistic radiopeptides. The

patent rights are assigned to his academic institution. No other potential conflicts of interest relevant to this article exist.

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KEY POINTS

QUESTION: Is the "Antagonist PRRT" with ^{177}Lu-DOTA-LM3 safe, effective and feasible in patients with metastatic neuroendocrine neoplasms?

PERTINENT FINDINGS: In a cohort study comprising 51 patients with progressive, heavily pretreated disease—in particular, 68.6% were previously treated with the ^{177}Lu-DOTATOC/TATE agonist PRRT—with any grade of NENs, SSTR antagonist ^{177}Lu-DOTA-LM3 was administered without severe adverse effects and resulted in excellent tumor response with a disease control rate of 85.1%. Antagonist ^{177}Lu-DOTA-LM3 provided favorable biodistribution and higher tumor radiation doses than SSTR agonists.

IMPLICATIONS FOR PATIENT CARE: PRRT with the SSTR antagonist ^{177}Lu-DOTA-LM3 is feasible and may lead to improved outcomes in patients with neuroendocrine neoplasms.

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Table 1. Demographic and baseline clinical characteristics of patients with NENs (n = 51)

Characteristic	Number (N)	Percentage (%)
Sex - no. (%)		
Male	33	64.7
Female	18	35.3
Age - yr	51.6 ± 13.9	
Primary tumor site - no. (%)		
Cancer of unknown primary (CUP)	7	13.7
Pancreas	13	25.5
Midgut	15	29.4
Rectum	3	5.9
Lung	4	7.8
Others	9	17.6
Functional vs. Nonfunctional - no. (%)		
Functional NEN	26	51.0
Nonfunctional NEN	25	49.0
Ki-67 index grading		
G1 (Ki-67 <3%)	14	27.5
G2 (Ki-67 =3%-20%)	27	52.9
G3 (Ki-67 >20%)	10	19.6
Primary treatment before PRRT		
Surgery	36	70.6
Somatostatin analogue	32	62.7
Chemotherapy	11	21.6
Liver-directed therapy	12	23.5
-TACE	7	13.7
-SIRT (Radioembosization)	2	3.9
-Others	3	5.9
Everolimus	7	13.7
External beam radiotherapy	8	15.7
Previously treated with ^{177}Lu-DOTATOC/TATE PRRT		
Yes	35	68.6
No (PRRT-naïve patients)	16	31.4

Table 2. Treatment cycles and cumulative administered radioactivity for ^{177}Lu-DOTA-LM3 PRRT (n = 51)

Variables	N	%	Cumulative radioactivity (GBq)	
			Mean	SD
Number of ^{177}Lu-LM3 PRRT cycles	51	100		
1	25	49.0	6.1	0.8
2	15	29.4	11.4	2.1
3	7	13.7	19.4	1.1
4	4	7.8	26.0	1.2
Number of ^{177}Lu-LM3 PRRT cycles in patients previously treated with TOC/TATE PRRT	35	68.6		
1	25	49.0	6.1	0.8
2	6	11.8	10.9	1.5
3	3	5.9	18.8	1.2
4	1	2.0	25.6	/
Number of ^{177}Lu-LM3 PRRT cycles in PRRT-naïve patients	16	31.4		
2	9	17.6	12.0	2.5
3	4	7.8	19.9	0.8
4	3	5.9	26.1	1.4

Table 3. Hematotoxicity and nephrotoxicity after ^{177}Lu-DOTA-LM3 PRRT according to CTCAE v.5.0

	Numbers of patients with:											
	Anemia		Leukocytopenia		Thrombocytopenia		Lymphopenia		Neutropenia		Nephrotoxicity	
Grade	Before LM3 PRRT	After LM3 PRRT	Before LM3 PRRT	After LM3 PRRT	Before LM3 PRRT	After LM3 PRRT	Before LM3 PRRT	After LM3 PRRT	Before LM3 PRRT	After LM3 PRRT	Before LM3 PRRT	After LM3 PRRT
CTC-1	10	18	2	5	6	9	9	15	1	2	6	7
CTC-2	6	5	1	3	1	0	8	5	0	2	4	2
CTC-3	0	0	0	0	0	3	1	4	0	0	0	0
CTC-4	0	0	0	0	0	0	0	0	0	0	0	0
CTC-5	NA	0	NA	0	NA	0	NA	0	NA	0	NA	0

NA = not applicable before ^{177}Lu-DOTA-LM3 PRRT (grade 5 represents death).

Table 4. Treatment response at 3-6 months after ^{177}Lu-DOTA-LM3 PRRT

Response after ^{177}Lu-DOTA-LM3 PRRT	**Total**		**PRRT-naïve**		**Previously treated with TOC/TATE PRRT**	
	N	**%**	**N**	**%**	**N**	**%**
RECIST - CT and/or MRI response - no. (%)	n=47		n=14		n=33	
Complete response	0	0	0	0	0	0
Partial response	17	36.2	10	71.4	7	21.2
Stable disease	23	48.9	3	21.4	20	60.6
Progressive disease	7	14.9	1	7.1	6	18.2
DCR	40	85.1	13	92.9	27	81.8
EORTC - SSTR imaging response - no. (%)	n=47		n=14		n=33	
Complete response	2	4.3	1	7.1	1	3.0
Partial response	21	44.7	9	64.3	12	36.4
Stable disease	18	38.3	3	21.4	15	45.5
Progressive disease	6	12.8	1	7.1	5	15.2
DCR	41	87.2	13	92.9	28	84.8

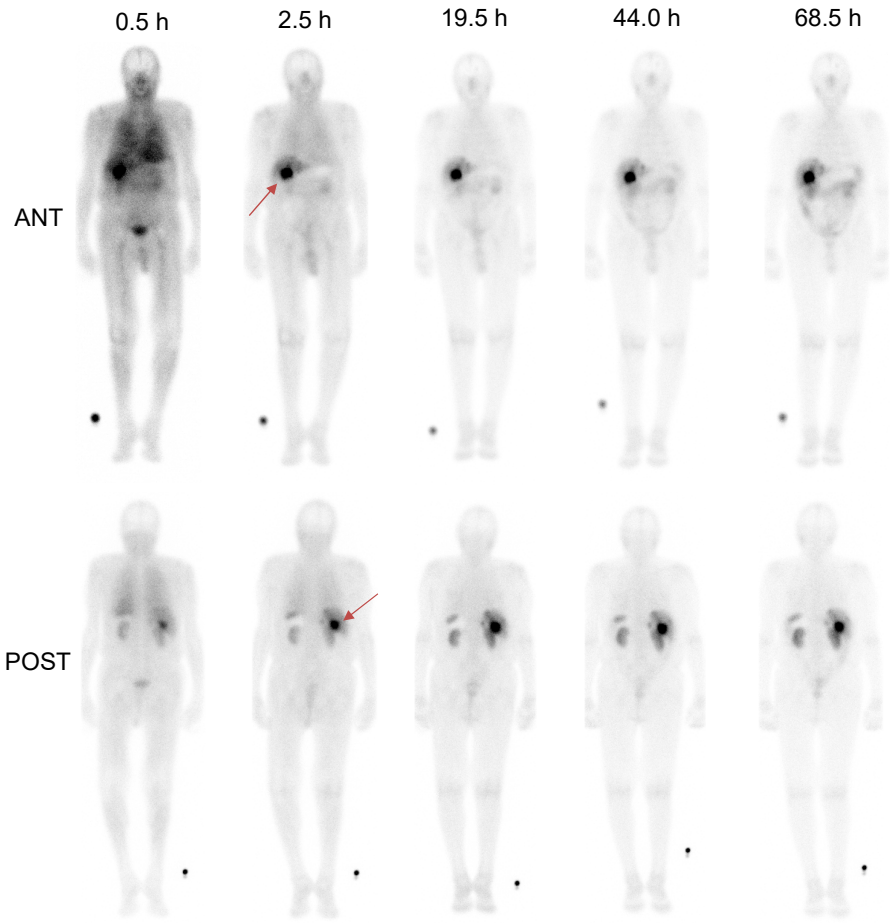

Figure 1. Representative planar whole-body anterior and posterior scintigraphic images of a patient with pancreatic NEN liver metastases at 0.5, 2.5, 19.5, 44.0, and 68.5 hours after intravenous administration of ^{177}Lu-DOTA-LM3, with an administered radioactivity of 5.3 GBq. Intense tumor uptake in liver metastases (arrows) as well as pulmonary uptake (at 0.5 and 2.5 h) and significant uptake in the kidneys, spleen, and liver (at 0.5, 2.5, 19.5, 44.0, and 68.5 h) was observed after intravenous administration of ^{177}Lu-DOTA-LM3.

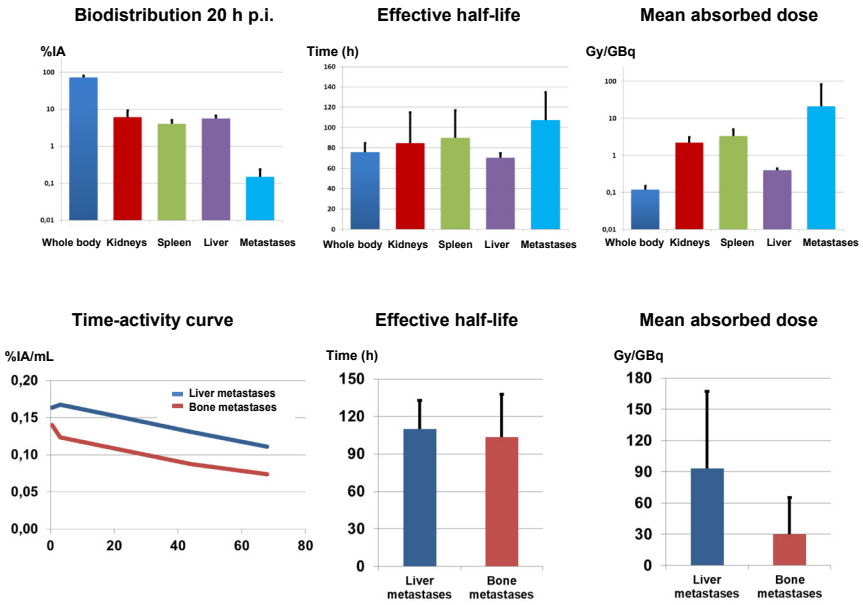

Figure 2. Biodistribution, effective half-life, and mean absorbed organ and tumor doses of ^{177}Lu-DOTA-LM3. The longest effective half-life was obtained in metastases. The spleen had the highest absorbed dose of all analyzed normal organs. Higher uptake, longer effective half-life, and higher mean absorbed doses in liver metastases as compared to bone lesions were observed. All results showed high variability, as demonstrated by the error bars, which represent the standard deviation.

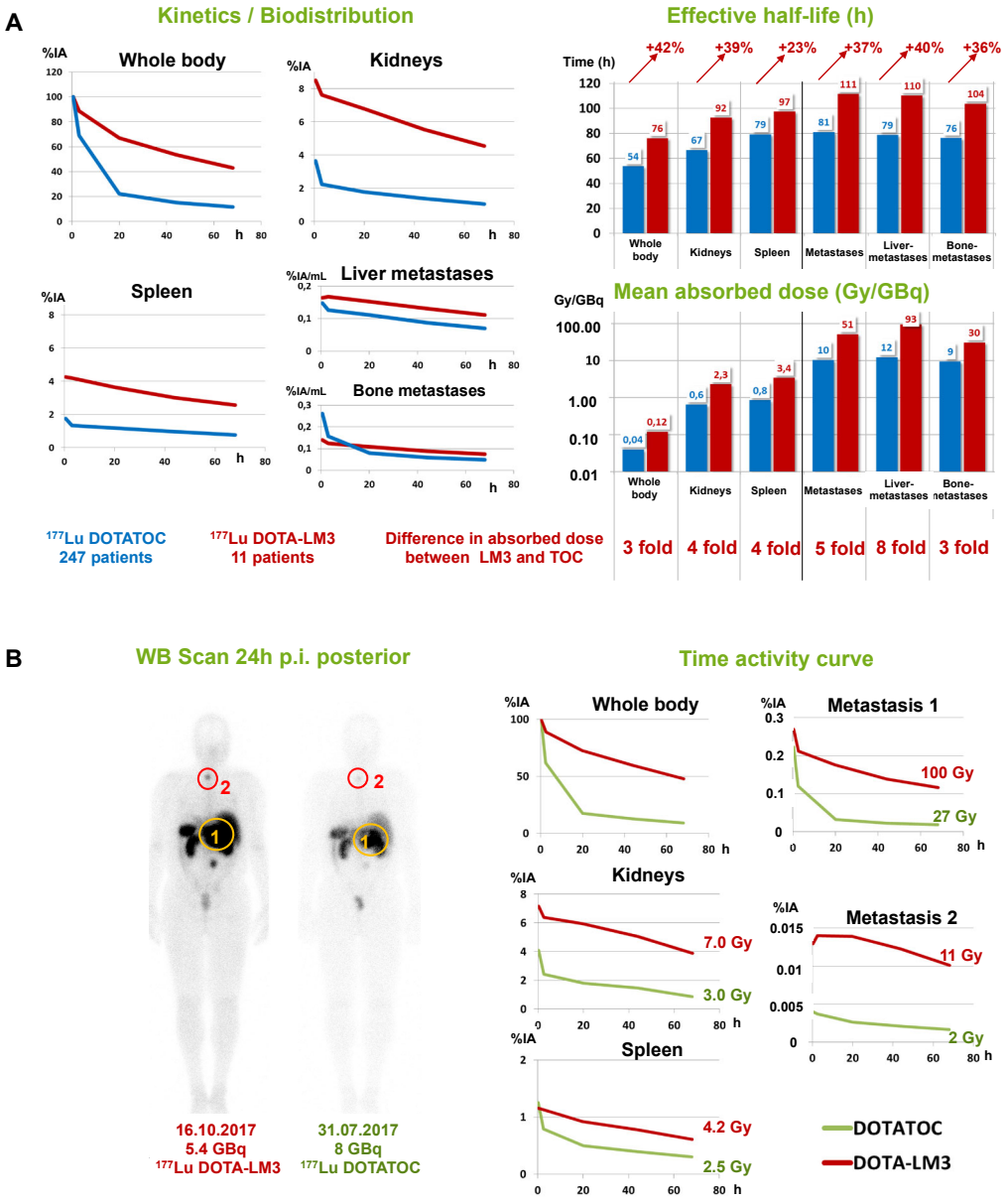

Figure 3. (A) Comparison of biodistribution and dosimetry results of the antagonist ^{177}Lu-DOTA-LM3 (n = 11) and the agonist ^{177}Lu-DOTA-TOC (n = 247). Higher uptake and a longer effective half-life of ^{177}Lu-DOTA-LM3 were found for whole-body as well as kidneys, spleen, and metastases, resulting in higher mean absorbed organ and tumor doses for ^{177}Lu-DOTA-LM3 than for ^{177}Lu-DOTA-TOC. (B) Patient example: ^{177}Lu-DOTA-LM3 and ^{177}Lu-DOTA-TOC in the same patient.

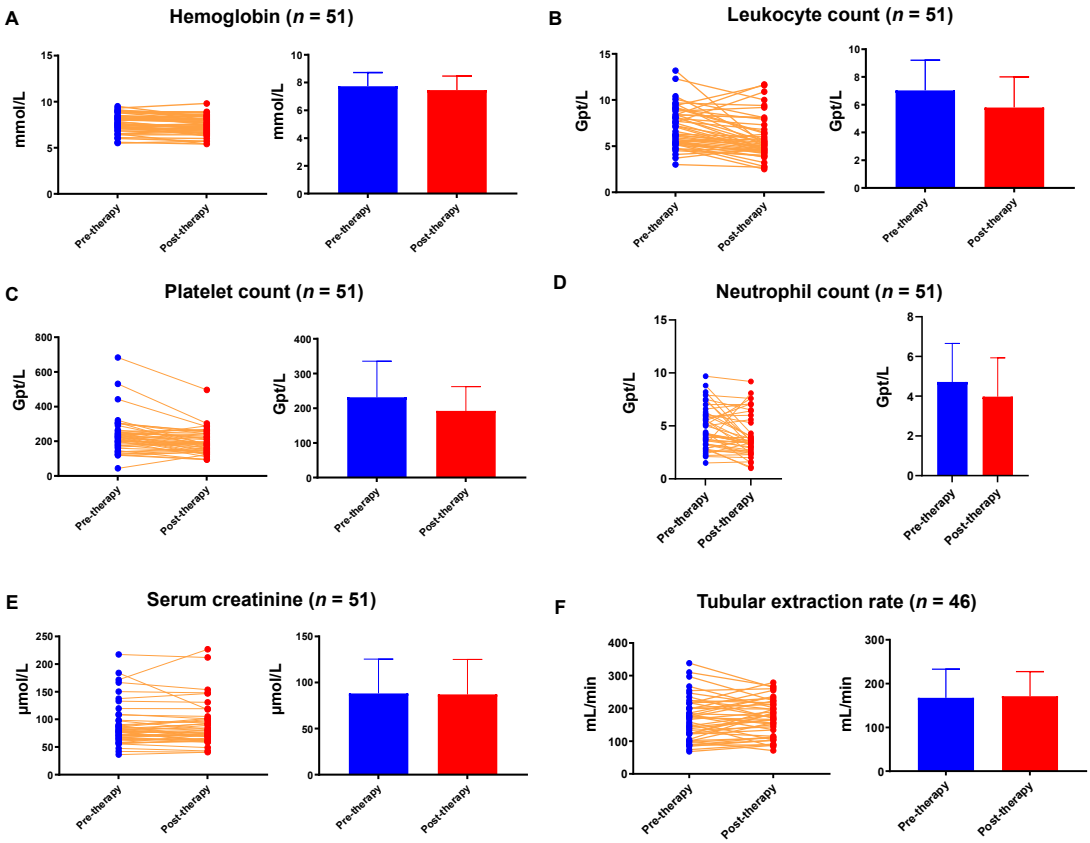

Figure 4. Comparison of laboratory parameters before and after ^{177}Lu-DOTA-LM3 PRRT (A, hemoglobin; B, leukocyte; C, platelet; D, neutrophil). Comparison of laboratory parameter (E, serum creatinine) and renal function quantified by measuring the tubular extraction rate using ^{99m}Tc-MAG3 renal scintigraphy (F) before and after ^{177}Lu-DOTA-LM3 PRRT, which did not reveal any significant nephrotoxicity.

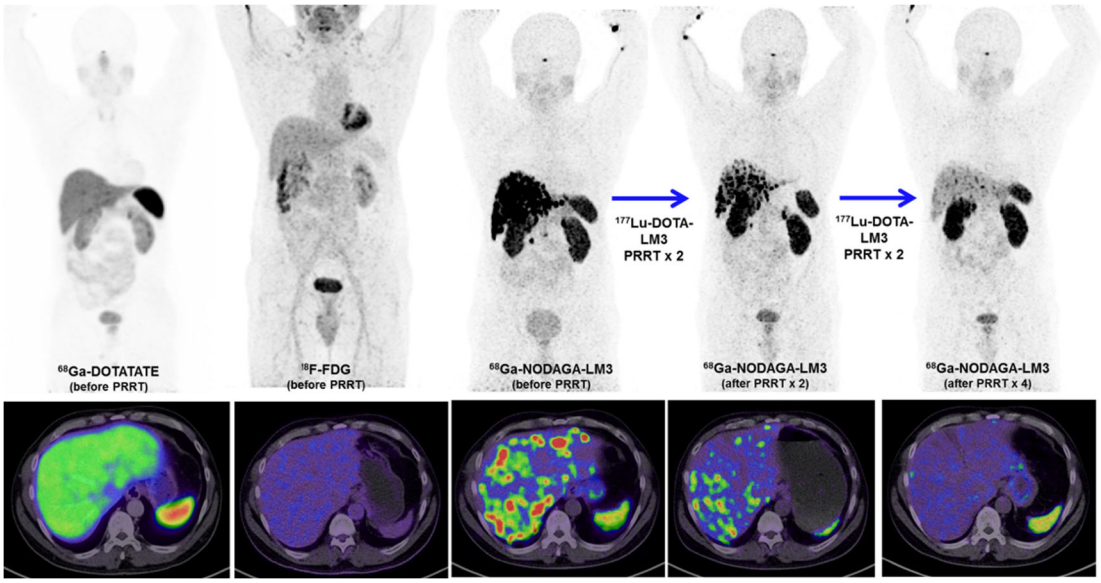

Figure 5. 55-year-old man with well-differentiated, non-functioning metastatic pancreatic NEN and a Ki-67 index of 13%. Patient underwent Whipple procedure, with histologically confirmed G2 pancreatic NEN. MRI had revealed multiple small volume liver metastases. ^{68}Ga-DOTA-TATE PET/CT showed very weak DOTATATE-avid small volume lesions in the liver and lymph nodes with extremely low uptake (left), which did not exhibit significant glucose hypermetabolism (second from left). ^{68}Ga-NODAGA-LM3 PET/CT then showed disseminated bilobar liver metastases, demonstrating very intense SSTR antagonist (LM3) uptake in the liver and lymph node metastases (third from left). Patient was treated with four cycles of ^{177}Lu-DOTA-LM3 PRRT with a cumulative administered radioactivity of 25.7 GBq. Restaging ^{68}Ga-NODAGA-LM3 PET/CT scans showed excellent response to ^{177}Lu-DOTA-LM3 PRRT with partial remission of the disease according to RECIST and EORTC criteria (right).

Graphical Abstract