First-in-Humans Study of the SSTR Antagonist ^{177}Lu-DOTA-LM3 for Peptide Receptor Radionuclide Therapy in Patients with Metastatic Neuroendocrine Neoplasms: Dosimetry, Safety, and Efficacy

Richard P. Baum*[1,2], Jingjing Zhang*[1,3,4], Christiane Schuchardt[1], Dirk Müller[1], and Helmut Mäcke[5]

[1]*Theranostics Center for Molecular Radiotherapy and Precision Oncology, ENETS Center of Excellence, Zentralklinik Bad Berka, Bad Berka, Germany;* [2]*CURANOSTICUM Wiesbaden-Frankfurt, Center for Advanced Radiomolecular Precision Oncology, Wiesbaden, Germany;* [3]*Departments of Diagnostic Radiology, Surgery, Chemical and Biomolecular Engineering, and Biomedical Engineering, Yong Loo Lin School of Medicine and Faculty of Engineering, National University of Singapore, Singapore, Singapore;* [4]*Clinical Imaging Research Centre, Centre for Translational Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; and* [5]*Department of Nuclear Medicine, Medical Center, University Hospital of Freiburg, Freiburg, Germany*

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-NH_2 (^{177}Lu-DOTA-LM3) in patients with metastatic neuroendocrine neoplasms (NENs). **Methods:** Fifty-one patients (aged 27–76 y; mean, 51.6 ± 13.9 y) 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 the criteria of the European Organisation for Research and Treatment of Cancer (EORTC). Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Dosimetry was performed on 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 were found for ^{177}Lu-DOTA-LM3 than for the agonist ^{177}Lu-DOTATOC in the whole body and in the kidneys, spleen, and metastases, resulting in higher mean absorbed organ and tumor doses. 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 Common Terminology Criteria (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 the 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 patients (14.9%) had progressive disease, and by EORTC criteria, there was complete remission in 2 patients (4.3%), partial remission in 21 (44.7%), stable disease in 18 (38.3%), and progressive disease in 6 (12.8%). **Conclusion:** The antagonist PRRT with ^{177}Lu-DOTA-LM3 could be administered without severe adverse effects and was well tolerated by most patients, with thrombocytopenia occurring in only a few. No other severe adverse effects were observed; in particular, there was no nephrotoxicity. The SSTR antagonist ^{177}Lu-DOTA-LM3 appears to be promising for PRRT, provides a favorable biodistribution and higher tumor radiation doses than SSTR agonists, and was 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; 177Lu-DOTA-LM3; first-in-humans; neuroendocrine neoplasms (NENs)

J Nucl Med 2021; 62:1571–1581
DOI: 10.2967/jnumed.120.258889

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*). NENs 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*). Most NENs overexpress somatostatin receptors (SSTRs), making them accessible for radiodiagnostic and therapeutic approaches to NENs.

Over the past 2 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 NENs (*7–10*). SSTR-targeted imaging of NENs, particularly with ^{68}Ga-labeled somatostatin analogs for PET/CT, plays an important role in detecting the primary tumor, staging, restaging, assessing treatment response (*11*), and selecting 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

Received Oct. 28, 2020; revision accepted Feb. 16, 2020.
For correspondence or reprints, contact Jingjing Zhang (zhangjingjingtag@163.com).
*Contributed equally to this work.
Published online March 5, 2021.

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-DOTA-TATE (Lutathera; Advanced Accelerator Applications) 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 labeled with ^{68}Ga, ^{90}Y, or ^{177}Lu. 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 SSTR 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 than for agonists, likely because a larger number of binding sites (receptor activation state) can be recognized by the antagonists than by the SSTR agonists (*17*). This finding was confirmed by ex vivo autoradiography of patient-derived tumor samples, which demonstrated a more than 4-fold increase on average in tumor binding of the SSTR antagonist ^{177}Lu-DOTA-BASS as compared with the SSTR agonist ^{177}Lu-DOTATATE (*20*), suggesting that this binding may increase not only localization accuracy for tumors but also the efficacy of radionuclide therapy with SSTR antagonists. The first clinical evaluation of SSTR antagonists confirmed the preclinical data by showing higher tumor uptake of the antagonist ^{111}In-DOTA-BASS and better tumor-to-background ratios than for the agonist ^{111}In-DTPA-octreotide (*21*).

Among the recently developed somatostatin antagonists, several analogs, 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-DOTA-TOC (*25*). In a pilot study on 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-humans study was to explore the safety, dosimetry, and preliminary efficacy of the ^{177}Lu-labeled SSTR antagonist DOTA-*p*-Cl-Phe-cyclo(D-Cys-Tyr-D-4-amino-Phe(carbamoyl)-Lys-Thr-Cys)D-Tyr-NH_2 (^{177}Lu-DOTA-LM3) in patients with metastatic NENs. The kinetics and dosimetry of the antagonist ^{177}Lu-DOTA-LM3 were 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; aged 27–76 y; mean age, 51.6 ± 13.9 y) with metastatic NENs met the eligibility criteria for the study (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 mo before ^{177}Lu-DOTA-LM3 PRRT). 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, that is, insufficient for agonist PRRT with ^{177}Lu-DOTATOC or ^{177}Lu-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 the 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 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 were added to prevent radiolysis. Quality control parameters were monitored (radiochemical purity, radiochemical identity, pH, 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 (1,600 mL of 5% lysine HCl and 10% L-arginine HCl) was administered for nephroprotection during each PRRT cycle starting at least 30 min before tracer administration and lasting for 4 h. The radiopharmaceutical was coadministered by slow intravenous injection over 10–15 min with a dedicated second infusion pump system for radionuclide therapy. ^{177}Lu-DOTA-LM3 administered activity was individually 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 wk.

Posttherapy whole-body scintigraphy was performed with a Spirit DH-V dual-head γ-camera (Mediso Medical Imaging Systems) using a 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 h after injection. SPECT/CT imaging was obtained approximately 24 h after injection.

Dosimetry

Dosimetry was performed on 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 on the basis of planar whole-body scans and SPECT/CT, and dosimetric calculations were performed using OLINDA software (MIRD scheme). To analyze kinetics, we used the

TABLE 1
Demographic and Baseline Clinical Characteristics of Patients with NENs ($n = 51$)

Characteristic	Data
Sex	
Male	33 (64.7%)
Female	18 (35.3%)
Age, mean ± SD (y)	51.6 ± 13.9
Primary tumor site	
Cancer of unknown primary (CUP)	7 (13.7%)
Pancreas	13 (25.5%)
Midgut	15 (29.4%)
Rectum	3 (5.9%)
Lung	4 (7.8%)
Other	9 (17.6%)
Functional vs. nonfunctional	
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 analog	32 (62.7%)
Chemotherapy	11 (21.6%)
Liver-directed therapy	12 (23.5%)
TACE	7 (13.7%)
SIRT (radioembolization)	2 (3.9%)
Other	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%)

Data are number followed by percentage in parentheses, except for age.

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 biexponential function.

Safety

All patients were clinically monitored during therapy and for at least 2–4 d 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 using ^{99m}Tc-mercaptoacetyltriglycine renal scintigraphy. Treatment-related adverse events were recorded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Response Assessment

Molecular and morphologic responses were evaluated in accordance with the criteria of the European Organisation for Research and Treatment of Cancer (EORTC) (*31–34*) and with RECIST, version 1.1 (*35*), respectively. Imaging was performed before each PRRT cycle and at restaging. The disease control rate was defined as complete remission, partial remission, or stable disease.

Statistical Analysis

Continuous variables were denoted as mean ± SD. The rates of adverse events at baseline and at the end of treatment were compared. Differences between paired samples before and after treatment were

TABLE 2
Treatment Cycles and Cumulative Administered Radioactivity for ^{177}Lu-DOTA-LM3 PRRT (n = 51)

Variable	n	%	Cumulative radioactivity (GBq)	
			Mean	SD
No. 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
No. 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	/
No. 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

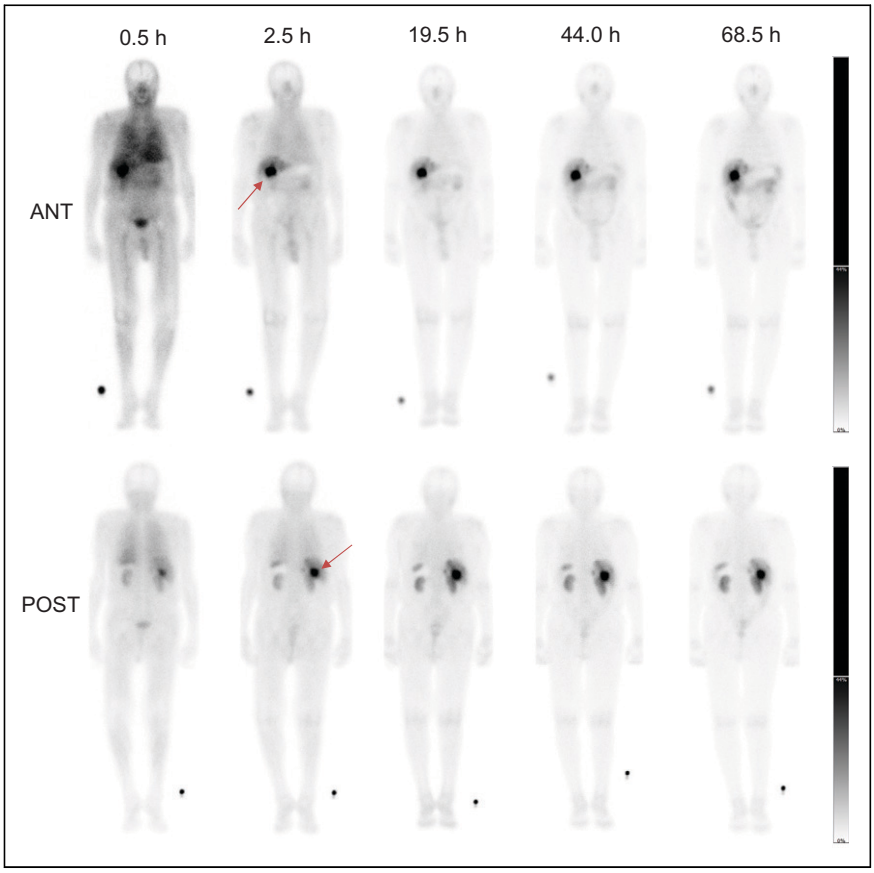

FIGURE 1. Representative planar whole-body anterior and posterior scintigraphic images of patient with pancreatic NEN liver metastases at various times after intravenous administration of 5.3 GBq of ^{177}Lu-DOTA-LM3. Intense tumor uptake in liver metastases (arrows) was observed, as well as pulmonary uptake (at 0.5 and 2.5 h) and significant uptake in kidneys, spleen, and liver (at 0.5, 2.5, 19.5, 44.0, and 68.5 h). ANT = anterior; POST = posterior.

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. The Fisher exact test was performed to compare treatment response rates. All statistical tests were 2-tailed, and a P value of less than 0.05 was considered statistically significant.

RESULTS

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

In total, 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 mo (range, 1–29 mo) 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 posttherapy planar and SPECT/CT images (Fig. 1). The radiopharmaceutical was excreted predominantly through the kidneys.

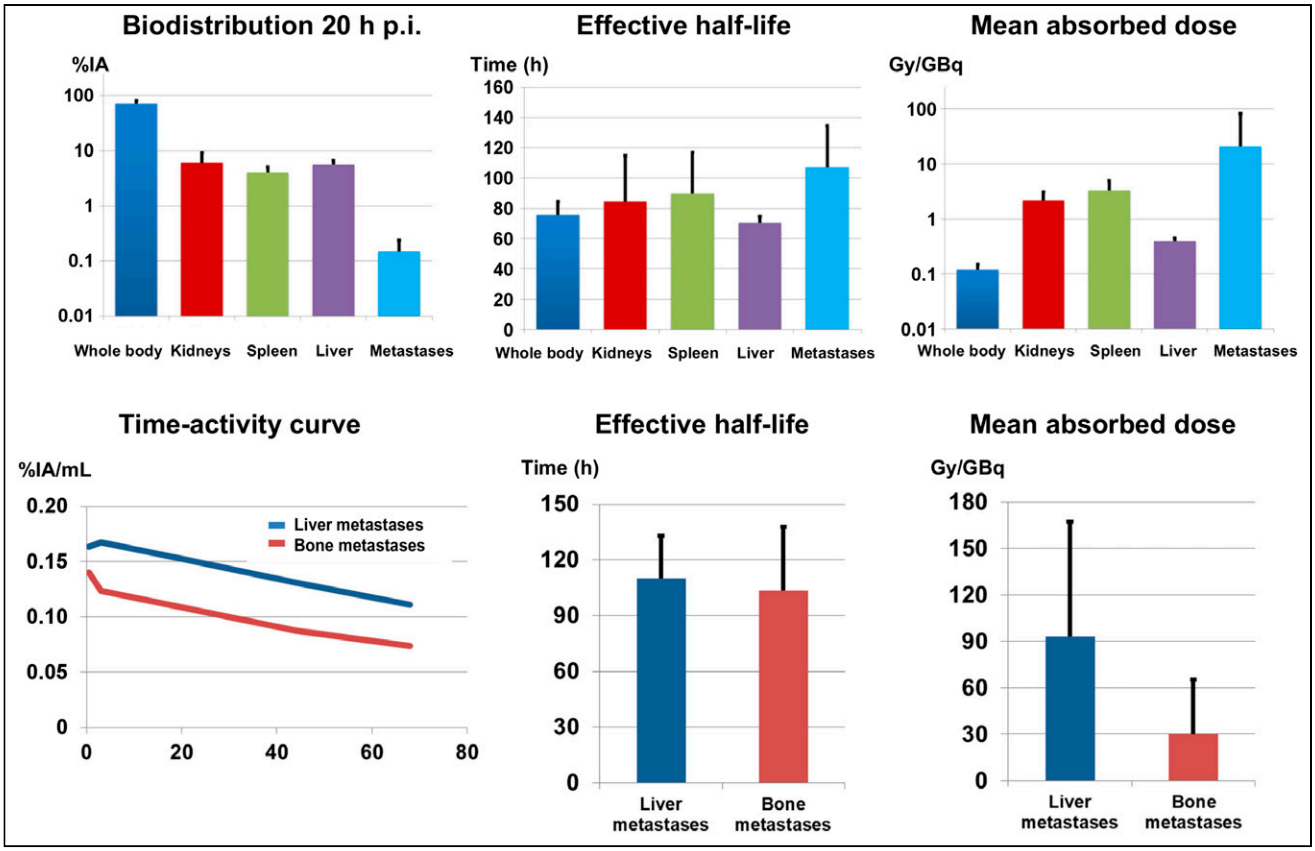

FIGURE 2. Biodistribution, effective half-life, and mean absorbed organ and tumor doses of ^{177}Lu-DOTA-LM3. Longest effective half-life was obtained in metastases. Spleen had highest absorbed dose of all analyzed normal organs. Higher uptake, longer effective half-life, and higher mean absorbed doses in liver metastases than in bone lesions were observed. All results showed high variability, as demonstrated by error bars, which represent SD. p.i. = after injection.

Dosimetry

Whole-body clearance of the tracer was rapid, with an effective half-life of 56–93 h. The maximum renal uptake at 20 h after injection was 15% IA (mean, 7% IA) and showed a washout with an effective half-life of 47–159 h. The highest uptake in the spleen was observed at 3 h after injection, at 5% IA, exhibiting an exponential decline with an effective half-life of 74–156 h. The liver also demonstrated moderate uptake at 20 h after injection, up to 7% IA and a half-life of 67–75 h. Concerning the radiation dose delivery of ^{177}Lu-DOTA-LM3 to NEN lesions, the maximum uptake at 20 h after injection 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 h.

Dosimetry results from 11 patients treated with 5.9 ± 1.2 GBq of ^{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 absorbed radiation doses in normal organs were 2.3 ± 0.9 Gy/GBq (0.5–3.6 Gy/GBq) for the 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 were 1–57 Gy/GBq to bone lesions and 15–81 Gy/GBq to liver lesions (Fig. 2).

The kinetics and dosimetry of ^{177}Lu-DOTA-LM3 were also compared with 247 NEN patients receiving 7 ± 1 GBq of ^{177}Lu-DOTATOC at our center, applying the same dosimetry protocol. ^{177}Lu-DOTA-LM3 showed a longer whole-body effective half-life (76 h) than did ^{177}Lu-DOTATOC (54 h), and the same was true for the kidneys (^{177}Lu-DOTA-LM3, 92 h; ^{177}Lu-DOTATOC, 67 h), the spleen (^{177}Lu-DOTA-LM3, 97 h; ^{177}Lu-DOTATOC, 79 h), and metastases (^{177}Lu-DOTA-LM3, 111 h; ^{177}Lu-DOTATOC, 81 h). Because of the longer effective half-life and higher uptake, mean absorbed organ and tumor doses were higher for ^{177}Lu-DOTA-LM3 (whole body: 0.04 Gy/GBq for ^{177}Lu-DOTATOC and 0.12 Gy/GBq for ^{177}Lu-DOTA-LM3; kidneys: 0.6 Gy/GBq for ^{177}Lu-DOTATOC and 2.3 Gy/GBq for ^{177}Lu-DOTA-LM3; spleen: 0.8 Gy/GBq for ^{177}Lu-DOTATOC and 3.4 Gy/GBq for ^{177}Lu-DOTA-LM3; tumor: 10 Gy/GBq for ^{177}Lu-DOTATOC and 51 Gy/GBq for ^{177}Lu-DOTA-LM3). Hepatic metastases, as compared with 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 (12 Gy/GBq for ^{177}Lu-DOTATOC and 93 Gy/GBq for ^{177}Lu-DOTA-LM3) (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 mo.

The most severe delayed adverse event was Common Terminology Criteria (CTC)-3 thrombocytopenia in 3 (5.9%) patients;

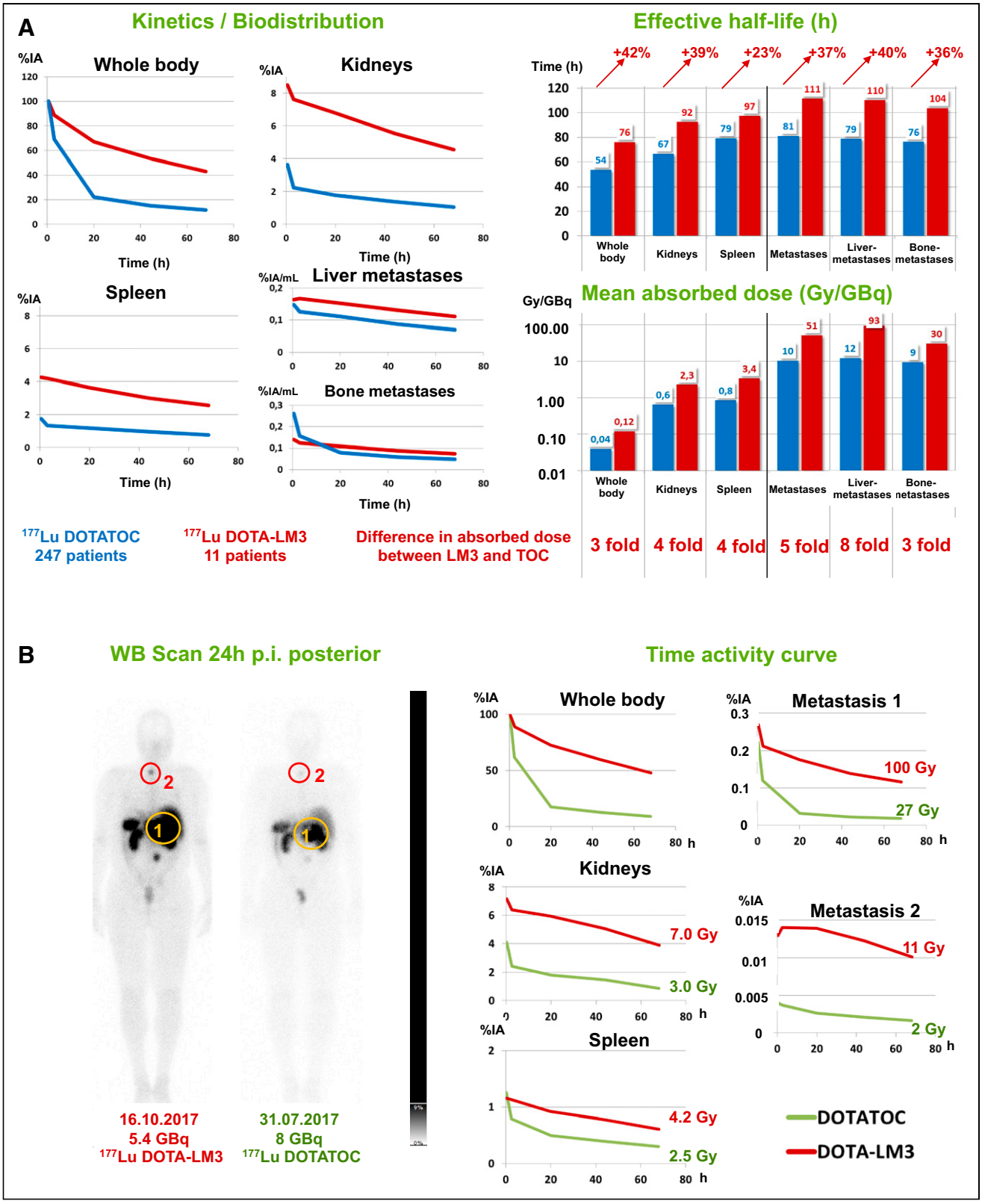

FIGURE 3. (A) Comparison of biodistribution and dosimetry results of antagonist ^{177}Lu-DOTA-LM3 ($n = 11$) and agonist ^{177}Lu-DOTATOC ($n = 247$). Higher uptake and longer effective half-life were found for ^{177}Lu-DOTA-LM3 in whole body as well as kidneys, spleen, and metastases, resulting in higher mean absorbed organ and tumor doses for ^{177}Lu-DOTA-LM3 than for ^{177}Lu-DOTATOC. (B) Example of ^{177}Lu-DOTA-LM3 and ^{177}Lu-DOTATOC in same patient. p.i. = after injection.

TABLE 3
Hematotoxicity and Nephrotoxicity Before and After ^{177}Lu-DOTA-LM3 PRRT According to Common Terminology Criteria for Adverse Events, Version 5.0

	Anemia		Leukocytopenia		Thrombocytopenia		Lymphopenia		Neutropenia		Nephrotoxicity	
Grade	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
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).
Data are numbers of patients.

however, no bleeding occurred and no thrombocyte infusions were necessary. CTC-3 lymphopenia was reported in 1 (2.0%) and 4 (7.8%) 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, 6.3, 5.4–8.4 [mean ± SD for count × 10^9/L, followed by median and

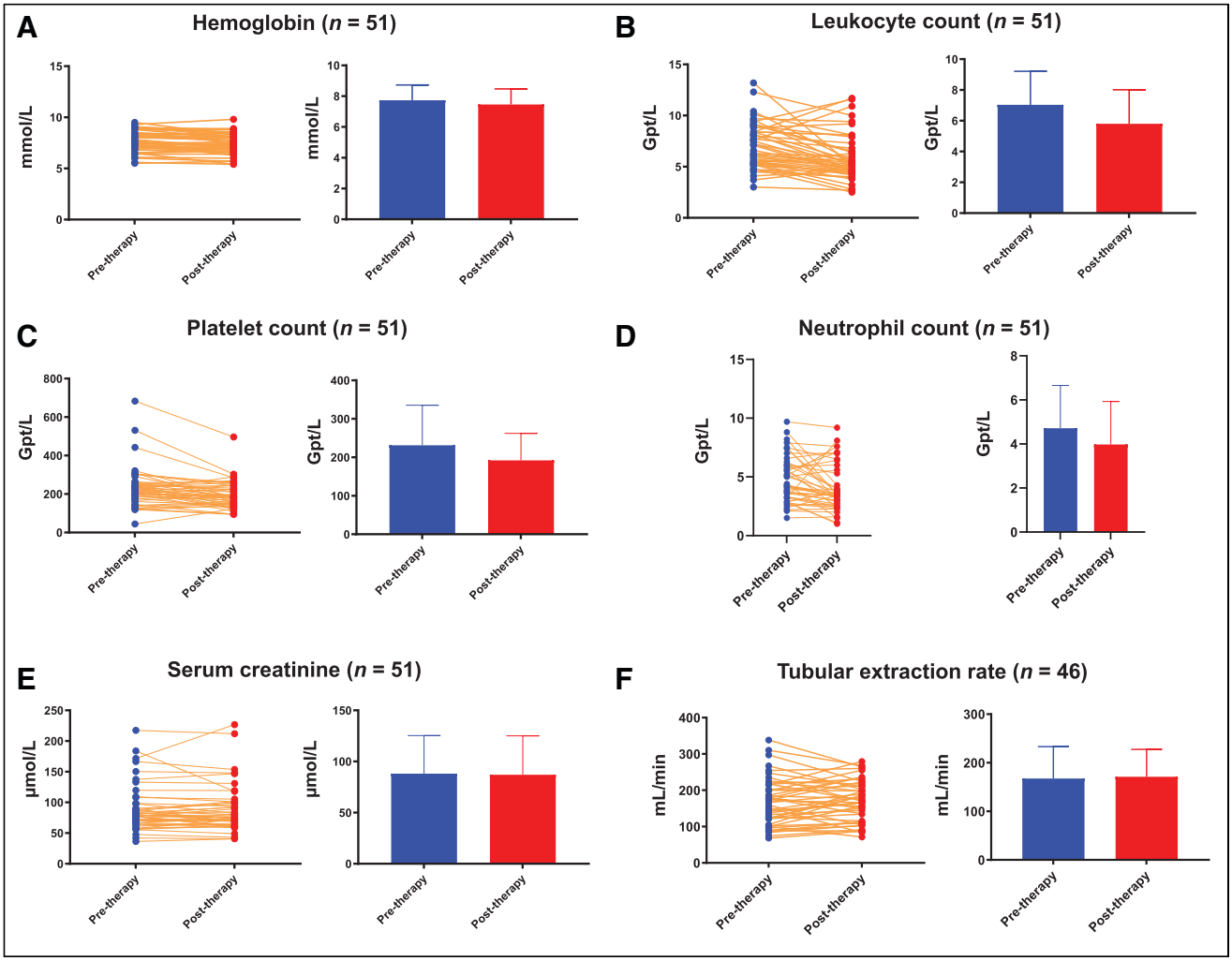

FIGURE 4. (A–D) Comparison of hemoglobin (A), leukocyte count (B), platelet count (C), and neutrophil count (D) before and after ^{177}Lu-DOTA-LM3 PRRT. (E and F) Comparison of serum creatinine (E) and renal function quantified by measuring tubular extraction rate using ^{99m}Tc-mercaptoacetyltriglycine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

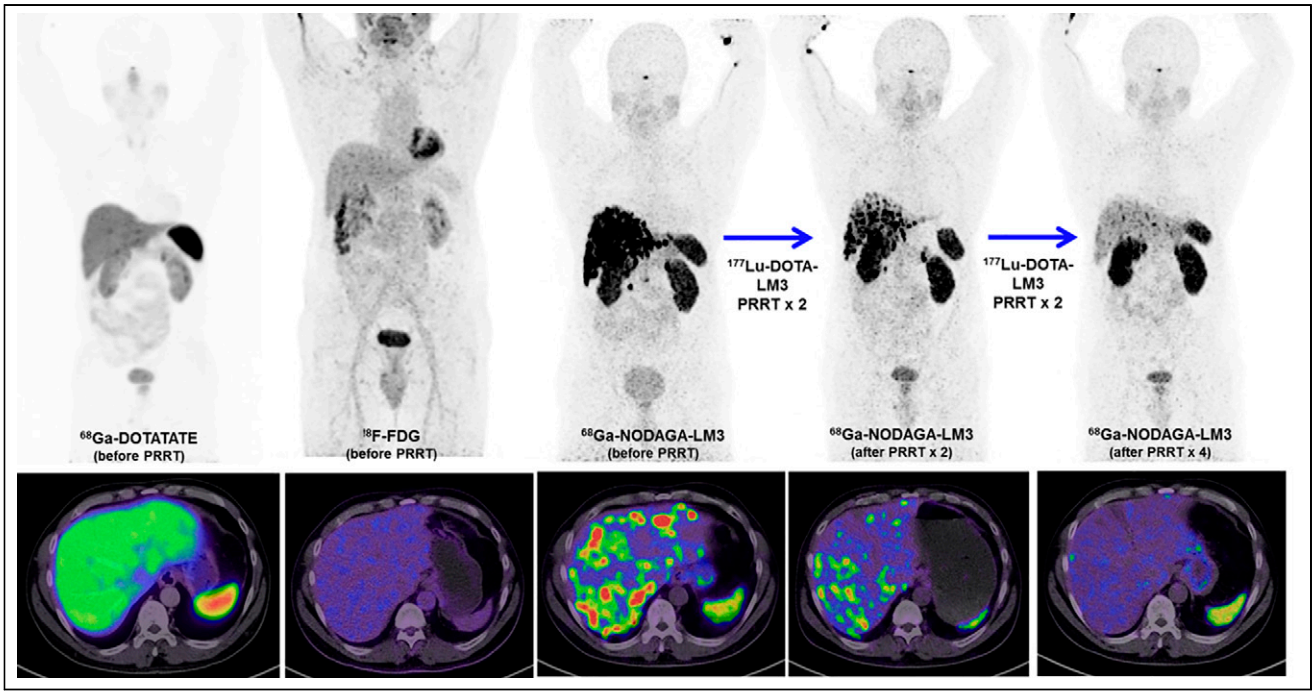

FIGURE 5. A 55-y-old man with well-differentiated, nonfunctioning metastatic pancreatic NEN and Ki-67 index of 13%. Patient underwent Whipple procedure, with histologically confirmed G2 pancreatic NEN. MRI had revealed multiple small-volume liver metastases. ^{68}Ga-DOTATATE PET/CT showed weakly ^{68}Ga-DOTATATE–avid small-volume lesions in liver and lymph nodes with extremely low uptake (leftmost image), which did not exhibit significant glucose hypermetabolism (second image from left). ^{68}Ga-NODAGA-LM3 PET/CT then showed disseminated bilobar liver metastases, demonstrating intense SSTR antagonist (LM3) uptake in liver and lymph node metastases (third image from left). Patient was treated with 4 cycles of ^{177}Lu-DOTA-LM3 PRRT, with cumulative administered radioactivity of 25.7 GBq. Restaging ^{68}Ga-NODAGA-LM3 PET/CT showed excellent response to ^{177}Lu-DOTA-LM3 PRRT, with partial remission of disease according to RECIST and EORTC criteria (rightmost image).

interquartile range]; after therapy: 5.81 ± 2.21, 5.1, 4.5–6.5; $P <$ 0.05), neutrophil counts (before therapy: 4.67 ± 1.93, 4.2, 3.2–5.7; after therapy: 4.08 ± 1.95, 3.2, 2.7–4.0; $P < 0.05$), lymphocyte counts (before therapy: 1.16 ± 0.64, 1.2, 0.9–1.6; after therapy: 0.87 ± 0.46, 0.9, 0.7–1.1; $P < 0.05$), and platelet counts (before therapy: 232 ± 104, 225, 178–250; after therapy: 192 ± 70, 182, 144–225; $P < 0.05$). 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 mo). 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 tubular extraction rate for renal function evaluation before and after treatment. Slightly decreased tubular extraction rates were noted in 21 of 46 (45.7%) patients treated with ^{177}Lu-DOTA-LM3, whereas 25 of 46 (54.3%) patients showed improvement after treatment. No statistically significant change occurred in tubular extraction rate (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, a response evaluation was possible in 47. Most were evaluated after 2 cycles of treatment. Among those patients who were evaluated after 1 cycle of treatment, 6 received only 1 cycle of ^{177}Lu-DOTA-LM3 treatment because of disease progression; 15 patients either were previously treated with agonist PRRT and planned at restaging after 1 cycle of ^{177}Lu-DOTA-LM3 PRRT or were 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 patients [36.2%], stable disease in 23 [48.9%], and progressive disease in 7 [14.9%]) or by molecular response evaluation based on EORTC criteria (complete remission in 2 patients [4.3%], partial remission in 21 [44.7%], stable disease in 18 [38.3%], and progressive disease in 6 [12.8%]). An example is shown in Figure 5. The disease control rate at 3–6 mo after PRRT was 85.1% according to RECIST 1.1 and 87.2% according to the EORTC criteria. The treatment responses are shown in Table 4.

DISCUSSION

To our knowledge, this was 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 an 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 at our center under the same dosimetry protocol. Our results were also consistent with the higher renal uptake and higher absorbed renal dose reported for the SSTR antagonist than for the SSTR agonist by Wild et al. (^{177}Lu-DOTA-JR11 vs. ^{177}Lu-DOTATATE, 1.8 vs. 1.2 Gy/GBq) (*26*) and by Nicolas et al. in a preclinical model (*36*).

TABLE 4
Treatment Response at 3–6 Months After ^{177}Lu-DOTA-LM3 PRRT

	Total (n = 47)		PRRT-naïve (n = 14)		Previously treated with TOC/TATE PRRT (n = 33)	
Response	n	%	n	%	n	%
RECIST CT or MRI response						
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
Disease control rate	40	85.1	13	92.9	27	81.8
EORTC SSTR imaging response						
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
Disease control rate	41	87.2	13	92.9	28	84.8

The kidney was considered one of the main organs at risk and was 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 or 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 with grade 1, 1 with a normal index), a finding that was likely explained by the ending of 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. Although the reasons are unclear, the different molecular structures and peptide amounts may help explain this finding. 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 (4/7 patients, or 57%) of grade 4 hematologic toxicity 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 and grade 3 lymphopenia in 4 (7.8%) patients, one of whom had also shown this grade 3 lymphopenia before treatment and one of whom had grade 3 thrombocytopenia in addition to the grade 3 lymphopenia. Among the 3 patients with grade 3 thrombocytopenia, two were previously treated with 6 cycles of ^{177}Lu-DOTATOC/TATE PRRT followed by 2 cycles of ^{177}Lu-DOTA-LM3 (6.4 GBq and 6.0 GBq) or by 7 cycles of ^{177}Lu-DOTATOC/TATE PRRT followed by 1 cycle of ^{177}Lu-DOTA-LM3 (6.9 GBq), and one was PRRT-naïve, receiving 2 cycles of ^{177}Lu-DOTA-LM3 (5.9 GBq and 6.8 GBq). The cumulative radioactivity in these 3 patients was within the average range of all patients. No special baseline characteristics or significant differences in intervention were found for these 3 patients who exhibited grade 3 hematologic toxicity when compared with other patients in the cohort. The rates of additional lymphopenia of any grade (11.8%) or of grade 3 or 4 (6%) after ^{177}Lu-DOTA-LM3 treatment were slightly lower than those after the agonist ^{177}Lu-DOTATATE reported in the NETTER-1 trial (18% and 9%, respectively) (*16*).

The rate of severe (grade 3 or 4) hematologic toxicity for PRRT with SSTR antagonist ^{177}Lu-DOTA-LM3 in this study was higher than for personalized PRRT with ^{90}Y- and ^{177}Lu-labeled SSTR agonists in 1,048 patients with NENs treated at our center (*13*) (<1% of patients with grade 3 or 4 adverse events after 1,048 initial cycles of PRRT and 2,633 follow-up cycles). However, 68.6% of the patients in the present study were retreated with PRRT. In a highly selected cohort of 168 patients who had previously received PRRT (*38*), grade 3 or 4 hematotoxicity occurred in 6.6% and 7.7% of patients after a first and second 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 (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. The antagonist ^{177}Lu-DOTA-LM3 demonstrated higher uptake and a longer effective half-life in tumor lesions, resulting in higher tumor radiation doses than for ^{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-DOTATATE; in a clinical pilot study by Wild et al. in 4 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 with 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-DOTATOC was estimated to be to liver metastases using ^{177}Lu-DOTA-LM3. These results indicate the potential applicability of predominantly liver-metastatic NENs treated with an SSTR antagonist and are also promising for intraarterial PRRT with ^{177}Lu-DOTA-LM3 to treat liver metastases of NENs.

This study had 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 was 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, to our knowledge, 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 a longer follow-up is warranted.

CONCLUSION

This study indicated the significant efficiency of a new type of SSTR antagonist, ^{177}Lu-DOTA-LM3, in advanced metastatic NENs. It provides a 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 most patients, with thrombocytopenia occurring in only a few patients. No other severe adverse effects were observed; in particular, there was no renal toxicity.

DISCLOSURE

Helmut Mäcke is a coinventor of SSTR-based antagonistic radiopeptides. The patent rights are assigned to his academic institution. No other potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We thank the patients who participated in this study; our physician colleagues, especially Harshad R. Kulkarni and Aviral Singh; the radiopharmacists, radiochemists, nursing staff, and nuclear medicine technologists of Radioisotope Therapy Ward D3 for patient care; and our database manager, Karin Niepsch.

KEY POINTS

QUESTION: Is antagonist PRRT with ^{177}Lu-DOTA-LM3 safe, effective, and feasible in patients with metastatic NENs?

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

REFERENCES

1. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol.* 2008;9:61–72.
2. Huguet I, Grossman AB, O'Toole D. Changes in the epidemiology of neuroendocrine tumours. *Neuroendocrinology.* 2017;104:105–111.
3. Ramírez-Rentería C, Ferreira-Hermosillo A, Marrero-Rodriguez D, Taniguchi-Ponciano K, Melgar-Manzanilla V, Mercado M. An update on gastroenteropancreatic neuroendocrine neoplasms: from mysteries to paradigm shifts. *Arch Med Res.* 2020;51:765–776.
4. Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol.* 2017;3:1335–1342.
5. Hofland J, Kaltsas G, de Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocr Rev.* 2020;41:371–403.
6. Refardt J, Hofland J, Kwadwo A, et al. Theranostics in neuroendocrine tumors: an overview of current approaches and future challenges. *Rev Endocr Metab Disord.* June 3, 2020 [Epub ahead of print].
7. Zhang J, Singh A, Kulkarni HR, et al. From bench to bedside: The Bad Berka experience with first-in-human studies. *Semin Nucl Med.* 2019;49:422–437.
8. Öberg K, Knigge U, Kwekkeboom D, Perren A, ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2012;23(suppl 7):vii124–vii130.
9. Mansi R, Fani M. Design and development of the theranostic pair ^{177}Lu-OPS201/^{68}Ga-OPS202 for targeting somatostatin receptor expressing tumors. *J Labelled Comp Radiopharm.* 2019;62:635–645.
10. Zhang J, Kulkarni HR, Baum RP. Peptide receptor radionuclide therapy using ^{225}Ac-DOTATOC achieves partial remission in a patient with progressive neuroendocrine liver metastases after repeated beta-emitter peptide receptor radionuclide therapy. *Clin Nucl Med.* 2020;45:241–243.
11. Baumann T, Rottenburger C, Nicolas G, Wild D. Gastroenteropancreatic neuroendocrine tumours (GEP-NET): imaging and staging. *Best Pract Res Clin Endocrinol Metab.* 2016;30:45–57.
12. Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23:4617–4624.
13. Baum RP, Kulkarni HR, Singh A, et al. Results and adverse events of personalized peptide receptor radionuclide therapy with ^{90}yttrium and ^{177}lutetium in 1048 patients with neuroendocrine neoplasms. *Oncotarget.* 2018;9:16932–16950.
14. Werner RA, Weich A, Kircher M, et al. The theranostic promise for neuroendocrine tumors in the late 2010s: where do we stand, where do we go? *Theranostics.* 2018;8:6088–6100.
15. Bodei L, Herrmann K, Baum RP, Kidd M, Malczewska A, Modlin IM. Caveat emptor: let our acclaim of the apotheosis of PRRT not blind us to the error of Prometheus. *J Nucl Med.* 2019;60:7–8.
16. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376:125–135.
17. Ginj M, Zhang H, Waser B, et al. Radiolabeled somatostatin receptor antagonists are preferable to agonists for in vivo peptide receptor targeting of tumors. *Proc Natl Acad Sci USA.* 2006;103:16436–16441.
18. Fani M, Nicolas GP, Wild D. Somatostatin receptor antagonists for imaging and therapy. *J Nucl Med.* 2017;58(suppl):61S–66S.
19. Bodei L, Weber WA. Somatostatin receptor imaging of neuroendocrine tumors: from agonists to antagonists. *J Nucl Med.* 2018;59:907–908.
20. Cescato R, Waser B, Fani M, Reubi JC. Evaluation of ^{177}Lu-DOTA-sst2 antagonist versus ^{177}Lu-DOTA-sst2 agonist binding in human cancers in vitro. *J Nucl Med.* 2011;52:1886–1890.
21. Wild D, Fani M, Behe M, et al. First clinical evidence that imaging with somatostatin receptor antagonists is feasible. *J Nucl Med.* 2011;52:1412–1417.
22. Fani M, Braun F, Waser B, et al. Unexpected sensitivity of sst2 antagonists to N-terminal radiometal modifications. *J Nucl Med.* 2012;53:1481–1489.
23. Cescato R, Erchegyi J, Waser B, et al. Design and in vitro characterization of highly sst2-selective somatostatin antagonists suitable for radiotargeting. *J Med Chem.* 2008;51:4030–4037.
24. Fani M, Del Pozzo L, Abiraj K, et al. PET of somatostatin receptor-positive tumors using ^{64}Cu- and ^{68}Ga-somatostatin antagonists: the chelate makes the difference. *J Nucl Med.* 2011;52:1110–1118.
25. Nicolas GP, Schreiter N, Kaul F, et al. Sensitivity comparison of ^{68}Ga-OPS202 and ^{68}Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors: a prospective phase II imaging study. *J Nucl Med.* 2018;59:915–921.
26. Wild D, Fani M, Fischer R, et al. Comparison of somatostatin receptor agonist and antagonist for peptide receptor radionuclide therapy: a pilot study. *J Nucl Med.* 2014;55:1248–1252.

27. Baum RP, Kulkarni HR. THERANOSTICS: from molecular imaging using Ga-68 labeled tracers and PET/CT to personalized radionuclide therapy—the Bad Berka experience. *Theranostics.* 2012;2:437–447.
28. Zhang J, Kulkarni HR, Singh A, Niepsch K, Muller D, Baum RP. Peptide receptor radionuclide therapy in grade 3 neuroendocrine neoplasms: safety and survival analysis in 69 patients. *J Nucl Med.* 2019;60:377–385.
29. Baum RP, Kulkarni HR, Carreras C. Peptides and receptors in image-guided therapy: theranostics for neuroendocrine neoplasms. *Semin Nucl Med.* 2012;42:190–207.
30. Schuchardt C, Kulkarni HR, Prasad V, Zachert C, Muller D, Baum RP. The Bad Berka dose protocol: comparative results of dosimetry in peptide receptor radionuclide therapy using ^{177}Lu-DOTATATE, ^{177}Lu-DOTANOC, and ^{177}Lu-DOTATOC. *Recent Results Cancer Res.* 2013;194:519–536.
31. Young H, Baum R, Cremerius U, et al. Measurement of clinical and subclinical tumour response using [^{18}F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. *Eur J Cancer.* 1999;35:1773–1782.
32. Aras M, Erdil TY, Dane F, et al. Comparison of WHO, RECIST 1.1, EORTC, and PERCIST criteria in the evaluation of treatment response in malignant solid tumors. *Nucl Med Commun.* 2016;37:9–15.
33. Gupta M, Choudhury PS, Rawal S, Goel HC, Rao SA. Evaluation of RECIST, PERCIST, EORTC, and MDA criteria for assessing treatment response with Ga68-PSMA PET-CT in metastatic prostate cancer patient with biochemical progression: a comparative study. *Nucl Med Mol Imaging.* 2018;52:420–429.
34. Aide N, Lasnon C, Veit-Haibach P, Sera T, Sattler B, Boellaard R. EANM/EARL harmonization strategies in PET quantification: from daily practice to multicentre oncological studies. *Eur J Nucl Med Mol Imaging.* 2017;44:17–31.
35. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228–247.
36. Nicolas GP, Mansi R, McDougall L, et al. Biodistribution, pharmacokinetics, and dosimetry of ^{177}Lu-, ^{90}Y-, and ^{111}In-labeled somatostatin receptor antagonist OPS201 in comparison to the agonist ^{177}Lu-DOTATATE: the mass effect. *J Nucl Med.* 2017;58:1435–1441.
37. Reidy-Lagunes D, Pandit-Taskar N, O'Donoghue JA, et al. Phase I trial of well-differentiated neuroendocrine tumors (NETs) with radiolabeled somatostatin antagonist ^{177}Lu-satoreotide tetraxetan. *Clin Cancer Res.* 2019;25:6939–6947.
38. van der Zwan WA, Brabander T, Kam BLR, et al. Salvage peptide receptor radionuclide therapy with [^{177}Lu-DOTA,Tyr^3]octreotate in patients with bronchial and gastroenteropancreatic neuroendocrine tumours. *Eur J Nucl Med Mol Imaging.* 2019;46:704–717.