Targeted α-Emitter Therapy with ^{212}Pb-DOTAMTATE for the Treatment of Metastatic SSTR-Expressing Neuroendocrine Tumors: First-in-Humans Dose-Escalation Clinical Trial

Ebrahim S. Delpassand[1,2], Izabela Tworowska[2], Rouzbeh Esfandiari[1], Julien Torgue[3], Jason Hurt[3], Afshin Shafie[1], and Rodolfo Núñez[1]

[1]*Excel Diagnostics and Nuclear Oncology Center, Houston, Texas;* [2]*RadioMedix, Inc., Houston, Texas; and* [3]*Orano Med, Plano, Texas*

Peptide receptor radiotherapy with somatostatin analogs has been successfully used for years as a treatment for somatostatin-overexpressing tumors. Treatment of neuroendocrine tumors (NETs) with the β-particle emitter ^{177}Lu-DOTATATE is currently considered the standard of care for subjects with gastroenteropancreatic NETs. Despite the success of ^{177}Lu-DOTATATE, there remains significant room for improvement in terms of both safety and efficacy. Targeted α-emitter therapy with isotopes such as ^{212}Pb has the potential to improve both. Here, we present the preliminary results of the phase 1 first-in-humans dose-escalation trial evaluating ^{212}Pb-DOTAMTATE (a bifunctional metal chelator [DOTAM] and the SSTR-targeting peptide [TATE]) in patients with somatostatin receptor–positive NETs. **Methods:** Twenty subjects with histologically confirmed NETs, prior positive somatostatin analog scans, and no prior history of ^{177}Lu/^{90}Y/^{111}In peptide receptor radiotherapy, with different primary sites of the disease, were enrolled. Treatment began with single ascending doses of ^{212}Pb-DOTAMTATE, with subsequent cohorts receiving an incremental 30% dose increase, which was continued until a tumor response or a dose-limiting toxicity was observed. This was followed by a multiple ascending dose regimen. The recommended phase 2 dose regimen consisted of 4 cycles of 2.50 MBq/kg (67.6 μCi/kg) of ^{212}Pb-DOTAMTATE administered at 8-wk intervals, intravenously. **Results:** Ten subjects received the highest dose, 2.50 MBq/kg/cycle (67.6 μCi/kg/cycle). Treatment was well tolerated, with the most common treatment-emergent adverse events being nausea, fatigue, and alopecia. No serious treatment-emergent adverse events were related to the study drug, and no subjects required treatment delay or a dose reduction. An objective radiologic response of 80% was observed for the first 10 subjects treated at the recommended phase 2 dose. **Conclusion:** Targeted α-therapy with ^{212}Pb-DOTAMTATE has been shown to be well tolerated. Preliminary efficacy results are highly promising. If these results are confirmed in a larger, multicenter clinical trial, ^{212}Pb-DOTAMTATE would provide a substantial benefit over currently Food and Drug Administration–approved therapies for patients with metastatic or inoperable SSTR-expressing NETs regardless of the grade and location of the primary tumor.

Key Words: TAT; PRRT; ^{212}Pb-DOTAMTATE; NET; NEN, phase 1

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For correspondence or reprints, contact Rodolfo Núñez (rnunez@exceldiagnostics.com).
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Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that originate from neuroendocrine cells. These neoplasms occur mostly in the gastrointestinal tract and pancreas but can also occur in other tissues, including thymus and lung, as well as uncommon sites such as ovaries, heart, and prostate. Regardless of their primary site, NETs share histologic, immunohistochemical, and ultrastructural features. NETs retain multipotent differentiation capacities, including the ability to produce and secrete a variety of metabolically active substances such as amines, peptides, and prostaglandins (*1*).

Most NETs strongly express somatostatin receptors (SSTRs), predominantly of the somatostatin 2 subtype (*2*), providing the basis of antisecretory and antiproliferative therapy with somatostatin analogs (short- and long-acting octreotide and long-acting lanreotide). These drugs are highly effective in controlling symptoms associated with carcinoid syndrome and have been shown to improve progression-free survival (PFS) in the metastatic setting in gastroenteropancreatic NETs (*3*). Although PFS can be prolonged, a high percentage of patients will progress and require additional therapy. Current guidelines recommend that patients with locoregional advanced disease or distant metastases for NETS of the gastrointestinal tract be treated with systemic therapy such as everolimus, sunitinib, or peptide receptor radionuclide therapy (PRRT) with the β-emitter ^{177}Lu-DOTATATE (*4*). This is currently the only PRRT approved by the U.S. Food and Drug Administration for patients with SSTR-expressing gastroenteropancreatic NETs (*5*). The NETTER-1 study demonstrated a clinically meaningful and statistically significant increase in PFS and objective radiologic response (ORR) in subjects with advanced gastroenteropancreatic NETs treated with ^{177}Lu-DOTATATE and long-acting octreotide (30 mg) compared with those treated with high-dose long-acting octreotide. At the data-cutoff date for the primary analysis, the estimated PFS at month 20 was 65.2% in the ^{177}Lu-DOTATATE group and 10.8% in the control group (*6*). Although the NETTER-1 trial demonstrated a tremendous benefit in PFS and overall survival, the ORR was only 13% in the ^{177}Lu-DOTATATE group versus 3% in the octreotide group, with only 1 complete response (CR) and 14 (12%) partial responses (PR) in the ^{177}Lu-DOTATATE group (*7*). It stands to reason that a radiopharmaceutical that provides a superior ORR will likely also improve PFS and overall survival.

^{212}Pb-DOTAMTATE is the first ^{212}Pb-labeled octreotate analog to treat SSTR-expressing NETs and targets SSTR-expressing malignancies regardless of their primary organ of origin and their

proliferative index. The drug consists of 3 linked components: the ^{212}Pb isotope, a bifunctional metal chelator (DOTAM), and the SSTR-targeting peptide (TATE).

The physical half-life of ^{212}Pb is 10.6 h, and it is an in vivo generator of α-emitting particles. ^{212}Pb itself is not an α-emitter, but its decay scheme includes 2 α-particles (1 per branch) with potent cytotoxicity to cell nuclei (*8,9*).

Compared with currently used β-emitters such as ^{177}Lu-DOTATATE (*10,11*), ^{212}Pb-DOTAMTATE provides a significantly higher linear energy transfer delivered in a shorter pathlength. In theory, a higher linear energy transfer should induce more double-stranded DNA damage to the tumor cells, ultimately resulting in irreparable tumor cell injury, apoptosis, and cell death. Additionally, because of the shorter pathlength, there are fewer side effects for subjects receiving targeted α-therapy (TAT) (*12*). Accordingly, to address an unmet need of TAT in the field of PRRT for NET, we are undertaking a phase 1 study with the main objective of determining the safety and dose-limiting toxicity of ascending doses of ^{212}Pb-DOTAMTATE used for TAT in subjects with SSTR-expressing NETs. A secondary objective was to determine the pharmacokinetic properties as well as the preliminary effectiveness of ascending doses of ^{212}Pb-DOTAMTATE.

MATERIALS AND METHODS

Study Design

This open-label, nonrandomized, dose-escalation and dose-expansion phase 1 trial (NCT03466216) was conducted at a single center in the United States (Excel Diagnostics Nuclear Oncology Center, Houston, Texas). This prospective study was performed in accordance with the Helsinki Declaration and followed the International Conference on Harmonization good-clinical-practice guidelines. The study was approved by the Biomedical Research Alliance of New York Institutional Review Board; all subjects gave written informed consent before enrollment. The study was conducted in full compliance with the U.S. Health Insurance Portability and Accountability Act. Eligible patients included men and women at least 18 y old with an Eastern Cooperative Oncology Group performance status of 0–2. They had to have a life expectancy of at least 12 wk and a histologically confirmed diagnosis of NET, either unresectable or metastatic progressive disease, with at least 1 site of measurable disease per RECIST 1.1. All patients were required to have SSTR imaging within 4 wk of the first dose. Patients who had been treated with prior whole-body radiotherapy or PRRT using ^{177}Lu/^{90}Y/^{111}In-DOTATATE/DOTATOC or TAT were excluded. Therapeutic use of any somatostatin analog, including long-acting octreotide acetate (within 28 d) and octreotide acetate (within 1 d), before administration of the study drug was exclusionary.

The study was designed as a single-ascending-dose (SAD)/multiple-ascending-dose (MAD) trial using a 3 + 3 dose-escalation scheme with an 8-wk dose-limiting toxicity period. Dose escalation proceeded as per Table 1. The initial dose to be examined was 1.13 MBq/kg (30.7 μCi/kg), and subsequent cohorts received an incremental 30% dose increase until a tumor response or a dose-limiting toxicity was observed. The maximum total dose per subject in the SAD cohort was 296 MBq (8 mCi). The maximum total dose per subject in the MAD cohort was 888 MBq (24 mCi). All these limits were assigned by human dosimetry calculations performed on subjects having received the ^{203}Pb-AlphaMedix (RadioMedix, Inc.) surrogate under investigational new drug 130,960. The activity of each cycle was not to exceed 203.5 MBq ± 10%. (5.5 mCi ± 10%), regardless of the subject's weight, and the cumulative dose was not to exceed 888 MBq (24 mCi). The data safety monitoring board was responsible for determining both dose escalation in the SAD cohorts and dose at which expansion into the MAD cohorts would occur. The board recommended transitioning to the MAD cohort if there was clinical efficacy and lack of any dose-limiting toxicities.

TABLE 1
Dose Escalation per Cycle in SAD and MAD Cohorts

Cohort	Dose per cycle (MBq/kg ± 10%)
1	1.13 (30.7)
2	1.48 (40.0)
3	1.92 (52.0)
4	2.50 (67.6)

Data in parentheses are microcuries.

Nonhematologic dose-limiting toxicities were defined as all grade 3 toxicities (except alkaline phosphatase) not responsive within 72 h of supportive care and any grade 4 toxicities. Hematologic dose-limiting toxicities were defined as any toxicity that did not recover to grade 2 or less within 8 wk after administration of the study drug. A dose-modifying toxicity was defined as any grade 3 or 4 hematologic toxicity (except lymphopenia) that did not resolve within 8 wk from the prior administration or a grade 2 or higher serum creatinine level that did not resolve within 8 wk from the prior administration.

The MAD treatment regimen began at the 1.92 MBq/kg (52.0 μCi/kg) dose level and was escalated to the fourth cohort (MAD4) at a dose of 2.50 MBq/kg (67.6 μCi/kg/cycle). The cohort was then expanded to include 7 more patients for a total of 10. Thirty minutes before each dose, an amino acid solution of lysine and arginine was administered at 250 mL/h over 4 h for kidney protection against the effects of radiation. Before each injection cycle, the subjects had a physical exam, filled out the quality-of-life questionnaire of the European Organization for the Research and Treatment of Cancer, and had routine blood testing (including complete blood count, comprehensive metabolic panel with estimated glomerular filtration rate [eGFR], and tumor markers), an electrocardiogram, and medical imaging. Baseline and follow-up imaging included contrast-enhanced MRI or CT for RECIST 1.1 evaluation. ^{99m}Tc-diethylenetriaminepentaacetic acid renal scanning and ^{68}Ga-DOTATATE PET/CT were also performed. ^{18}F-FDG PET/CT and bone scanning were performed on selected patients at the principal investigator's discretion. ^{18}F-FDG PET/CT was repeated if positive at the baseline evaluation.

For all subjects, safety follow-up visits were scheduled at 2, 5, 8, and 12 mo after the single injection in the SAD cohorts and after the fourth injection in the MAD cohorts. The 12-mo safety follow-up visit was also the end-of-study visit. From months 13 to 36, a structured, semiannual telephone follow-up call was made to collect information on late toxicity, any hospitalizations, recent imaging results, and new treatment. Efficacy assessments per RECIST 1.1 were performed after each cycle, as was functional imaging. Objective radiographic response (ORR) was assessed according to RECIST 1.1. Following our own preestablished criteria, the PET/CT imaging response was defined as CR when all SSTR-positive lesions were resolved or as PR when there was a reduction of more than 50% of the visually estimated tumor burden. Visual estimation of the overall tumor burden for each patient by ^{68}Ga-DOTATATE PET/CT was subjective and done by an experienced (>25 y) board-certified nuclear medicine physician estimating the reduction in tumor burden, considering that the baseline ^{68}Ga-DOTATATE PET/CT scan reflected 100% of the tumor burden. Duration of response was defined as the time that measurement criteria were first met for CR/PR by RECIST 1.1 until the date that recurrent

TABLE 2
Patient Characteristics, Including Relevant Clinical Trial Data

Patient*	Age (y)	Sex	Type of NET	Grade	Ki-67	Stage	Time gap (y)	No. of cycles	Total dose (MBq)	RECIST 1.1 response†	^{68}Ga PET response‡	Duration of response (mo)§
SAD1-01	75	M	Small bowel	2	4	IV	6.4	1	81 (2.2)	Stable disease	NA	NP
SAD1-02	76	F	Pancreatic	2	NA	IV	8.8	1	85 (2.3)	Stable disease	NA	NP
SAD1-03	77	M	Pancreatic	3	27	IV	4.5	1	85 (2.3)	Stable disease	NA	NP
SAD2-01	56	M	Rectal	2	NA	IV	5.2	1	122 (3.3)	Stable disease	NA	NP
SAD2-02	27	F	Small bowel	1	NA	IV	4.7	1	100 (2.7)	Stable disease	NA	NP
SAD2-03	72	F	Small bowel	1	2	IV	6.1	1	115 (3.2)	Stable disease	NA	NP
MAD3-01	61	F	Small bowel	2	6	IV	10.7	3	574 (15.5)	Stable disease	NSC	0
MAD3-02	62	F	Pancreatic	2	3	IV	7.2	2‖	329 (8.9)	Stable disease	NSC	0
MAD3-03	68	F	Small bowel	NA	NA	IV	10.7	3	266 (7.2)	Stable disease	NSC	0
MAD3-04	51	M	Pancreatic	NA	NA	IV	5.6	3	455 (12.3)	Stable disease	−40%	0
MAD4-01	62	M	Small bowel	3	22	IV	2.2	4	814 (22.0)	PR	−95%	22
MAD4-02	45	M	Bronchial carcinoid	1	>20	IV	6.2	4	796 (21.5)	PR	−100%	22
MAD4-03	71	F	Bronchial carcinoid	2	15	III	4.8	4	707 (19.8)	CR	−100%	20
MAD4-04	39	F	Rectal	3	30	IV	5.1	4	807 (21.8)	Stable disease	−40%	0
MAD4-05	62	M	Pancreatic	1	2	IV	7.3	4	873 (23.6)	PR	−80%	8
MAD4-06	49	F	Pancreatic	2	19	IV	2.9	4	681 (18.4)	PR	−100%	14
MAD4-07	45	M	Rectal	2	12	IV	5.7	4	858 (23.2)	PR	−95%	5
MAD4-08	60	M	Small bowel	2	5	IV	0.3	4	692 (18.7)	Stable disease	−15%	0
MAD4-09	80	M	Bronchial carcinoid	2	10	IV	1.1	4	836 (22.6)	PR	−60%	1
MAD4–10	59	F	Bronchial carcinoid	2	5	IV	1.8	4	847 (22.9)	PR	−30%	5

*MAD3 cohort started as SAD3 cohort, with single injection of 1.92 MBq/kg (52.0 μCi/kg). When quality-of-life improvements were reported after first cycle, approval was obtained from disease safety monitoring board and these subjects were transitioned to MAD cohort, with 2 additional cycles at same dose administered at 8-wk intervals.

†For SAD cohort, response was established 2 mo after injection, before other therapies began.

‡Percentage decrease in overall tumor burden on ^{68}Ga-DOTATATE PET/CT was visually estimated.

§As of June 2021.

‖Subject dropped out of study after second cycle.

NA = not available; NP = not applicable; NSC = no significant change.

As per 2017 WHO classification: G1 = <3, G2 = 3–20, and G3 = >20 Ki-67 index. Data in parentheses are microcuries. Time gap is difference in years between original histopathologic diagnosis and first treatment cycle with ^{212}Pb-DOTAMTATE.

or progressive disease was objectively documented (*13*) or last clinical contact (June 2021). Time to response was defined as the time between the first administration of study drug and the time when RECIST measurement criteria were first met for CR/PR.

The primary endpoint was assessment of the safety and dose-limiting toxicities of ascending doses of ^{212}Pb-DOTAMTATE used for TAT of subjects with SSTR-expressing NETs. Secondary endpoints included pharmacokinetics, dosimetry, and determination of preliminary effectiveness of ^{212}Pb-DOTAMTATE. Adverse events were coded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Pharmacokinetics were evaluated through the collection of several blood samples at multiple time points and urine collection before and after the intravenous administration of ^{212}Pb-DOTAMTATE.

Dosimetry data were obtained for 6 subjects in the MAD4 cohort and will be reported in a separate article.

The Student *t* test was used to compare the means and derive *P* values using JMP Clinical, version 8.0 (SAS Institute Inc.).

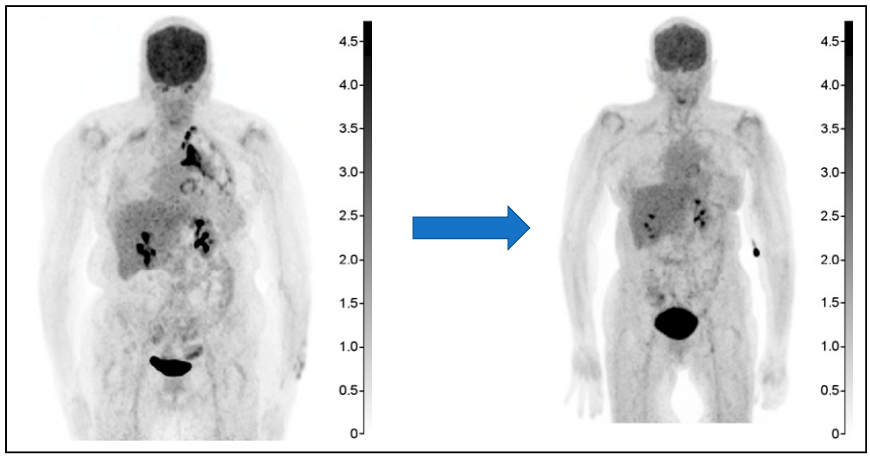

FIGURE 1. Volume-rendered images of ^{18}F-FDG PET/CT scans from subject MAD4-03 before (left) and after (right) treatment with 4 cycles of ^{212}Pb-DOTAMTATE.

RESULTS

Twenty PRRT-naïve subjects (10 male, 10 female) have been treated to date (median age, 62 y; range, 27–80 y), with 10 of 10 subjects (100%) receiving 4 cycles of ^{212}Pb-DOTAMTATE at the highest dose level, 2.50 MBq/kg/cycle (67.6 μCi/kg/cycle) (Table 2). The mean cumulative dose administered over 4 cycles based on a dose of 2.50 MBq/kg (67.6 μCi/kg) was 791 MBq (21.4 mCi), with a range of 681–873 MBq (18.4–23.6 mCi). All patients had received or declined all Food and Drug Administration–approved medications for their disease, except for PRRT, including somatostatin analogs, and progressed before enrollment. The time between the histopathologic diagnosis and the first cycle of treatment with ^{212}Pb-DOTAMTATE varied considerably from patient to patient, ranging from 0.3 to 10.7 y, with a mean of 5.36 y.

Radiographic Results

No ORR by RECIST 1.1 was seen in cohorts SAD1 or SAD2 or in the first MAD cohort (MAD3). In the MAD4 cohort, the ORR by RECIST was 80% (1 CR, 7 PR, 2 stable disease). One subject (10%) in the MAD4 cohort (MAD4-06) demonstrated an objective response 8 wk after the first injection, 6 of 7 subjects [86%]) demonstrated an objective response after the third cycle of therapy, and 1 subject (MAD4-07) achieved a PR after completion of all 4 cycles. The only CR by RECIST was in subject MAD4-03, after the 10-mo visit (Fig. 1). Four patients (40%) had at least a 50% decrease in the sum of the diameters of the target lesions. The largest percentage decrease in the sum of the diameters that was not a CR was seen in subject MAD4-02, with an 85% decrease (Figs. 2 and 3). The median decrease in the sum of the diameters for all patients was 41%.

Response by ^{68}Ga-DOTATATE PET/CT in the MAD4 cohort demonstrated 3 CR (patients MAD4-02, -03, and -06), 4 PR, and 3 stable disease (Fig. 4). The mean decrease in the sum of the diameters per RECIST in those patients who demonstrated a CR by ^{68}Ga-DOTATATE PET/CT was 84% (range, 70%–100%). Although patient MAD4-04 did not meet the definition of PR per RECIST,

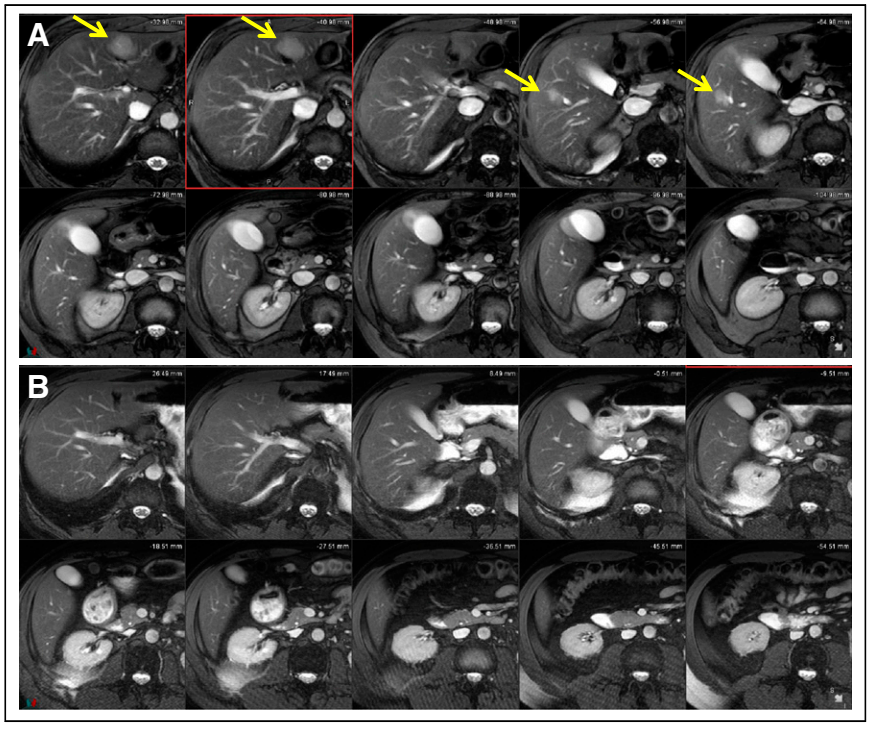

FIGURE 2. MRI of liver before (A) and after (B) treatment with 4 cycles of ^{212}Pb-DOTAMTATE in subject MAD4-02. Arrows point to liver metastases. Near-complete resolution of liver metastases is seen in B.

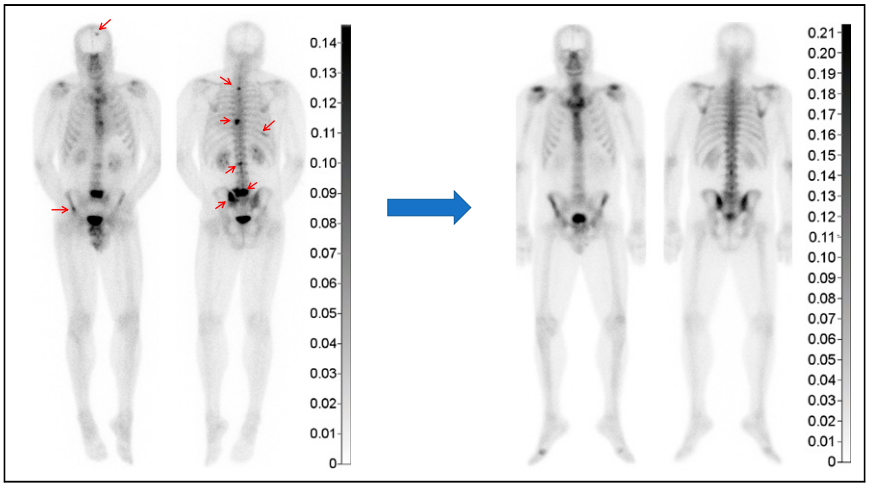

FIGURE 3. Bone scans of subject MAD4-02 before (left) and after (right) treatment with 4 cycles of ^{212}Pb-DOTAMTATE. Most lesions on initial baseline bone scan (arrows) are completely healed on bone scan after treatment.

with only a 26% decrease in the sum of the diameters of the target lesions, ^{68}Ga-DOTATATE PET/CT demonstrated obvious improvement in tumor burden.

No progression of disease was noted for 9 of 10 subjects (90%) who completed treatment. One subject experienced disease progression approximately 10 mo after completing all 4 cycles of treatment (16 mo after treatment initiation). Interestingly, the new lesions were not seen on ^{68}Ga-DOTATATE PET/CT but were seen on ^{18}F-FDG PET/CT, suggestive of an undifferentiated NET or a non–SSTR-expressing malignancy.

At the time of the last data collection, all MAD4 patients were alive, with the median length of follow-up being 17.4 mo (range, 9–26 mo). The median duration of response was 14 mo (range, 5–22 mo), and the median time to response was 5.2 mo (range, 1.7–10.3 mo).

Safety

No dose-limiting toxicities were noted during dose escalation or expansion, and no subject required a delay in treatment or a reduction or cancellation of dose. In total, 170 adverse events were reported. Eighty-two (46%) were reported in the SAD cohort and 97 (54%) in the MAD cohort. Of the adverse events, 49 (29%) were grade 2, 7 (5%) were grade 3, and none (0%) were grade 4. Thirty-two treatment-emergent adverse events (TEAEs) were considered related to the study drug, with the most common being alopecia (25%) and nausea (31%).

Fifteen serious TEAEs, including 2 deaths, were reported (Table 3). Most serious TEAEs were reported in the SAD cohorts (9/15) and were reported by 4 patients. Six serious TEAEs were reported in the MAD cohort by only 2 patients. The preferred terms for the reported serious TEAEs, by patient, were disease progression for SAD1-01; pain, malignancy-associated pain, dehydration, low eGFR (grade 3), and disease progression for SAD2-02; acute renal failure and renal failure for MAD3-01; worsening achalasia for MAD4-01; and fatigue, acute cerebrovascular accident, hypoglycemia, dyspnea, and chronic kidney disease for MAD4-03. None of the reported serious TEAEs were considered related to the study drug.

Vital Signs

There were no clinically significant changes in systolic blood pressure, diastolic blood pressure, heart rate, or QT interval from baseline compared with the last cycle of treatment for all subjects.

Hematologic, Hepatic, and Renal Parameters

In the MAD4 cohort after 6 mo of treatment, there was no statistically significant difference from screening in platelets (median,

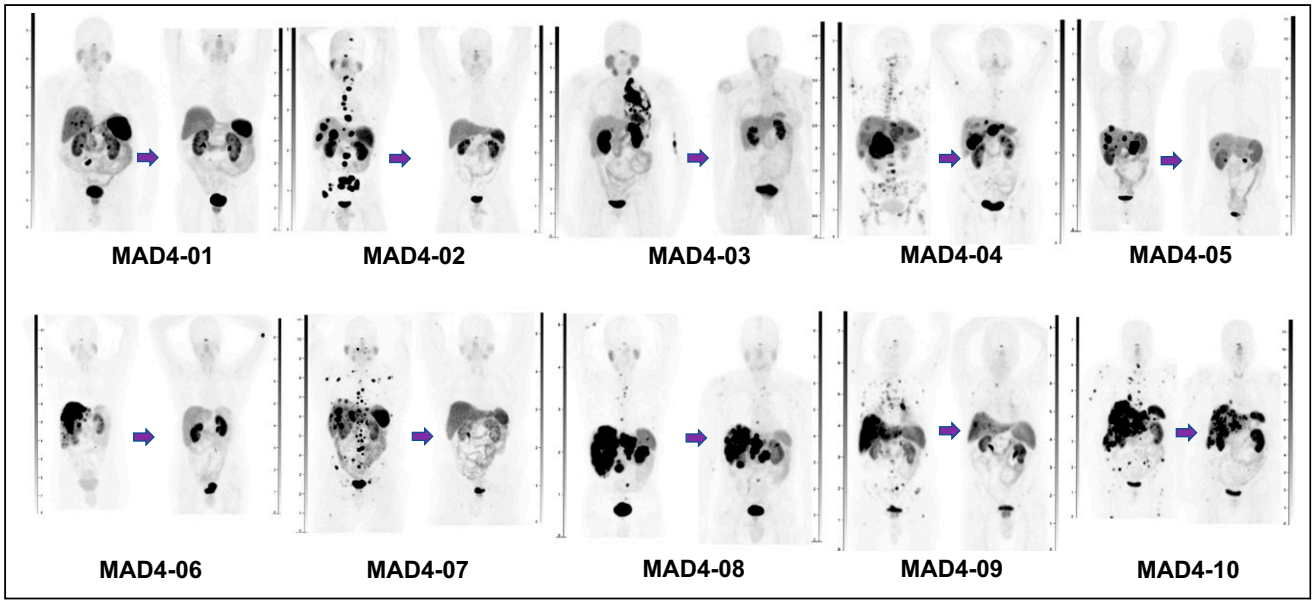

FIGURE 4. Volume-rendered images of ^{68}Ga-DOTATATE PET/CT scans from first 10 subjects enrolled in cohort 4 (MAD4) before treatment (left side of each panel) and after treatment (right side of each panel) with 4 cycles of ^{212}Pb-DOTAMTATE at dose of 2.50 MBq/kg (67.6 μCi/kg) for each cycle.

TABLE 3
All Serious Adverse Events

Subject	Event preferred term	Causality	Grade	Outcome
SAD1-01	Disease progression	Not related	5	Fatal
SAD2-02	Pain	Not related	2	Recovered
SAD2-02	Cancer pain	Not related	2	Recovered
SAD2-02	Dehydration	Not related	2	Recovered
SAD2-02	Disease progression	Not related	5	Fatal
SAD2-02	Low glomerular filtration rate	Not related	3	Recovered
MAD3-01	Acute kidney injury	Unlikely	2	Recovered
MAD3-01	Renal failure	Unlikely	3	Not recovered
MAD3-04	Abdominal pain	Unlikely	3	Recovering
MAD4-01	Worsening achalasia	Not related	3	Recovered
MAD4-03	Dyspnea	Unlikely	3	Recovered
MAD4-03	Fatigue	Unlikely	2	Resolved
MAD4-03	Hypoglycemia	Unlikely	2	Resolved
MAD4-03	Cerebrovascular accident	Unlikely	2	Resolved
MAD4-03	Chronic kidney disease	Unlikely	2	Not recovered

264×10^9/L; range, 124–417 $\times$ 10^9/L; $P = 0.304$), hemoglobin (median, 13.4 g/dL; range, 10.3–16.3 g/dL; $P = 0.1475$), absolute neutrophil count (median, 3.52 $\times$ 10^9/L; range, 2.08–5.1 $\times$ 10^9/L; $P = 0.1833$), or white blood cells (median, 5.7 $\times$ 10^9/L; range, 3.27–9 $\times$ 10^9/L; $P = 0.0868$).

Regarding the mean lymphocyte count, there was no significant change when comparing baseline screening with cycle 1. There was a statistically significant change when comparing cycle 2 with screening ($P = 0.0043$), cycle 3 with screening ($P = 0.0003$), and cycle 4 with screening ($P = 0.0014$); however, at 6 mo after treatment, there were no statistically significant differences from screening (median, 1.09 $\times$ 10^9/L; range, 0.3–2.42 10^9/L; $P = 0.0508$).

There were no statistically significant changes in alanine transaminase at 6 mo after treatment ($P = 0.091984$). There were statistically significant changes in aspartate aminotransferase ($P = 0.0454$) when comparing screening with the 6-mo time point.

The mean and median baseline eGFRs of all enrolled patients were 86.4 mL/min/1.72 m^2 and 92.7 mL/min/1.72 m^2, respectively. The mean eGFR for the MAD4 cohort at screening was 90.4 mL/min/1.72 m^2, and at the end of cycle 4 it was 86.64 mL/min/1.72 m^2. This was not a statistically significant difference ($P = 0.06499$). At 3 mo after completion of cycle 4, the mean eGFR was 78.34 mL/min/1.72 m^2, which was not significantly different from baseline ($P = 0.8650$). At the 6-mo follow-up, the mean eGFR was 73.38 mL/min/1.72 m^2, which was significantly different from screening ($P < 0.001$) but had no clinical significance.

DISCUSSION

The current study on adults with progressive metastatic or inoperable SSTR-expressing NETs suggests that treatment with ^{212}Pb-DOTAMTATE provides a clear clinical benefit regardless of the location of the primary site or grade of the tumor. This is a paradigm change from conventional ideas that PRRT needs to be done only on G1 or G2 gastroenteropancreatic NETs. We are treating these patients on the basis of their molecular biology and receptor affinity. Of the 10 subjects who received all 4 cycles, 8 (80%) demonstrated an objective, long-lasting radiologic response by RECIST 1.1, which is highly encouraging. In the pivotal multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic NETs, sunitinib demonstrated an ORR of 9.3%, compared with 0% in the placebo group (*14*). In the more recent NETTER-1 study, which enrolled only patients with midgut NETs, the initial ORR was 18% in the ^{177}Lu-DOTATATE group compared with only 3% in the octreotide group (*7*). These data were later updated to a 13% ORR in the ^{177}Lu-DOTATATE group and 4% in the control group (*6*). Despite the relatively low ORR, substantial improvements were made in both PFS and overall survival. In the current study, although the number of patients was small, at the time of this data evaluation (median follow-up, 17.4 mo) the duration of response (14 mo) was extremely encouraging. Follow-up continues to determine the true duration of response. The phase II study is planned.

In terms of safety, ^{212}Pb-DOTAMTATE appears to be well tolerated, with mild and manageable side effects. We did not find clinically significant hematologic or hepatic toxicity, although the number of patients treated at the highest dose was small and further follow-up is necessary. We did find a statistically significant change from baseline in aspartate aminotransferase, likely explained by 1 subject whose aspartate aminotransferase level was approximately 1.5 times the upper limit of normal and likely of no clinical concern.

We did not observe any statistically significant changes in most hematologic parameters; however, we did observe an expected, statistically significant decrease in the absolute lymphocyte count during treatment that trended toward normal after completion of therapy. Although there was a decrease in the lymphocyte count, the absolute neutrophil count remained normal throughout the treatment period. No other hematologic parameters had a statistically

significant change in values at the 6-mo follow-up compared with baseline.

Kidney reabsorption of radiolabeled peptides can lead to dose-limiting nephrotoxicity after PRRT. The time frame for kidney damage is unknown; however, data from external-beam radiotherapy indicate that chronic kidney failure may occur in up to 5% of patients within 5 y of a dose higher than 23 Gy (*15,16*). This concept has not been proven to be accurate for radioligand therapy but, at the moment, is the only available principle for regulatory agencies. Nevertheless, some centers strictly following the recommended kidney tolerance thresholds and not exceeding 4 × 7.4 GBq ^{177}Lu-DOTATATE reported either no grade 3 or 4 subacute nephrotoxicity (in 323 patients) (*17*) or only 1.5% grade 3 or 4 nephrotoxicity (in 807 patients) (*18*). Results from a recently published retrospective review on a 5-y follow-up of NET patients treated with ^{225}Ac-DOTATOC show there was an average eGFR loss of 8.4 mL/min per year, which was more pronounced in patients treated with higher doses (*19*). In the present study, 3 patients experienced serious TEAEs related to the kidney. Two patients in the SAD cohort had transient decreases in renal function due to dehydration; these were determined to be unrelated to the investigational drug. Patient MAD4-03, who obtained a CR from treatment, experienced acute kidney injury and resultant persistent chronic kidney disease. This 75-y-old patient had several confounding factors, including a longstanding history of obesity, hypertension, and poorly controlled type 2 diabetes mellitus and experienced a cerebrovascular accident before the kidney insult. Baseline serum creatinine and eGFR were 0.84 mg/dL and 92.5 mL/min/1.72 m^2, respectively. Both values remained relatively stable throughout treatment and began to change approximately 2 wk after the last treatment with ^{212}Pb-DOTAMTATE. The serum creatinine continued to rise to a high of 1.97 mg/dL, and the eGFR decreased to 28.5 mL/min/1.72 m^2, consistent with stage 3 chronic kidney disease. Renal function data collection continues for all MAD4 cohort patients, and long-term follow-up should shed light on what impact, if any, ^{212}Pb-DOTAMTATE has on the kidneys. The most common nonhematologic, nonrenal, or nonhepatic adverse event reported was nausea, followed by transient alopecia. Alopecia was moderate, and hair growth resumed quickly after treatment had been completed.

It is difficult to perform appropriate comparisons with the few published clinical trials of TAT in NET patients, since the radiopharmaceuticals used, and subject selection, among other factors, differ from ours. Nonetheless, data published by Kratochwil et al. in 2014 showed preliminary good results using ^{213}Bi-DOTATOC TAT (*20*). Prolonged responses were reported for the 7 patients in the study. Recently, data from Ballal et al. using ^{225}Ac-DOTATATE TAT in advanced, progressive, or PRRT-refractory gastroenteropancreatic NET patients reported a PR in 15 of 24 (62.5%) evaluable patients (by conventional imaging) and stable disease in 9 of 24 (37.5%) (*21*). In contrast to our study, all patients in the study of Ballal et al. had already been treated with ^{177}Lu-DOTATATE, and more than half (56%) had progressive disease. Nevertheless, the results show that ^{225}Ac-DOTATATE TAT is a promising treatment option, even in patients previously treated with ^{177}Lu-DOTATATE PRRT.

To the best of our knowledge, our study is the first in humans to evaluate the safety and response of ^{212}Pb-DOTAMTATE in NET. Although the number of patients is small, the results are promising (Fig. 4).

Strengths of this study include robust imaging data and inclusion of subjects with progressive metastatic NETs regardless of location of primary tumor and Ki-67 grade. Limitations of this study include a small number of patients recruited from only 1 clinical site, lack of central imaging, and limited follow-up.

CONCLUSION

^{212}Pb-DOTAMTATE is safe. Preliminary efficacy results are highly promising. If these results are confirmed in a larger, randomized, multicenter clinical trial, ^{212}Pb-DOTAMTATE would provide a substantial benefit over currently Food and Drug Administration–approved therapies for patients with metastatic or inoperable SSTR-expressing NETs regardless of the grade and location of the primary tumor.

DISCLOSURE

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KEY POINTS

QUESTION: Is ^{212}Pb-DOTAMTATE TAT a feasible and effective treatment modality for NET patients?

PERTINENT FINDINGS: The preliminary results in this first-in-humans study of ^{212}Pb-DOTAMTATE TAT show that it is a well-tolerated treatment with an overall response rate of 80% in the first 10 subjects treated with the effective dose.

IMPLICATIONS FOR PATIENT CARE: TAT with ^{212}Pb-DOTAMTATE in NET patients has shown great potential, exceeding the standard-of-care treatments currently available, and thus, a phase 2 study will start soon.

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