Radiolabeled Somatostatin Receptor Antagonist Versus Agonist for Peptide Receptor Radionuclide Therapy in Patients with Therapy-Resistant Meningioma: PROMENADE Phase 0 Study

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Our primary aim was to compare the therapeutic index (tumor–to–bone marrow and tumor-to-kidney absorbed-dose ratios) of the new radiolabeled somatostatin receptor antagonist [^{177}Lu]Lu-DOTA-JR11 with the established radiolabeled somatostatin receptor agonist [^{177}Lu]Lu-DOTATOC in the same patients with progressive, standard therapy-refractory meningioma. **Methods:** In this prospective, single-center, open-label phase 0 study (NCT04997317), 6 consecutive patients were included: 3 men and 3 women (mean age, 63.5 y). Patients received 6.9–7.3 GBq (standard injected radioactivity) of [^{177}Lu]Lu-DOTATOC followed by 3.3–4.9 GBq (2 GBq/m^2 × body surface area) of [^{177}Lu]Lu-DOTA-JR11 at an interval of 10 ± 1 wk. In total, 1 [^{177}Lu]Lu-DOTATOC and 2–3 [^{177}Lu]Lu-DOTA-JR11 treatment cycles were performed. Quantitative SPECT/CT was done at approximately 24, 48, and 168 h after injection of both radiopharmaceuticals to calculate meningioma and organ absorbed doses as well as tumor-to-organ absorbed-dose ratios (3-dimensional segmentation approach for meningioma, kidneys, liver, bone marrow, and spleen). **Results:** The median of the meningioma absorbed dose of 1 treatment cycle was 3.4 Gy (range, 0.8–10.2 Gy) for [^{177}Lu]Lu-DOTATOC and 11.5 Gy (range, 4.7–22.7 Gy) for [^{177}Lu]Lu-DOTA-JR11. The median bone marrow and kidney absorbed doses after 1 treatment cycle were 0.11 Gy (range, 0.05–0.17 Gy) and 2.7 Gy (range, 1.3–5.3 Gy) for [^{177}Lu]Lu-DOTATOC and 0.29 Gy (range, 0.16–0.39 Gy) and 3.3 Gy (range, 1.6–5.9 Gy) for [^{177}Lu]Lu-DOTA-JR11, resulting in a 1.4 (range, 0.9–1.9) times higher median tumor–to–bone marrow absorbed-dose ratio and a 2.9 (range, 2.0–4.8) times higher median tumor-to-kidney absorbed-dose ratio with [^{177}Lu]Lu-DOTA-JR11. According to the Common Terminology Criteria for Adverse Events version 5.0, 2 patients developed reversible grade 2 lymphopenia after 1 cycle of [^{177}Lu]Lu-DOTATOC. Afterward, 2 patients developed reversible grade 3 lymphopenia and 1 patient developed reversible grade 3 lymphopenia and neutropenia after 2–3 cycles of [^{177}Lu]Lu-DOTA-JR11. No grade 4 or 5 adverse events were observed at 15 mo or more after the start of therapy. The disease control rate was 83% (95% CI, 53%–100%) at 12 mo or more after inclusion. **Conclusion:** Treatment with 1 cycle of [^{177}Lu]Lu-DOTA-JR11 showed 2.2–5.7 times higher meningioma absorbed doses and a favorable therapeutic index compared with [^{177}Lu]Lu-DOTATOC after injection of 1.4–2.1 times lower activities. The first efficacy results demonstrated a high disease control rate with an acceptable safety profile in the standard therapy for refractory meningioma patients. Therefore, larger studies with [^{177}Lu]Lu-DOTA-JR11 are warranted in meningioma patients.

Key Words: meningioma; peptide receptor radionuclide therapy; DOTA-JR11; DOTATOC

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Meningiomas are among the intracranial tumors with the highest prevalence. They arise from the dura mater and occur in World Health Organization grades I–III. Sparse improvement in treatment results over recent decades is reflected by a 5-y survival between 55% and 70% (*1*). Surgery, as the main treatment option, is limited in a subgroup of patients because of anatomic involvement of critical neural or vascular structures or a diffuse growth pattern (*2*). Adjuvant external-beam radiotherapy improves recurrence rates (*3*) but may induce neurologic morbidity (*4*).

About 70% of meningiomas express somatostatin receptor subtype 2 (SST2) at a high density, and SST2 acts as a target for peptide receptor radionuclide therapy (*5*). Peptide receptor radionuclide therapy with the SST2 agonists [^{90}Y]Y-DOTATOC, [^{177}Lu]Lu-DOTATOC, and [^{177}Lu]Lu-DOTATATE (Lutathera; Novartis) has been used as second- or third-line therapy for meningiomas that, on the basis of a poor risk–benefit ratio, are not treatable with standard therapies (*6–10*). Gerster-Gilliéron et al. demonstrated a median progression-free survival of 24 mo and a stabilization of the disease in 87% of patients after treatment with 1.7–14.8 GBq of [^{90}Y]Y-DOTATOC (*7*). Because of severe renal toxicity (grades 4 and 5) in about 10% of patients (*11*), [^{90}Y]Y-DOTATOC is hardly used anymore and has been replaced by [^{177}Lu]Lu-DOTATOC and [^{177}Lu]Lu-DOTATATE, which are less toxic to kidneys. Although peptide receptor radionuclide therapy is efficient for the management of World Health Organization grade I and II meningiomas at an advanced stage, it stabilizes the disease for only up to 24 mo (*7,9,12*). Thus, there is an unmet need to develop more effective radiopharmaceuticals to improve the treatment of patients with advanced meningioma.

Until recently, it was assumed that internalization of the radiolabeled agonists was mandatory for somatostatin receptor–targeted

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therapy. About 20 y ago, Ginj et al. hypothesized that radiolabeled somatostatin receptor antagonists may perform better than agonists despite lacking internalization (*13*). In the meantime, there has been compelling evidence that ^{177}Lu-labeled SST2 antagonists (e.g., [^{177}Lu]Lu-DOTA-JR11, [^{177}Lu]Lu-OPS201, and [^{177}Lu]Lu-satoreotide tetraxetan) bind to many more SST2-binding sites on the cell surface, resulting in higher tumor absorbed doses (*14*). For example, the SST2 antagonist [^{177}Lu]Lu-DOTA-JR11 was superior to the SST2 agonist [^{177}Lu]Lu-DOTATATE in a single-center, prospective first-in-humans phase 0 study with 4 patients who had advanced metastatic neuroendocrine tumors (*15*). The most relevant findings of this study were the 3.5-fold higher median tumor absorbed dose, the more than 2-fold higher tumor–to–bone marrow absorbed-dose ratio with [^{177}Lu]Lu-DOTA-JR11 than with [^{177}Lu]Lu-DOTATATE, and moderate adverse events with 1 grade 3 thrombocytopenia after treatment with 3 cycles of approximately 5 GBq (15.2 GBq total) of [^{177}Lu]Lu-DOTA-JR11.

Therefore, we hypothesized that [^{177}Lu]Lu-DOTA-JR11 would also have a favorable therapeutic index in meningioma patients compared with [^{177}Lu]Lu-DOTATOC. The primary aim was to compare the therapeutic index (tumor–to–bone marrow and tumor-to-kidney absorbed-dose ratios) of the radiolabeled SST2 antagonist [^{177}Lu]Lu-DOTA-JR11 with the established radiolabeled SST2 agonist [^{177}Lu]Lu-DOTATOC in the same patients with progressive meningiomas that were refractory to standard treatment.

MATERIALS AND METHODS

Study Design and Patients

Six consecutive meningioma patients were included for this prospective, phase 0, single-center, open-label, dosimetry comparison study (ClinicalTrials.gov; NCT04997317). The ethics committee of Northwest and Central Switzerland approved this study, and all patients signed an informed consent form. The main inclusion criteria were a histologically confirmed meningioma that was progressive within less than 30 mo before inclusion, a lack of efficient standard treatment (assessment by the local multidisciplinary neurooncologic tumor board), a Karnofsky index of at least 60, a meningioma measurable in 3 dimensions, and confirmed expression of SST2 on [^{68}Ga]Ga-DOTATOC and [^{68}Ga]Ga-DOTATATE PET/CT imaging. The main exclusion criterion was the administration of another therapeutic substance 30 d before or during the ongoing study. Further inclusion and exclusion criteria are provided in the supplemental materials (available at http://jnm.snmjournals.org) (*16–18*).

Preparation of Radiotracers, SPECT/CT Imaging, and Therapy Protocol

DOTA-JR11 (*15*) and DOTATOC were synthesized according to good manufacturing practices established by piChEM GmbH and Bachem AG, respectively. [^{177}Lu]Lu-DOTA-JR11 was produced on an automated synthesis module (Pharmtracer; Eckert & Ziegler Medical). Briefly, 300 μg of DOTA-JR11 were dissolved in sodium acetate and ascorbic acid buffer (pH 4.5) and reacted with 4–6 GBq of no-carrier-added [^{177}Lu]$LuCl_3$ (EndolucinBeta; ITM) at 83°C for 20 min, followed by C18 solid-phase extraction. The final product was formulated in a physiologic saline solution containing ascorbic acid as the radioprotectant, calcium-diethylenetriamine pentaacetate as the radioisotope scavenger, and ethanol as the excipient. Radiochemical purity was assessed by radio–high-performance liquid chromatography and was 95% or better. The incorporation yield was measured by radio–thin-layer chromatography with levels of unbound ^{177}Lu of no more than 0.2%.

[^{177}Lu]Lu-DOTATOC was produced in a kit-labeling procedure by adding 240 μg of DOTATOC dissolved in sodium ascorbate buffer (pH 5) to a vial containing 8 GBq of no-carrier-added [^{177}Lu]Cl_3 and subsequently heating at 95°C for 30 min. The final product was formulated in a physiologic saline solution containing calcium-diethylenetriamine pentaacetate as the radioisotope scavenger. Radiochemical purity was assessed by radio–high-performance liquid chromatography and was 95% or better. The incorporation yield was measured by radio–thin-layer chromatography with levels of unbound ^{177}Lu of no more than 0.5%.

Patients received [^{177}Lu]Lu-DOTATOC (~7.4 GBq) followed by [^{177}Lu]Lu-DOTA-JR11 (2 GBq/m^2 × body surface area) at an interval of about 10 wk. Quantitative SPECT/CT scans were performed at approximately 24, 48, and 168 h after injection of both compounds using a Symbia Intevo 16 system (Siemens Healthineers) equipped with a medium-energy, low-penetration collimator (supplemental materials).

Meningioma Volumetry and Treatment Response Evaluation with MRI

All external and internal MRI studies were viewed with our institution's PACS, and the T1-weighted postcontrast 3-dimensional sequences were uploaded to mint Lesion software (Mint Medical GmbH). Meningioma volumetry was measured by a U.S. board-certified neuroradiologist with 20 y of experience. Meningioma response assessment was determined by comparison with the inclusion MRI study: progressive disease was defined as at least a 40% increase of meningioma volume or the appearance of new lesions, and stable disease was defined as less than a 40% increase in volume (*19*).

Dosimetry

All meningioma volumetry was based on MRI segmentation. The volume of kidneys, liver, bone marrow (red marrow), and spleen was determined by segmentation of CT images acquired from posttherapy SPECT/CT scans. The number of disintegrations and the absorbed doses were calculated with OLINDA 1.0 (Hermes Medical Solutions). The phantom organ weight was adjusted to the patient organ weight for kidneys, liver, and spleen. The meningioma absorbed dose was calculated using the spheres model in OLINDA. The red marrow activity was determined by drawing 4-mL volumes of interest in each vertebra from T2 to L5 for each time point. If needed, the volume of interest was adjusted to include only the bone marrow and no cortical bone, as the uptake in the vertebrae was assumed to be in the red marrow compartment of the cancellous bone. The red marrow compartment of the ilium was segmented as visible in the CT images. The red marrow absorbed dose was calculated by multiplying the absorbed energy from a ^{177}Lu decay by the time-integrated activity concentration in the red marrow. More details are available in the supplemental materials.

Toxicity

To reduce the risk of nephrotoxicity, the patients received a continuous infusion of 1,000 mL of physiologic NaCl solution containing 20.0 mg/mL of lysine and 20.7 mg/mL of arginine over 5 h (*15*). One hour after the start of this infusion, [^{177}Lu]Lu-DOTATOC or [^{177}Lu]Lu-DOTA-JR11 was infused over 1 min or 2 h, respectively. Two hours of slow infusion of [^{177}Lu]Lu-DOTA-JR11 was well tolerated without relevant nausea and hypotension as found in a previous study (*20*). Vital parameters (blood pressure, heart frequency, and oxygen saturation) were monitored every 15 min during the 2-h infusion of [^{177}Lu]Lu-DOTA-JR11. A full blood count and a comprehensive metabolic panel were performed on the day of each therapy cycle as well as 2, 4, and 6 wk after treatment. Common Terminology Criteria for Adverse Events version 5.0 was used to evaluate possible negative effects.

TABLE 1
Summary of Patient Characteristics, Treatment Protocol, Remission Status, and Adverse Events

Parameter	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Baseline characteristics						
Sex	Male	Female	Male	Male	Female	Female
Age (y)	52	58	83	73	75	39
Meningioma WHO grade	III	II	II	II	II	I
First diagnosed (mo before inclusion)	20	89	192	60	60	96
Previous therapy						
Last surgical treatment (mo before inclusion)	8	64	31	7	59	83
Last radiation therapy (mo before inclusion)	16	ND	13	54	55	54
Last systemic treatment (mo before inclusion)	1	ND	ND	ND	ND	ND
Treatment protocol						
[^{177}Lu]Lu-DOTATOC therapy						
Number of cycles	1	1	1	1	1	1
Total injected activity (GBq)	7.1	7.1	6.9	7.3	7.3	7.0
[^{177}Lu]Lu-DOTA-JR11 therapy						
Injected activity at first cycle (GBq)	4.5	4.9	3.3	4.0	4.1	3.7
Number of cycles	2	2	2	3	3	2
Total injected activity (GBq)	9.0	8.9	7.4	11.6	10.4	7.1
Remission status*						
Remission status before inclusion	PD	PD	PD	PD	PD	PD
Progression interval before inclusion (mo)	4	27	27	4	23	5
Meningioma volume change before inclusion (%)	+8,280	+45	+88	+50	+40	+61
Remission status after maximum follow-up	PD	SD	SD	SD	SD	SD
Additional treatments after inclusion†	Yes	Yes	No	No	No	No
Maximum follow-up after inclusion (mo)	15	22	16	15	17	12
Meningioma volume change at maximum follow-up (%)	+778	+9	+31	+19	0	−3
Adverse events (grade)						
Up to 10 wk after [^{177}Lu]Lu-DOTATOC						
Anemia	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	0
Lymphopenia	0	2	0	0	1	2
Thrombocytopenia	0	0	0	0	0	0
Up to 10 wk after first cycle of [^{177}Lu]Lu-DOTA-JR11						
Anemia	0	0	0	0	0	0
Neutropenia	0	0	0	0	3	0
Lymphopenia	0	2	0	0	2	3
Thrombocytopenia	0	0	0	0	0	0
Up to 13 mo after first cycle of [^{177}Lu]Lu-DOTA-JR11						
Anemia	0	0	0	0	0	0
Neutropenia	0	0	0	0	0	2
Lymphopenia	0	3	0	0	3	3
Thrombocytopenia	0	0	0	0	0	0

*Remission status of meningiomas assessed with MRI volumetry.

†Patient 1 received high-dose chemotherapy with ifosamid 7 mo after termination of [^{177}Lu]Lu-DOTA-JR11 therapy followed by therapy with mitogen-activated extracellular signal-regulated kinase inhibitor (cobimetinib). Patient 2 was treated with humanized monoclonal antibody (bevacizumab) 6 mo after termination of [-Lu]Lu-DOTA-JR11 therapy.

ND = not done; PD = progressive disease; SD = stable disease.

TABLE 2
Summary of Tumor Radiation Dose Estimations

	[^{177}Lu]Lu-DOTATOC, 1 cycle*				[^{177}Lu]Lu-DOTA-JR11, 1 cycle†				2–3 cycles†
Patient	Meningioma dose (Gy/cycle)	Red marrow dose (Gy/cycle)	T/BM	T/K	Meningioma dose (Gy/cycle)	Red marrow dose (Gy/cycle)	T/BM ratio	T/K ratio	Meningioma dose (Gy)
1	0.8	0.05	16	0.6	4.7	0.16	30	3.0	9.5
2	1.9	0.10	19	0.6	8.4	0.31	27	1.8	15.3
3	4.4	0.15	28	1.5	14.5	0.27	54	4.6	32.3
4	5.0	0.17	30	0.9	15.0	0.39	38	2.5	43.4
5	10.2	0.13	78	4.0	22.7	0.34	66	8.1	57.7
6	2.5	0.08	29	1.0	7.1	0.24	30	2.0	13.5
Median	3.4	0.11	29	1.0	11.5	0.29	34	2.8	23.8
Range	0.8–10.2	0.05–0.17	16–78	0.6–4.0	4.7–22.7	0.16–0.39	25–66	1.8–8.1	9.5–57.7

*First therapy cycle was performed with 7.4 GBq ± 10% [^{177}Lu]Lu-DOTATOC.
†All [^{177}Lu]Lu-DOTA-JR11 therapy cycles were conducted with 2 GBq × body surface area ± 10% per cycle.
T/BM = tumor-to-red bone marrow ratio; T/K = tumor-to-kidney ratio.

Statistical Analysis

For this phase 0 study, no sample size calculation was performed. All data were summarized using descriptive statistics. Unless otherwise stated, all data are expressed as median with range.

RESULTS

Dosimetry Results and Response

In total, 7 patients were recruited between May 2021 and March 2022. The first patient without histologic proof of a meningioma did not meet the inclusion criteria. Therefore, 6 patients received 1 cycle of [^{177}Lu]Lu-DOTATOC at an activity of 6.9–7.3 GBq (peptide amount, ~190 μg) followed by 1 cycle of [^{177}Lu]Lu-DOTA-JR11 at an activity of 3.3–4.9 GBq (peptide amount, ~240 μg) at an interval of 10 ± 1 wk. Afterward, additional [^{177}Lu]Lu-DOTA-JR11 treatment cycles were performed according to clinical needs (patient characteristics and treatment protocol in Table 1). Table 2 shows the results of tumor and bone marrow absorbed-dose estimations as well as tumor–to–bone marrow and tumor-to-kidney absorbed-dose ratios for all 6 patients. The effective tumor half-life was considerably higher with [^{177}Lu]Lu-DOTA-JR11 (half-life, 71.7 h; range, 56.4–87.0 h) than with [^{177}Lu]Lu-DOTATOC (half-life, 51.7 h; range, 49.2–64.2 h). Furthermore, the median tumor–to–bone marrow absorbed-dose ratio was 1.4 (range, 0.9–1.9) times higher with [^{177}Lu]Lu-DOTA-JR11. Only 1 of 6 patients showed a slightly lower tumor–to–bone marrow absorbed-dose ratio with [^{177}Lu]Lu-DOTA-JR11 than with [^{177}Lu]Lu-DOTATOC. Absorbed-dose estimations for most relevant organs with [^{177}Lu]Lu-DOTATOC and [^{177}Lu]Lu-DOTA-JR11 are summarized in Supplemental Table 1. In correlation with the dosimetry results, quantitative posttreatment SPECT scans showed more pronounced accumulation in meningioma lesions and in the bone marrow with [^{177}Lu]Lu-DOTA-JR11 than with [^{177}Lu]Lu-DOTATOC. Figure 1 shows the maximum-intensity projection SPECT images of all patients. Because of the favorable dosimetry results for the SST2 antagonist, 1–2 additional treatment cycles were performed with [^{177}Lu]Lu-DOTA-JR11, resulting in a disease control rate of 83% (95% CI, 53%–100%) at least 12 mo after inclusion. Remission status is provided in Table 2. Figure 2 shows the treatment response of patient 4.

Toxicity

All adverse events are summarized in Table 1. There was no nausea, vomiting, or hypotension after injection of either compound. In all patients, the reported adverse events resolved after a few weeks and there were no grade 4 or 5 adverse events. Up to 13 mo after the first therapy cycle with [^{177}Lu]Lu-DOTA-JR11, there was no worsening of kidney function and no evidence for myelodysplastic syndrome or other neoplasms.

DISCUSSION

The main results of this study can be summarized as follows. First, although [^{177}Lu]Lu-DOTA-JR11 therapy was performed with 1.4–2.1 times lower activity, the meningioma absorbed dose per treatment cycle was 2.2–5.7 times higher than that with [^{177}Lu]Lu-DOTATOC, resulting in promising efficacy results (disease control rate of 83% at ≥12 mo) in these therapy-resistant meningioma patients. Second, the therapeutic index indicates that [^{177}Lu]Lu-DOTA-JR11 is favorable for the treatment of meningioma patients because the tumor–to–bone marrow and tumor-to-kidney absorbed-dose ratios are 0.9–1.9 and 2.0–4.8 times higher with [^{177}Lu]Lu-DOTA-JR11 than with [^{177}Lu]Lu-DOTATOC. Third, renal toxicity is expected to be negligible with [^{177}Lu]Lu-DOTA-JR11 because of the several times higher tumor-to-kidney absorbed-dose ratios; in fact, there was no observed renal toxicity for up to 13 mo after the start of [^{177}Lu]Lu-DOTA-JR11 therapy. Lastly, although the estimated absorbed bone marrow dose was 1.7–3.1 times higher with [^{177}Lu]Lu-DOTA-JR11 than with [^{177}Lu]Lu-DOTATOC, bone marrow toxicity was only moderate, with reversible grade 3 lymphopenia and neutropenia, respectively, in 33% of patients after treatment with 1 cycle of [^{177}Lu]Lu-DOTATOC and 2 or 3 cycles of [^{177}Lu]Lu-DOTA-JR11.

These observations give rise to the expectation that the higher meningioma absorbed dose delivered by [^{177}Lu]Lu-DOTA-JR11

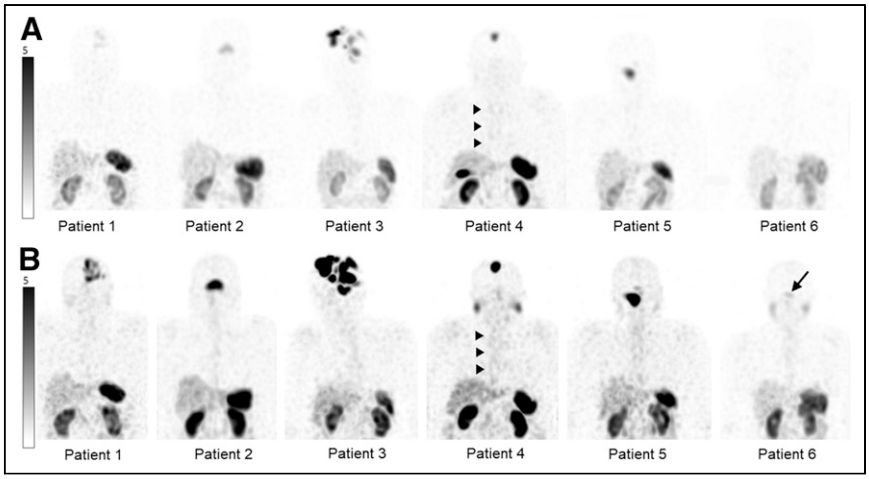

FIGURE 1. Posttreatment maximum-intensity projection of quantitative SPECT images acquired 48 h after injection of [^{177}Lu]Lu-DOTATOC (A) and [^{177}Lu]Lu-DOTA-JR11 (B) in same patients 10 ± 1 wk apart. SUV window threshold was set at 5 for all images, and scales indicate SUVs. In all patients, bone marrow uptake in spine was more pronounced with [^{177}Lu]Lu-DOTA-JR11 than with [^{177}Lu]Lu-DOTATOC (arrowheads in patient 4). In patient 6, small meningioma with volume of 0.3 cm^3 was visible only in posttreatment [^{177}Lu]Lu-DOTA-JR11 SPECT image (arrow).

may result in higher tumor control rates, at least in advanced World Health Organization grade I and II meningiomas. Unlike [^{90}Y]Y-DOTATOC, in which the maximum injected activity was limited by renal or hematologic adverse effects, [^{177}Lu]Lu-DOTA-JR11 is likely to overcome renal toxicity and, furthermore, may improve the bone marrow toxicity profile by enabling higher meningioma doses at a lower injected activity than is possible with [^{177}Lu]Lu-DOTATOC. [^{177}Lu]Lu-DOTA-JR11 administered at less than 5 GBq (2 GBq/m^2 × body surface area) per cycle for 3 cycles appears to offer additional advantages such as reduction of radioactive waste and radionuclide costs.

Nevertheless, bone marrow toxicity remains the dose-limiting adverse effect for the application of [^{177}Lu]Lu-DOTA-JR11 and other radiolabeled SST2 antagonists. This is of particular importance because there is no established bone marrow protection strategy. According to current clinical data, SST2 antagonists such as [^{177}Lu]Lu-DOTA-JR11 and [^{177}Lu]Lu-DOTA-LM3 have induced grade 3 or worse hematologic toxicity (according to the Common Terminology Criteria for Adverse Events) in 20%–23% of patients (*20,21*), which was more than the 9%–13% toxicity induced by [^{177}Lu]Lu-DOTATATE (NETTER-1 study) or [^{90}Y]Y-DOTATOC (*11,22*). For example, Reidy-Lagunes et al. described grade 4 hematotoxicity (leukopenia, neutropenia, and thrombocytopenia) in 4 of the first 7 patients with neuroendocrine tumors treated with 2 cycles of approximately 7.4 GBq (50–100 μg) of [^{177}Lu]Lu-DOTA-JR11 (cumulative radioactivity between 10.5 and 15.0 GBq) (*21*). Hence, their single-center phase I study was suspended, and the protocol was modified to limit the cumulative absorbed bone marrow dose. Importantly, there is evidence that a subpopulation of the hematopoietic cells, especially CD34-positive stem cells, shows some SST2 expression in red marrow (*23*). This is likely the reason for the more pronounced hematotoxicity of [^{177}Lu]Lu-DOTA-JR11 and [^{177}Lu]Lu-DOTA-LM3, as both compounds exhibit an SST2 binding capacity higher than that of [^{177}Lu]Lu-DOTATOC and [^{177}Lu]Lu-DOTATATE (*24*). Furthermore, SPECT images (Fig. 1) of our study show higher accumulation of [^{177}Lu]Lu-DOTA-JR11 than of [^{177}Lu]Lu-DOTATOC in the bone marrow, further supporting the evidence of a more pronounced SST2-mediated accumulation of [^{177}Lu]Lu-DOTA-JR11 in hematopoietic cells. Consequently, blood-based bone marrow dosimetry of SST2-targeting radioligands should be replaced by imaging-based bone marrow dosimetry because the former does not consider specific accumulation of radioligands in red bone marrow (*25*). The only limitation of imaging-based bone marrow dosimetry might be the presence of bone metastases, which is not relevant to meningioma.

One reason for the lower hematologic toxicity in our study than in the 2 other clinical [^{177}Lu]Lu-DOTA-JR11 studies (*20,21*) could be that the injected activities of [^{177}Lu]Lu-DOTA-JR11 in our study were adapted to the body surface area and were generally lower (2.9–4.9 GBq per cycle) than in the 2 other studies (~4.5 and 6.2–7.9 GBq

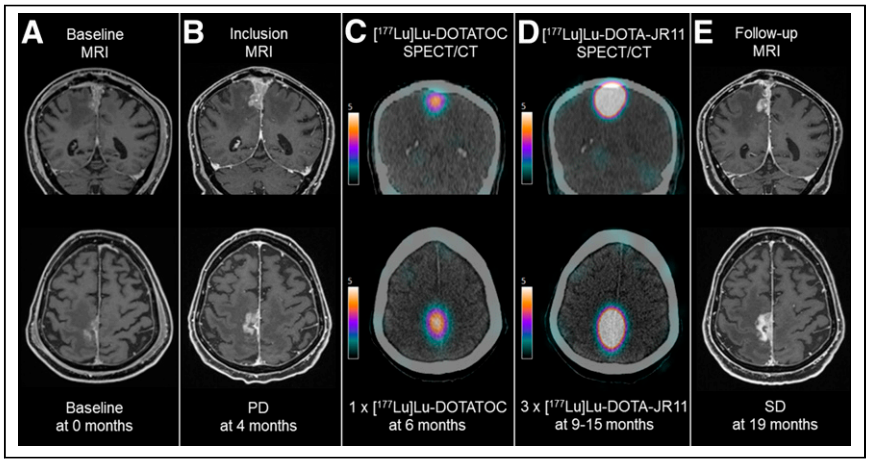

FIGURE 2. Patient 4 with therapy-resistant World Health Organization grade II meningioma. Baseline MRI (A) at 0 mo, inclusion MRI (B) 4 mo after baseline, [^{177}Lu]Lu-DOTATOC SPECT/CT (C) 6 mo after treatment, and [^{177}Lu]Lu-DOTA-JR11 SPECT/CT (D) 9 mo after treatment are shown. Follow-up MRI (E) was performed 19 mo after baseline MRI. Top row shows corresponding coronal images, and bottom row shows corresponding axial images. All MRI examinations were contrast-enhanced T1-weighted volumetric interpolated breath-hold examination sequences, and SPECT/CT scans were acquired 48 h after injection of 7.3 GBq of [^{177}Lu]Lu-DOTATOC and 4.0 GBq of [^{177}Lu]Lu-DOTA-JR11. SUV window threshold was set at 5 for all SPECT images. Patient had progressive disease (PD) with 50% meningioma volume increase within 4 mo at time of inclusion and received 1 cycle of [^{177}Lu]Lu-DOTATOC and 3 cycles of [^{177}Lu]Lu-DOTA-JR11. Follow-up MRI 15 mo after inclusion indicated stable disease (SD) with only 19% meningioma volume increase in comparison to inclusion MRI.

per cycle), resulting in a maximum bone marrow absorbed dose of 0.39 Gy per cycle and 1.13 Gy in total. Another possibility is that the injected amount of DOTA-JR11 (peptide amount) per cycle was approximately 240 μg, resulting in specific activities of between 26 and 35 GBq/μmol for [^{177}Lu]Lu-DOTA-JR11, 4–10 times lower than in the study of Reidy-Lagunes et al. This could be relevant for bone marrow protection, as a lower specific activity (lower ratio of radioactive to nonradioactive compound) causes better saturation of SST2-expressing CD34-positive stem cells, which account for only approximately 2% of total bone marrow cells. In fact, the mean bone marrow absorbed dose and absorbed dose in other SST2-positive organs were lower in our study than in the study of Reidy-Lagunes et al.: the bone marrow dose was 0.07 Gy/GBq (0.04–0.10) versus 0.09 Gy/GBq (0.06–0.15), respectively. Of note, the comparability of dosimetry results is limited by differences in equipment and calculation. Nevertheless, in a preclinical study, Nicolas et al. showed a decrease of bone marrow absorbed dose and absorbed dose in other SST2-positive organs after injection of [^{177}Lu]Lu-DOTA-JR11 at a lower specific activity (*26*). Future clinical studies will be necessary to confirm the protective effect of a lower specific activity to the bone marrow. However, our study showed that 2 or 3 cycles of [^{177}Lu]Lu-DOTA-JR11 with an injected radioactivity of 2 GBq/m^2 times the body surface area and a peptide amount of approximately 240 μg seem to be safe in not only meningioma patients but also other patients (e.g., neuroendocrine tumor patients) who qualify for the treatment with [^{177}Lu]Lu-DOTA-JR11 (*24*).

Previous results with radiolabeled somatostatin receptor agonists demonstrate feasibility and tolerance in the setting of ineffective external-beam radiotherapy followed by radiolabeled SST2 agonists (*27*); however, with the higher doses delivered by radiolabeled SST2 antagonists, the question of tolerance and feasibility should be addressed again.

One main limitation to this study is the application of therapeutic amounts of [^{177}Lu]Lu-DOTATOC and then [^{177}Lu]Lu-DOTA-JR11 10 wk later without using a crossover study design, resulting in a potential carry-over effect (treatment effect) from the first treatment with [^{177}Lu]Lu-DOTATOC onto the [^{177}Lu]Lu-DOTA-JR11 biodistribution. Thus, the dosimetry calculation could reflect a falsely lower meningioma absorbed-dose estimation of [^{177}Lu]Lu-DOTA-JR11. However, the risk for such a carry-over effect is low because the meningioma maximum absorbed dose was only 10.2 Gy with [^{177}Lu]Lu-DOTATOC. A second limitation is the small phase 0 study design that, nevertheless, produced direct comparison data with only 6 patients.

CONCLUSION

This phase 0 study provides, to our knowledge, the first clinical evidence that radiolabeled SST2 antagonists such as [^{177}Lu]Lu-DOTA-JR11 exhibit, in meningiomas, absorbed doses higher than those of standard peptide receptor radionuclide therapy with [^{177}Lu]Lu-DOTATOC despite application of lower activities. Furthermore, SPECT imaging indicates higher accumulation of [^{177}Lu]Lu-DOTA-JR11 than of [^{177}Lu]Lu-DOTATOC in the dose-limiting bone marrow, resulting in higher bone marrow absorbed doses with [^{177}Lu]Lu-DOTA-JR11. At the same time, a favorable therapeutic index was observed with [^{177}Lu]Lu-DOTA-JR11 without relevant hematologic toxicity. Preliminary data on disease control rates are encouraging and support a possible therapeutic role for radiolabeled SST2 antagonists in the treatment of otherwise therapy-refractory meningiomas. Further evaluation of [^{177}Lu]Lu-DOTA-JR11 in meningioma patients is planned in a PROMENADE phase I/II study (ClinicalTrials.gov; NCT04997317).

DISCLOSURE

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KEY POINTS

QUESTION: Is the therapeutic index (tumor–to–bone marrow and tumor-to-kidney absorbed-dose ratios) of the SST2 antagonist [^{177}Lu]Lu-DOTA-JR11 superior to that of the established radiolabeled SST2 agonist [^{177}Lu]Lu-DOTATOC in standard therapy-resistant meningioma?

PERTINENT FINDINGS: In this single-center, phase 0 study, [^{177}Lu]Lu-DOTA-JR11 showed much higher meningioma absorbed doses despite application of lower activities in all 6 patients. At the same time, a favorable therapeutic index and no relevant hematologic toxicity were observed after body surface area–based dosing of [^{177}Lu]Lu-DOTA-JR11.

IMPLICATIONS FOR PATIENT CARE: For the treatment of meningioma, [^{177}Lu]Lu-DOTA-JR11 is a promising and safe radiopharmaceutical that needs further clinical evaluation.

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