Theranostics of Radiolabeled Somatostatin Antagonists ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11 in Patients with Neuroendocrine Tumors

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department:	Lisa Bodei, MD	Radiology/Molecular Imaging and Therapy Service (MITS)
Co-Principal Investigator(s)/Department:	Diane Reidy-Lagunes, MD	Medicine/ Solid Tumor Service, GI Oncology (GI)
	Neeta Pandit-Taskar, MD	Radiology/MITS
	Joseph O'Donoghue, PhD	Medical Physics
Investigator(s)/Department:	Jorge A. Carrasquillo, MD	Radiology/MITS
	Ryan Reddy, MD	Radiology
	John Humm, PhD	Medical Physics
	Ghassan Abou-Alfa, MD	Medicine/GI
	Andrea Cercek, MD	Medicine/GI
	Andrew Epstein, MD	Medicine/GI
	James Harding, MD	Medicine/GI
	David Ilson, MD, PhD	Medicine/GI
	Yelena Janjigian, MD	Medicine/GI
	David Kelsen, MD	Medicine/GI
	Nancy Kemeny, MD	Medicine/GI
	Geoffrey Ku, MD	Medicine/GI
	Eileen O'Reilly, MD	Medicine/GI
	Leonard Saltz, MD	Medicine/GI
	Neil Segal, MD, PhD	Medicine/GI
	Armin Shahrokni, MD	Medicine/GI
	Zsofia Stadler, MD	Medicine/GI
	Anna Varghese, MD	Medicine/GI
	Rona Yaeger, MD	Medicine/GI
	Kenneth Yu, MD	Medicine/GI
	Carlos Flombaum, MD	General Medicine/Nephrology Service
	Jason Lewis, PhD	Radiochemistry and Imaging Sciences Service
	Serge Lyashchenko, Pharm D	Radiochemistry and Imaging Sciences Service
	Simone Krebs, MD	Radiology/MITS
	Mithat Gonen, PhD	Biostatistics
	Laure Michaud, MD	SKI
	Romina Giancipoli, MD	Sloan Kettering Institute Radiology
Consenting Professional(s)/Department:	Lisa Bodei, MD	Radiology/MITS
	Diane Reidy-Lagunes, MD	Medicine/GI Oncology
	Neeta Pandit-Taskar, MD	Radiology/MITS
	Jorge Carrasquillo, MD	Radiology/MITS
	Ghassan Abou-Alfa, MD	Medicine/GI
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	Anna Varghese, MD	Medicine/GI
	Rona Yaeger, MD	Medicine/GI
	Kenneth Yu, MD	Medicine/GI

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, New York 10065

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Peptide-receptor radionuclide therapy (PRRT) with radiolabeled somatostatin (sst) analogs was developed in the 1990s (1), and is now frequently used in Europe for the treatment of metastatic neuroendocrine tumors (NETs) (2-4). However, not all patients respond well to PRRT. In addition, there are serious and potentially irreversible side effects, most notably chronic renal failure due to renal excretion of the radiopeptides (2, 5). Thus, there is a clear need to develop new ligands with higher tumor uptake and a more favorable tumor-to-kidney dose ratio.

To address this need, members of our group have developed radiolabeled somatostatin receptor type 2 (sstr2) *antagonists* (6-10*)*. Preclinical studies have indicated that these compounds bind to significantly more receptor sites than the sstr agonists currently used for PRRT (6). This finding was confirmed by quantitative autoradiography of patient-derived tumor samples (11), which demonstrated a more than four-fold increase in the ex vivo binding of the somatostatin receptor antagonist ^{177}Lu-DOTA-BASS when compared to the somatostatin receptor agonist ^{177}Lu-DOTA-TATE. In a pilot imaging study with an ^{111}In-labeled DOTA-BASS, we have shown that this ligand detects significantly more metastases of NETs in patients than the current standard ^{111}In-DTPA-Octreotide (9). We have also performed a preliminary clinical study comparing the dosimetry of a ^{177}Lu-labeled therapeutic sstr antagonist ^{177}Lu-JR11 with ^{177}Lu-DOTA-TATE, an sstr agonist frequently used for PRRT. In this study, the antagonist demonstrated on average a three-fold higher tumor dose and a two-fold higher tumor-to-kidney ratio (10).

The goal of this study is to evaluate the sstr antagonists, ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11 as a pair of diagnostic/therapeutic radiopharmaceuticals (theranostics) in patients with NETs. Specifically, we will (i) assess biodistribution and tumor uptake of ^{68}Ga-DOTA-JR11 and compare the sensitivity of ^{68}Ga-DOTA-JR11 PET with ^{111}In-DTPA-Octreotide SPECT (the current clinical standard); (ii) determine tumor and normal organ doses after administration of ^{177}Lu-DOTA-JR11; and (iii) obtain preliminary data on tumor response to ^{177}Lu-DOTA-JR11.

We will include 20 evaluable patients with, progressive, and inoperable well differentiated NETs. Patients will first undergo a PET/CT with ^{68}Ga-DOTA-JR11. Patients with sufficient tumor uptake of ^{68}Ga-DOTA-JR11 will be offered therapy with ^{177}Lu-DOTA-JR11. Patients with no ^{68}Ga-DOTA-JR11 positive disease will be replaced. We expect this to be the case in 10% or less of the patients. Therapy will be preceded by a dosimetric study to determine the amount of radioactivity that can be safely administered. The study will be performed under an MSKCC IND.

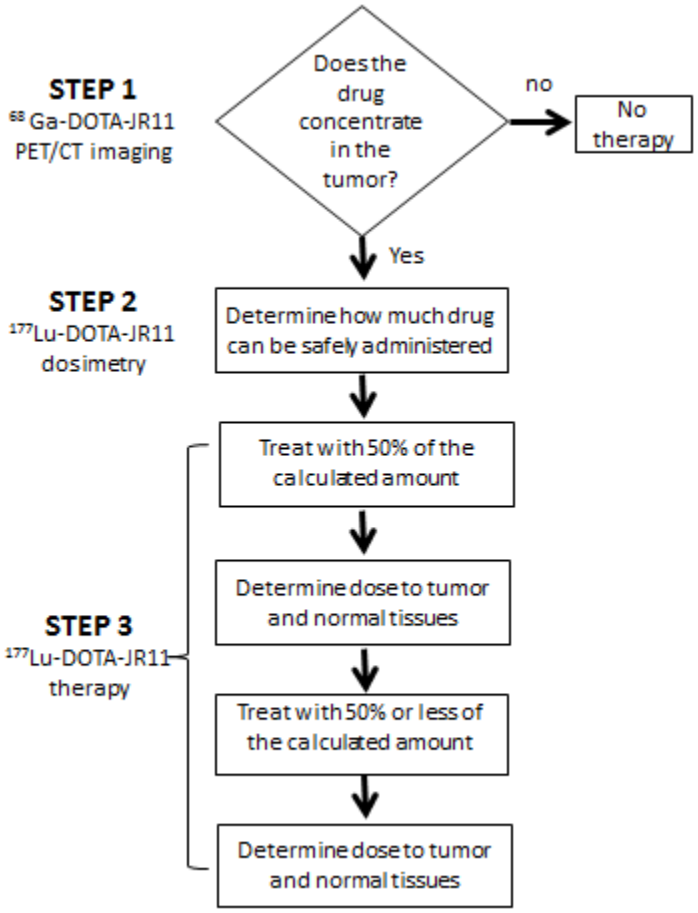


Figure 1. Flowchart giving an overview of the study procedures.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives:

1. To evaluate the safety, tolerability, and adverse event profiles of the theranostic pair of radiopharmaceuticals ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11 in patients with advanced, well differentiated neuroendocrine tumors.
2. To assess the biodistribution, tumor uptake, and dosimetry of the new diagnostic sstr2 antagonists, ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11.
3. To obtain a preliminary comparison of the sensitivity of PET with ^{68}Ga-DOTA-JR11 with the clinically used sstr agonist ^{111}In-DTPA-octreotide.

Secondary Objectives:

1. To determine if ^{68}Ga-DOTA-JR11 uptake correlates with the radiation dose to tumor and normal organs after administration of ^{177}Lu-DOTA-JR11.

2. To obtain preliminary data on overall tumor response of ^{177}Lu-DOTA-JR11 according to Response Evaluation Criteria in Solid Tumors guidelines, Version 1.1 (RECIST 1.1).
3. To obtain preliminary data on progression-free survival, overall survival, and stable disease in patients treated with ^{177}Lu-DOTA-JR11.

3.1 BACKGROUND AND RATIONALE

To date, all clinical sstr imaging and therapy approaches have been based on sstr *agonists*. The sstr ligands described in this protocol are the first-in-class radiolabeled sstr antagonists. Despite the novelty of the tested compounds, the risk of failure for the clinical trial is low, since the effectiveness of radiolabeled sstr agonists is well known. The key difference between antagonists and agonists is the higher uptake and retention of antagonists in NETs, resulting in a higher radiation dose to the tumors and a lower radiation dose to the kidneys. This is likely to translate in a safer and more effective therapy of NETs if our study confirms the higher uptake and retention of sstr antagonists predicted from preclinical and pilot clinical studies (6, 9, 10).

NETs are frequently perceived to represent a rare group of malignancies, but this is not entirely correct. There are about 15,000 new cases in the U.S. per year—about twice the number of Hodgkin's lymphomas (12)—but the prevalence of the disease is much higher. More than 100,000 patients are currently living with NETs in the U.S. (14), a higher number of patients than those with pancreatic and stomach cancer combined (12). Accordingly, there is a clear need to improve the diagnosis and therapy of NETs. This is especially true in the U.S., where PRRT is not available and sstr2-based imaging is still performed with a low-affinity sstr ligand (111-In-DTPA-octreotide, OctreoScan®) (15).

3.2 Somatostatin Receptor-based Imaging and Therapy of NETs

Tumor cells originating from neuroendocrine tissues generally express high levels of G protein-coupled receptors, which can be used as targets for therapeutic interventions (16). The most commonly overexpressed class of receptors are the somatostatin receptors (sstrs), specifically the somatostatin receptor subtype 2 (sstr2) (17). Using autoradiographic studies with radiolabeled somatostatin-28 and Tyr^3-octreotide (an sstr ligand with predominant binding to sstr2), somatostatin receptors were found in more than 87% of patients with carcinoids of the gut or lung (54 of 62 patients) and in 100% of the pancreatic NETs (15 of 15). Homogenous expression of sstr2 was found throughout the tumor tissue and the level of expression was high, compared to surrounding normal tissues (17).

Binding of somatostatin to sstr2 leads to internalization of the receptor (18) and inhibition of adenylate cyclase activity (19). This inhibits the secretion of various gastrointestinal hormones including gastrin, serotonin, and vasoactive intestinal polypeptide. The somatostatin analogs octreotide and lanreotide are therefore effective for controlling symptoms of hormone-producing NETs (16). In addition, they have anti-angiogenic effects and can inhibit the proliferation of NETs (16, 19). Treatment with octreotide or

lanreotide has been shown to improve progression-free survival in two randomized trials (20, 21). Monthly injections of a long-acting formulation of octreotide (octreotide LAR) improved progression-free survival of well differentiated NETs to 14.3 months compared to 6 months for placebo (20). Lanreotide improved progression-free survival from 18 months to more than 24 months (21).

The first clinically used radiolabeled somatostatin receptor ligands for imaging of NETs were ^{123}I-Tyr3-octreotide and ^{111}In-DTPA-octreotide (OctreoScan®), which is still in broad clinical use in the U.S. (15) Studies in the 1990s have indicated that planar and single photon computed emission tomography (SPECT) with ^{111}In-DTPA-octreotide improves the detection of hormone active NETs and the staging of metastatic NETs compared to CT and MRI (22). Due to the progress of CT and MR technology, the sensitivity of both modalities for detection of NETs has significantly improved. In a retrospective review of 104 patients in our institution, we found that ^{111}In-DTPA-octreotide SPECT picked up only 6% more asymptomatic bone lesions (23). The key limitations of ^{111}In-DTPA-octreotide are the need for delayed imaging 24 or even 48 hours post-injection because of slow blood clearance; the relatively high radiation dose caused by the comparatively long physical half-life of ^{111}In; and the low spatial resolution of SPECT.

Because of their high uptake in NETs, radiolabeled sstr ligands can be used not only for imaging, but also for treatment. To this end, H.R. Mäcke and his group have developed a variety of octreotide analogs that can be labeled with beta-emitting radiometals (Table 1). Various combinations of peptides, chelators, and radionuclides have been tested in the last decade, but by far the most commonly used radiopeptides are ^{90}Y-DOTA-3Tyr-Octreotide (^{90}Y-DOTA-TOC) and ^{177}Lu-DOTA-3Tyr-Octretate (^{177}Lu-DOTA-TATE). Table 2 summarizes the results of clinical studies evaluating ^{90}Y-DOTA-TOC and ^{177}Lu-DOTA-TATE therapy in patients with NETs.

Unfortunately, no randomized comparisons have been made between the two peptides or between PRRT and other forms of targeted therapy of NETs. Considering the heterogeneity of NETs and the difficulties in reproducibly assessing tumor response in patients with extensive metastatic disease, comparing the response rates reported by the individual studies is problematic. Nevertheless, the objective response rates are markedly higher than reported in clinical trials with octreotide LAR (7), everolimus (21), and sunitinib (22). This indicates that PRRT is more likely to induce significant tumor shrinkage than these other forms of targeted therapy. Furthermore, objective responses to PRRT were not only observed in pancreatic NETs, but also in midgut and lung carcinoids (19, 20). For these tumors, there are currently no FDA-approved agents that can induce significant tumor shrinkage (23, 24). Furthermore, the duration of response to PRRT can be remarkably long. Kwekkeboom et al. report a median progression-free survival of 40 months from the start of treatment (19).

Ligand (reference)	sstr1	sstr2	sstr3	sstr4	sstr5
SS-28 (24)	5.2±0.3	2.7±0.3	7.7±0.9	5.6±0.4	4.0±0.3

Octreotide (24)	>10,000	2.0±0.7	187±55	>1,000	22±6
In-DTPA-octreotide (24)	>10,000	22±3.6	182±13	>1,000	237±52
Y-DOTA-TOC (24)	>10,000	11±1.7	389±135	>10,000	114±29
Ga-DOTA-TOC (24)	>10,000	2.5±0.5	613±140	>1,000	73±21
Y-DOTA-[Tyr3]-octreotate (24)	>10,000	1.6±0.4	>1,000	523±239	187±50
Ga-DOTA-[Tyr3]-octreotate (24)	>10,000	0.2±0.04	>1,000	300±140	377±18
Lu- DOTA[Ty3]-octreotate (11)	>1,000	1.5±0.4	>1000	453±179	547±160
In-DOTA-BASS (6)	n.d.	9.4±0.4	n.d.	n.d.	n.d.
DOTA-JR11 (7)	>1,000	0.72±0.12	>1,000	>1,000	>1,000
Lu-DOTA-JR11 (7)	>1000	0.73±0.15	>1000	>1000	>1000
Ga-DOTA-JR11 (7)	>1000	29±2.7	>1000	>1000	>1000

Table 1. Overview of the affinity profiles of radiolabeled somatostatin receptor binding peptides. Data show the concentration in nM for 50% inhibition of binding (IC50) of the radiolabeled natural ligand somatostatin-28. n.d. - Not determined. Data show mean and standard deviation.

Treatment with ^{177}Lu-DOTA-TATE and ^{90}Y-DOTA-TOC is generally very well tolerated. However, renal toxicity is an important side effect since the peptides are excreted by the kidney and partly stored in the renal tubulus system (25). Renal toxicity grade 4-5 has been reported in 0.4% to 9.2% of the treated patients (19, 20). The cumulative radiation dose to the kidneys is currently limited to 23 Gy in order to decrease the risk of renal toxicity (26). Kidney dose typically limits the amount of ^{177}Lu-DOTA-TOC and ^{90}Y-DOTA-TATE that can safely be administered to a patient.

First author (reference)	Peptide	N	CR	PR	SD	PD	Response criteria
Otte et al. 1999 (1)	^{90}Y-TOC	16	0	1 (6%)	14 (88%)	1 (6%)	Own definition
Bodei et al. 2003 (25)	^{90}Y-TOC	21	0	6 (29%)	11 (52%)	4 (19%)	WHO
Valkema et al. 2006 (26)	^{90}Y-TOC	58	0	5 (9%)	29 (53%)	14 (25%)	SWOG
Bushnell et al. 2010 (27)	^{90}Y-TOC	90	0	4 (4%)	63 (70%)	23 (26%)	SWOG
Kwekkeboom et al. 2008 (3)	^{177}Lu-TATE	310	5 (2%)	86 (28%)	107 (35%)	61 (20%)	SWOG
Imhof et al. 2011 (2)	^{90}Y-TOC	1109	7 (0.6%)	371 (34%)	436 (39%)	295 (27%)	Own definition*

Table 2. Overview of clinical trials evaluating ^{90}Y-DOTA-TOC and ^{177}Lu-DOTA-TATE therapy in patients with NETs. N – numbers of patients included. *Any measurable decrease or increase of the sum of longest tumor diameters was considered PR or PD, respectively.

3.3 Somatostatin Receptor Antagonist-based Imaging and Therapy of NETs

In order to improve imaging and treatment of NETs, the study PI have developed a new class of radiolabeled somatostatin receptor ligands. In contrast to all previously studied radiolabeled somatostatin receptor ligands, these compounds are somatostatin *antagonists*, not *agonists*. Previous work has ignored somatostatin antagonists, because

it was believed that internalization of the ligand is key for high tumor uptake and retention. Since sstr antagonists lack receptor-mediated internalization, they were considered not to be suitable for radionuclide therapy.

However, preclinical studies have shown that sstr-expressing tumors demonstrate higher uptake of radiolabeled sstr *antagonists* than sstr *agonists* (6). In mice bearing HEK-sstr2 tumors, tumor uptake of the antagonist ^{111}In-DOTA-BASS was twice as high as the uptake of the potent agonist ^{111}In-DTPA-TATE, despite the fact that the affinity of DOTA-BASS for sstr2 is lower than that of DTPA-TATE (Table 1). Importantly, antagonists not only demonstrated higher peak uptake, but were also retained longer within the tumors. This unexpected finding is probably explained by a markedly higher number of binding sites for sstr antagonists as compared to agonists. Scatchard analysis showed more than ten times the number of binding sites for ^{111}In-DOTA-BASS (Bmax = 354±14 pM) than for ^{111}In-DTPA-TATE (Bmax = 23±1.0 pM). Ex vivo studies with human tumors (12) have also demonstrated markedly higher binding of sstr2 antagonists than of sstr2 agonists (11). This suggests that antagonists bind to more receptor confirmations (activated and inactive) than agonists.

Based on these encouraging data, the study PI performed a pilot trial at the University of Freiburg that compared the biodistribution and tumor uptake of the sst2 receptor antagonist ^{111}In-DOTA-BASS with the clinically used ^{111}In-`DTPA-octreotide (OctreoScan®) (9). These two ligands have a similar affinity for sstr2 (Table 1). In this study, ^{111}In-DOTA-BASS detected 25/28 lesions (89.3%), whereas ^{111}In-DTPA-Octreotide detected only 17/28 (60.7%) lesions (P = 0.013). In pair-wise comparisons, ^{111}In-DOTA-BASS showed significantly higher tumor and lower renal uptake than ^{111}In-DTPA-Octreotide at 4 hours post-injection, resulting in up to 5.2 times higher tumor-to-kidney uptake ratios (9). This study demonstrated for the first time the feasibility of using sstr2 antagonists for imaging of NETs and suggested that sstr antagonists may enable the delivery of higher radiation doses to NETs than sstr2 agonists.

The affinity of ^{111}In-DOTA-BASS for sstr2 is lower than for the therapeutically used peptides ^{90}Y-DOTA-TOC or ^{177}Lu-DOTA-TATE (Table 1). In our subsequent studies, we therefore used a new somatostatin antagonist, DOTA-JR11 (Table 1), which demonstrates a subnanomolar affinity for sstr2 (Table 1). Labeling with Lutetium did not affect the affinity for sstr2. In contrast, labeling with Gallium unexpectedly decreased the affinity (Table 1). Nevertheless, PET and biodistribution studies in mice bearing sstr2-expressing xenografts demonstrated slightly higher tumor uptake of ^{68}Ga-DOTA-JR11 than the high-affinity sstr2 *agonist* ^{68}Ga-DOTA-TATE (7). This indicates that the lower affinity of ^{68}Ga-DOTA-JR11 for sstr2 is compensated by its ability to bind to more receptor sites than ^{68}Ga-DOTA-TATE. Since ^{68}Ga-DOTA-TATE is clinically clearly superior to ^{111}In-DTPA-Octreotide (28-30), these findings are promising for the clinical use of ^{68}Ga-DOTA-JR11 for NET imaging.

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Age (y)	77	74	44	74
Sex	F	M	F	F
Diagnosis	Neuroendocrine carcinoma (bladder)	Neuroendocrine tumor (lung)	Neuroendocrine tumor (ileum)	Neuroendocrine tumor (ileum)
Tumor grade	G3	G1	G2	G2
First diagnosed	5 mo ago	3 y ago	5 y ago	11 mo ago
Pretreatment evaluation				
ECOG performance status	2	0	1	0
Remission status*	PD	PD	PD	PD
Chronic kidney disease†	Grade 3	Grade 3	Grade 2	Grade 3
Three-mo follow-up				
ECOG performance status	2	0	0	0
Remission status*	Mixed response	PR	SD	PR
Chronic kidney disease†	Grade 3	Grade 3	Grade 2	Grade 3
Adverse events‡				
Anemia (reversible)	Grade 2	Grade 1	Grade 2	Grade 2
Leukopenia (reversible)	Grade 2	Grade 1	Grade 2	Grade 0
Thrombocytopenia (reversible)	Grade 0	Grade 3	Grade 0	Grade 0
Maximum follow-up (mo)	15	12	13	12
Remission status†	PD	PR	SD	PR

Table 3. Characteristics of patients treated with ^{177}Lu-DOTA-JR11.

^{177}Lu-DOTA-JR11 was studied in four patients with progressive, unresectable NETs at the University of Freiburg in Germany. Renal function was impaired in all patients, thus limiting the amount of ^{177}Lu-DOTA-TATE that could be safely administered. These patients were offered to undergo a dosimetry study with ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11. If this study indicated a higher tumor radiation dose of ^{177}Lu-DOTA-JR11 and an acceptable renal radiation dose, patients were offered treatment with ^{177}Lu-DOTA-JR11 (10). Table 3 summarizes the clinical characteristics of the patients.

After infusion of an arginine/lysine solution (kidney protection), patients were injected with 1-2 GBq ^{177}Lu-DOTA-TATE and ^{177}Lu-DOTA-JR11 (crossover design in an interval of three weeks). No acute adverse effects of 200 µg ^{177}Lu-DOTA-JR11 were observed.

Dosimetric calculation was possible for 13 lesions. **Table 4.** Radiation doses for ^{177}Lu-

		Pretreatment evaluation							Treatment	Three-mo follow-up CT	
			^{177}Lu-DOTATATE			^{177}Lu-DOTA-JR11					
Tumor no.	Tumor site	CT tumor volume (cm^3)	Tumor dose (Gy/GBq)	T/K ratio	T/BM ratio	Tumor dose (Gy/GBq)	T/K ratio	T/BM ratio	^{177}Lu-DOTA-JR11 total tumor dose* (Gy)	Tumor volume (cm^3)	Tumor reduction (%)
Patient 1											
1	LN	23	2.0	1.6	22	7.4	3.3	56	59	13	45
2	LN	1.7	1.2	0.9	13	7.0	3.1	53	31	1.5	13
3	LN	22	1.4	1.1	15	5.7	2.5	44	47	5.9	73
4	LN	0.4	1.1	0.9	12	5.9	2.6	45	23	0.1	80
5	LN	0.9	2.0	1.6	22	7.4	3.3	56	39	0	100
Patient 2											
6	Liver	59	13	9.0	133	22	15	223	374	5.4	91
7	Liver	66	6.3	4.4	65	29	20	294	487	29	56
8	Lung	26	5.6	3.9	57	16	11	162	283	6.8	73
Patient 3											
9	LN	9.3	0.5	0.6	7.9	5.3	3.7	57	130	5.9	37
10	Liver	26	2.7	3.6	43	5.9	4.1	63	33	25	5
11	Liver	7.7	2.2	3.0	35	4.8	3.3	52	37	5.8	24
Patient 4											
12	Liver	0.4	4.6	3.2	68	20	9.3	245	302	0	100
13	Liver	2.2	1.5	1.0	22	4.2	1.9	51	39	0.4	82
Median		9.3	2.0	1.6	22	7.0	3.3	56	47	5.8	73
Interquartile range		1.7–26	1.2–4.6	1.0–3.6	15–57	5.7–16	3.1–9.3	52–162	37–283	0.4–6.8	37–82

DOTA-TATE and ^{177}Lu-DOTA-JR11 and treatment effects for 13 lesions evaluated in the 4 patients.

In pair-wise comparisons, ^{177}Lu-DOTA-JR11 showed significantly higher tumor doses than ^{177}Lu-DOTA-TATE (10.1 ± 8.2 vs. 3.2 ± 3.4 Gy/GBq, P < 0.001). *Importantly, the mean tumor-to-kidney dose ratio was more than two-fold higher for ^{177}Lu-DOTA-JR11 than for ^{177}Lu-DOTA-TATE (6.0 ± 5.6 vs. 2.5 ± 2.3, P < 0.01).* As a result, all four patients were treated with ^{177}Lu-DOTA-JR11 (up to 15.2 GBq in two-three cycles every three months): two patients showed a partial response, one patient had stable disease, and one patient progressed (Table 3). These results are remarkable given the low dose of ^{177}Lu administered and the advanced stage of these tumors. Follow-up laboratory evaluations showed only a mild increase of serum creatinine and mild, temporary myelosuppression.

One patient with a high-grade NET of the bladder died due to progressive disease, whereas the other patients are well, with no evidence of progressive disease (Table 3).

One patient experienced a short episode of flush just after injection of ^{177}Lu-DOTA-JR11. Another patient developed grade 3 thrombocytopenia (41,000/mm^3), which completely recovered within eight weeks after injection of ^{177}Lu-DOTA-JR11 (Table 3). There was no relevant decrease of tubular kidney function within 12 months of follow-up (mercaptoacetyltriglycine clearance, 136 mL/min/1.73 m^2 vs. 127 mL/min/1.73 m^2). Also, creatinine levels did not change significantly before and after treatment (approximately 12 months post-treatment; 1.32 mg/dL vs. 1.39 mg/dL) (10).

The radiation dosimetry of ^{177}Lu-DOTA-JR11 in comparison to ^{177}Lu-DOTA-TATE for the four patients studied is summarized in Table 5.

Organ	^{177}Lu-DOTATATE	^{177}Lu-DOTA-JR11
Adrenals	0.072 ± 0.019	0.11 ± 0.024
Brain	0.061 ± 0.018	0.10 ± 0.020
Breasts	0.061 ± 0.018	0.10 ± 0.020
Gallbladder wall	0.070 ± 0.020	0.11 ± 0.023
GI (LLI wall)	0.065 ± 0.019	0.11 ± 0.021
GI (small intestine)	0.066 ± 0.019	0.11 ± 0.021
GI (stomach wall)	0.069 ± 0.020	0.11 ± 0.024
GI (ULI wall)	0.066 ± 0.019	0.11 ± 0.021
Heart wall	0.065 ± 0.019	0.11 ± 0.021
Kidneys*	1.2 ± 0.35	1.8 ± 0.44
Liver	0.25 ± 0.096	0.33 ± 0.16
Lungs	0.065 ± 0.019	0.11 ± 0.021
Muscle	0.063 ± 0.019	0.10 ± 0.020
Ovaries	0.056 ± 0.009	0.10 ± 0.025
Pancreas	0.075 ± 0.021	0.12 ± 0.027
Red marrow	0.079 ± 0.018	0.10 ± 0.021
Osteogenic cells	0.22 ± 0.053	0.35 ± 0.068
Skin	0.060 ± 0.018	0.10 ± 0.019
Spleen	2.5 ± 1.5	3.0 ± 2.3
Thymus	0.063 ± 0.019	0.10 ± 0.020
Thyroid	0.062 ± 0.019	0.10 ± 0.020
Urinary bladder wall	0.26 ± 0.13	0.37 ± 0.21
Uterus	0.066 ± 0.019	0.11 ± 0.021
Total body	0.083 ± 0.021	0.13 ± 0.031
Effective dose (Sv/GBq)	0.15 ± 0.046	0.20 ± 0.075

Table 5. Radiation dosimetry calculations. Data show mean and standard deviation.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Patient will first undergo PET/CT imaging with ^{68}Ga-DOTA-JR11 to determine eligibility for treatment with ^{177}Lu-DOTA-JR11 (Figure 1). Only patients that have ^{68}Ga-DOTA-JR11 uptake greater than that in the liver in at least one metastasis of more than 2 cm diameter will be considered for therapy. Patients with ^{68}Ga-DOTA-JR11 positive disease will then undergo a dosimetry study to determine the amount activity of ^{177}Lu-DOTA-JR11 that can be safely administered. Based on the human biodistribution we expect the kidney and the bone marrow to be the two dose limiting organs. The dose limit for the kidney will be 23 Gy as suggested by the QUANTEC guidelines for external beam radiotherapy (https://www.astro.org/Clinical-Practice/Quantec/QUANTEC.aspx). We

realize that this dose limit has been defined for external beam therapy and that higher doses may be feasible for low dose rate internal radiation. However, since the dose distribution in the kidney is heterogeneous we will use this relatively low whole organ limit as a safety precaution. In addition, the red marrow dose will be limited to 1.5 Gy. Again this a relatively low value, especially as the radioactivity is administered over multiple cycles. Other organs are not expected to become dose limiting, but we will compare the radiation doses for all organs with detectable ^{177}Lu-DOTA-JR11 uptake with the QUANTEC dose limits and adjust the therapeutic activity if necessary.
The clinical intention is that the combined dosimetry and therapy administrations of ^{177}Lu-DOTA-JR11 will deliver the lower of the two dose limits (23 Gy to kidney, 1.5 Gy to red marrow). The administered activity for the pre-therapy dosimetry study will be fixed (1.85 GBq = 50 mCi). Thereafter, the balance of activity that is predicted to deliver the lower of the two dose limits will be calculated. This will be split into two equal amounts to be delivered approximately 3 months apart. However if the first treatment results in estimated doses that differ from the initial predictions, the second treatment will be adjusted (either decreased or increased) so that the intended dose limits are achieved. Note that administered activities listed will be +/- 10% as per institutional practice.

4.3 Intervention

^{68}Ga-DOTA-JR11 PET/CT Imaging

Following informed consent, eligible patients will first undergo a PET/CT study with approximately 150-200 MBq of ^{68}Ga-DOTA-JR11 as described in section 9.1.

Normal and altered biodistribution of ^{68}Ga-DOTA-JR11

^{68}Ga-DOTA-JR11 is expected to demonstrate a similar biodistribution as other somatostatin receptor ligands, such as ^{111}In-Octreotide, ^{68}Ga-DOTA-TATE, and ^{177}Lu-DOTA-JR (10). Pituitary gland, adrenal glands and the pancreatic head are expected to demonstrate focal uptake of ^{68}Ga-DOTA-JR11. In addition, we expect diffuse tracer uptake by the liver, spleen and kidneys as well as excretion of activity to the bladder with no or low hepatobiliary excretion.

Altered biodistribution is defined as any deviation from the expected biodistribution, specifically focal uptake in lesions or absence of focal uptake in organs with known physiologic expression of somatostatin receptors (pituitary gland, adrenal glands and pancreatic head). Another sign of an altered biodistribution is predominantly hepatobiliary excretion of the tracer.

Image Interpretation

PET/CT scans will first be interpreted without information on the results of other imaging modalities. Any lesions with focal radiotracer uptake not explained by physiologic sstr2 expression will be interpreted as metastatic disease.

The likelihood of malignancy will be described by a 5-point Likert scale. Following the blinded read of the ^{68}Ga-DOTA-JR11 PET/CT scan, all recorded findings will be correlated with the results of ^{111}In-Octreotide SPECT, and CT/MRI performed as part of standard clinical care. The relative sensitivity of ^{68}Ga-DOTA-JR11 will be determined by a consensus of the clinical investigators and systemic analysis of all available imaging studies and follow-up. We will consider a score of 3 or above malignant and a score of 1 or 2 as benign for the purposes of this protocol.

^{177}Lu-DOTA-JR11 Dosimetry

If ^{68}Ga-DOTA-JR11 uptake by metastases with a diameter of more than 2 cm is less than the physiologic radiotracer uptake by the liver, no further imaging and therapy will be performed as part of the study, as it is unlikely that patients with this low radiotracer uptake will benefit from PRRT (2).

All other patients will undergo a dosimetric study with 1850 MBq (less than 100 µg peptide) of ^{177}Lu-DOTA-JR11. This amount of radioactivity is required in order to obtain images with sufficient count statistics to reliably quantify radiotracer uptake in tumor lesions and organs (the abundance of imagable gamma emissions for ^{177}Lu is only 11%). Replacing ^{177}Lu with another radiometal such as ^{111}In carries the risk of a different tumor uptake, because the radiometal can have a significant impact on the affinity of sstr2 antagonists (Table 1).

^{177}Lu-DOTA-JR11 Therapy

From the results of the dosimetry study, we will determine the balance of activity of ^{177}Lu-DOTA-JR11 that can be administered without exceeding the radiation dose limits. This activity will be split into two equal amounts to be delivered in two cycles, approximately three months apart. However if the first treatment cycle results in estimated doses that differ from the predictions, the activity administered for second treatment cycle will be adjusted so that the dose limits are maintained. Based on the preliminary clinical data (table 5), we anticipate that the typical activities of ^{177}Lu-DOTA-JR11 administered over the full course of dosimetry and treatment will be approximately 1.85, 5.4, and 5.4 GBq (50, 147, and 147 mCi, respectively). After each therapy cycle, patients will be followed clinically for three months.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

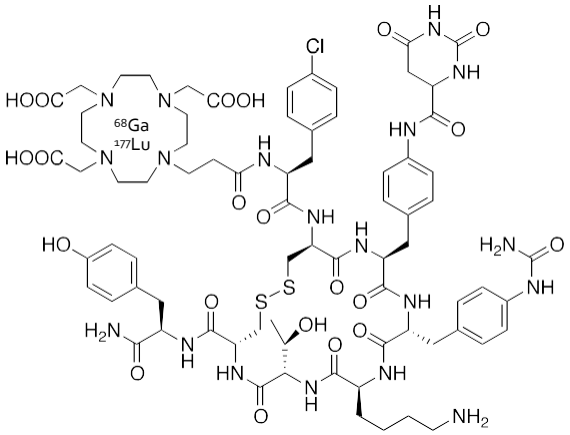
[^{68}Ga]-DOTA-JR11 and [^{177}Lu]-DOTA-JR11

This study will use the investigational theranostic products [^{68}Ga]-DOTA-JR11 and [^{177}Lu]-DOTA-JR11 which are manufactured and released by the Radiochemistry and Molecular Imaging Probes (RMIP) Core at MSKCC following the guidelines of GMP appropriate for Phase I clinical trials, local and Institutional Quality Controls and in full compliance with the applicable FDA and local regulatory bodies. ^{68}Ga- and ^{177}Lu- radioligands are obtained from qualified

vendors, accompanied by a certificate of analysis. The investigational products are delivered to Nuclear Pharmacy and compounded/dispensed by a pharmacist per physician order. The Nuclear Pharmacy operates in full compliance with the applicable FDA and local regulatory bodies.

To ensure administration within the expiration time, [^{68}Ga]-DOTA-JR11 and [^{177}Lu]-DOTA-JR11 are delivered to Nuclear Pharmacy labeled with a 6 and 3 hour expiration and placed in inventory, which will not allow dispensing of an expired product. A licensed pharmacist dispenses each labeled product in accordance with the physician order.

The chemical structure of ^{68}Ga/^{177}Lu-DOTA-JR11 is shown in Figure 2. DOTA-JR11 is a high-



affinity antagonist of somatostatin at the somatostatin type 2 receptor (sstr2). This is the subtype of somatostatin receptors most commonly overexpressed in GEP-NET tumors. DOTA-JR11 has low affinity for other somatostatin receptors (Table 1).

This study will be performed under an FDA approved IND for ^{68}Ga- DOTA-JR11 and ^{177}Lu-DOTA-JR11. The synthesis, reagents, testing and composition of the final product ^{68}Ga/^{177}Lu-DOTA-JR11 are described in detail in the chemistry, manufacturing and controls (CMC) section of the IND application. The synthesis method is based on the published previous human experience at the University of Freiburg (10). ^{68}Ga-DOTA-JR11 is administered as an intravenous microdose (<100 µg peptide mass) and will contain approximately 150-200 MBq radioactivity. In the dosimetric study, ^{177}Lu-DOTA-JR11 is given at a dose of 1,850-6,000 MBq (<100 µg peptide mass). The therapeutic radioactive dose of ^{177}Lu-DOTA-JR11 will be determined by the dosimetric study. Based on the preliminary clinical data described above, we anticipate that the typical amounts of ^{177}Lu-DOTA-JR11 administered over the full course of dosimetry and treatment will be approximately 1.85, 5.4, and 5.4 GBq (50, 147, and 147 mCi, respectively). A lower mass dose than 100 µg of ^{68}Ga-DOTA-JR11 is technically feasible for the imaging studies, but may lead to systematic differences in the biodistribution of ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11. Therefore, we will use a similar peptide mass for both ^{68}Ga-DOTA-JR11 and ^{177}Lu-DOTA-JR11.

Figure 2. Chemical structure of ^{68}Ga/^{177}Lu-DOTA-JR11.

Renal Protection Solutions: Aminosyn II (10%), Clinisol (15%), or "2.5% L-Lysine HCl – 2.5% L-Arginine HCl, Renal Protectant Solution, RMIPC"

Aminosyn II (10%) is an FDA approved amino acid injection obtained from MSKCC pharmacy.

Baxter 15% CLINISOL (sulfite-free) is an FDA approved amino acid injection obtained from MSKCC compounding pharmacy.

"2.5% L-Lysine HCl – 2.5% L-Arginine HCl, Renal Protectant Solution, RMIPC" will be compounded under the practice of pharmacy compounding pursuant to a prescription from a physician for a specific patient by RMIP Core at MSKCC.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Only adult patients will be studied (≥ 18 years old). There will be no other restrictions in terms of age or race. Patients must be referred by members of MSK's Medical Oncology Service.

Due to special dosimetry considerations in pediatric patients, children will be excluded from this study. There is no safety data in children at this point.

6.2 Subject Inclusion Criteria

- Ability to understand and the willingness to sign a written informed consent document
- Adults ≥ 18 years old
- Histologically or cytologically confirmed metastatic and/or unresectable progressive, well differentiated carcinoid or pancreatic NET carcinoids
- Progressive metastatic disease defined by one of the following, occurring within 6 months of study entry:
    - At least a 20% increase in radiologically or clinically measurable disease
    - Appearance of any new lesion
    - Symptomatic disease (including worsening hormonal symptoms or symptoms related to tumor burden)
- Measurable disease as defined by RECIST 1.1.
- At least one metastasis must show uptake of ^{111}In-DTPA-octreotide on SPECT that is higher than the physiologic radiotracer uptake by the liver
- ECOG performance status ≤ 2 (Karnofsky ≥ 60%)
- Patients must have normal organ and marrow function as defined below:
    - Leukocytes ≥ 3.0 x 10^9/L
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Hemoglobin ≥ 9.0 g/dL
    - Platelets ≥ 200 x 10^9/L
    - Total bilirubin ≤ 1.25 x Upper Limit Normal (ULN)

  - AST (SGOT)/ ALT(SGPT) ≤ 2.5 x ULN with liver metastases
  - Alkaline phosphatase < 2 x ULN (if known liver or bone disease)
  - Serum albumin > 30 g/L, or serum albumin = 30 g/L but normal prothrombin time
  - Creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) calculated CrCl ≥ 60 mL/min/1.73m^2
- Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for the duration of study participation
- Previous local therapy (e.g., chemoembolization or bland embolization) is allowed if completed > 6 weeks prior to study entry. For such patients, there must be either progression of measurable disease documented within the treatment field, or measurable progressive disease outside the treatment field prior to study entry.
- Previous chemotherapy and/or investigational agents are allowed if completed > 4 weeks prior to study entry (> 6 weeks if last regimen contained bis-chloroethyl nitrosourea (BCNU) or mitomycin C). For patients who received systemic therapy prior to study entry, there must be documented progression of measurable disease since receiving systemic therapy prior to study entry.
- Patients must not have disease that is currently amenable to surgery. Prior surgery is allowed no less than 6 weeks prior to study entry.

6.3 Subject Exclusion Criteria

- History of allergic reactions attributed to compounds of similar chemical or biologic composition to ^{177}Lu-DOTA-JR11 as assessed from medical records
- Life expectancy < 6 months as assessed by the treating physician.
- Treatment with short-acting somatostatin analogs less than 3 days and Sandostatin® depot injection less than 5 weeks before scanning and treatment
- Uncontrolled, intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
- Women who are pregnant or breastfeeding
- Toxicities from prior therapies that have not resolved to grade 1 or grade 0
- Known CNS metastases and/or carcinomatous meningitis
- Active malignancy of metastatic potential other than the known carcinoid or pancreatic NET within the past three years
- >20% bone marrow external beam radiotherapy and/or previous radioisotope therapy

7.0 RECRUITMENT PLAN

A member of the patient's treatment team at MSK will identify potential study participants. Adults of all races and ethnic groups will be considered for study participation. Candidates must conform to all inclusion and exclusion criteria to be accepted into the study.

If the investigator is a member of the treatment team, s/he will screen their patients' medical records for suitable research participants and discuss the study and the possibility of enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

8.1 PRETREATMENT EVALUATION

Before any protocol-specified procedures are conducted, each prospective participant must sign an informed consent form. The following screening tests and procedures must be obtained within four weeks prior to study entry:

- Medical history confirmation of tumor diagnosis by submission of archived tumor tissue (archived material can be submitted any time prior to study entry).
- Physical examination, including vitals
- Documentation of concurrent medications
- Karnofsky or ECOG performance status
- EKG
- Laboratory assessment (within two weeks prior to study entry):
    - Complete Blood Count (CBC)
    - Comprehensive Metabolic Panel (CMP)
    - PTT, PT/INR
    - Chromogranin A
    - Urinalysis
    - ^{99m}DTPA scan with filtration rate
    - Hormone levels (if patient is symptomatic and the tumor is functional; hormone levels will be based on tumor type); for example:
        - Carcinoid tumor: 24-hr HIAA
        - VIPoma: VIP
        - Glucagonoma: glucagon
        - Insulinoma: insulin
        - Gastrinoma: gastrin
        - Somatostatinoma: somatostatin
- ^{111}In-Octreotide SPECT (within 8 weeks of study entry)
- CT triphasic or MRI of the liver

To be completed within 7-14 days prior to treatment:

- Physical exam, including vital signs
- Review of prior/concomitant medications
- Performance status

- CBC, CMP
- LDH
- Haptoglobin
- Serum or urinary pregnancy test in women of child-bearing age. This will be performed prior to each administration of radioactivity (diagnostic or therapeutic).
- Tc-99m DTPA scan with GFR determination. This will be repeated within 2 weeks prior to second therapy and 10 to 14 weeks after second therapy.

9.0 TREATMENT/INTERVENTION PLAN

Drug Accountability

The investigator is obliged to keep sufficient documentation of the delivery and use of the investigational product. These records will include administration date/time, calibration date/time, quantity, patient code, lot number, and date of destruction. The investigator should maintain records that adequately document that the patients were provided the dose specified in the protocol and reconcile the medication received for the study. The label of each vial will contain the patient code and lot number, and patient and radiopharmaceutical information will be entered in the radiopharmacy drug accountability forms. The investigator may assign some or all of his/her duties regarding drug accountability to an appropriate individual such as a pharmacist or nuclear medicine technician, under the supervision of the investigator.

9.1 PET/CT Imaging

No specific patient preparation is required before ^{68}Ga-DOTA-JR11 injection. One intravenous catheter (Hep-Lock) will be placed by staff in the Molecular Imaging and Therapy Service for radiopharmaceutical administration. Vital signs will be obtained prior to ^{68}Ga-DOTA-JR11 injection.

Images will be corrected for attenuation and scatter and adjusted for system sensitivity, and will provide parametric data in terms of standardized uptake values (SUV) (= MBq found/gm tissue/ MBq injected/gm body mass).

In order to provide reproducible clinical data, we will acquire all ^{68}Ga-DOTA-JR11 PET/CT scans on GE PET/CT 690 and 710 scanners (or a newer-generation scanner), providing reconstructed images with the same spatial resolution. Intravenous injection of ^{68}Ga-DOTA-JR11 will be given as a bolus. In all patients a PET-CT scan extending from top of skull to mid-thigh will be performed to determine the biodistribution 60-70 min after injection. We will perform a low-dose CT scan for attenuation correction and anatomical localization. Total acquisition time for these studies will be less than 40 min.

In 6 patients (3 female and 3 male patients) additional imaging studies will be performed to obtain data on the dosimetry of ^{68}Ga-DOTA-JR11. These studies will include a dynamic PET study of the upper abdomen including (parts of) the left ventricle, liver and kidneys to study the initial distribution of ^{68}Ga-DOTA-JR11 for 25 minutes after injection.

This will be followed immediately by a PET/CT scan extending from the top of the skull to mid-thighs. The total duration for patients undergoing these enhanced studies for radiation dosimetry is approximately 85 minutes. Radiation doses will be calculated using OLINDA/EXM using the same principles described in section 9.2 for ^{177}Lu-DOTA-JR11.

9.2 Dosimetry Study

The dosimetry study will begin within 5 weeks of completion of PET imaging. An infusion of 2,000 mL renal protectant solution will be initiated approximately 30 minutes before and continued for 3.5 hours after the ^{177}Lu-DOTA-JR11 injection to inhibit tubular reabsorption of the radiopeptide (25). This solution contains 21 g lysine and 20 g arginine and will be infused at constant rate of 500 ml/hr. The same amino acid infusion schedule will be used during treatment with ^{177}Lu-DOTA-JR11. Patients may receive 8 mg of the 5-HT$_3$ antagonist Ondansetron I.V. and/or other antiemetics, as clinically indicated, prior to the start of the amino acid infusion in order to prevent nausea and vomiting, potentially caused by the amino acid infusion. In case of persistent nausea/vomiting despite these measures infusion rate can be lowered and the duration of the amino acid infusion extended. In such situations, the scan at 1-5 hours post injection will be adjusted and completed following the amino acid infusion. It will not be considered a protocol violation.

For the dosimetry study, patients will undergo whole body planar imaging at nominal times of approximately 1-5, 18-30, 66-120, and 144-192 hours post-injection with a SPECT/CT study of the abdomen, including kidneys and sites of known disease, to be performed at 18-30 hours.

Radiation-absorbed doses to kidneys, red marrow, whole body and any individual organs displaying ^{177}Lu-DOTA-JR11 accumulation will be calculated based on patient images and blood-based measurements. Specifically, activity-time curves for normal tissues will be generated from region-of-interest (ROI) analysis of conjugate view whole body scans supplemented by the single SPECT-CT scan. Activity-time curves for heart contents and red marrow will be generated from the measured blood values. Activity-time curves will be integrated (either analytically or numerically as appropriate) to yield residence times used as input to the FDA-approved dosimetry software package OLINDA/EXM, which will then generate absorbed dose estimates to normal tissues. Additional dosimetry analysis will include: (1) lesion dose estimates based on ROI data assuming only self-dose; and (2) if differential retention in cortical and medullary sub-regions of the kidney is observed, the SPECT images will be used to quantify partitioning and enable sub-regional absorbed dose estimates.

Blood Samples

Blood samples will be drawn at approximately 5-10 min, 15-20 min, 30-40 min, 60-90 min, 120-150 min, and 4-6 hours post-injection and, subsequently, at the times of imaging. These data will be used to determine the clearance of the radiotracer from the

blood and calculate the radiation dose to red marrow. Specifically, absorbed dose to red marrow is calculated as the sum of self-dose from activity in the marrow itself (estimated from the activity concentration in blood) and cross-dose from activity in other organs and from the generalized remainder of body. The calculation is performed using the OLINDA/EXM dosimetry software package. For red marrow we make the assumption, common in radiation dose calculations for radiolabeled small molecules, that the activity concentration in the marrow is the same as that measured in blood. A standard value (taken from OLINDA/EXM) is used for the total red marrow mass or, if the patient is significantly heavier than "standard human", a rescaled value is used, based on the ratio of patient mass to standard mass. The total activity in the red marrow is integrated with respect to time to derive the AUC which is then divided by the administered activity to yield the residence time for red marrow. This, together with all the other residence times is input into OLINDA/EXM to generate absorbed radiation doses.

9.3 ^{177}Lu-DOTA-JR11 Therapy

9.3.1 Treatment Cycle 1

Cycle 1 will begin within 6 weeks of the completion of dosimetry study. Patients will be given an intravenous injection of ^{177}Lu-DOTA-JR11 over 5-10 minutes. An infusion of 2,000 mL renal protectant solution will be initiated approximately 30 minutes before and continued for 3.5 hours after the ^{177}Lu-DOTA-JR11 injection to inhibit tubular reabsorption of the radiopeptide (25). This solution contains 21 g lysine and 20 g arginine and will be infused at constant rate of 500 ml/hr. Imaging and blood sample collections will be performed at the same times as described for the dosimetry study and radiation doses calculated.

The activity of ^{177}Lu-DOTA-JR11 administered per cycle will not exceed 200 mCi (7.4 GBq) independent from the radiation dose to the kidneys and/or red marrow.

9.3.2 Treatment Cycle 2

Cycle 2 will be performed 10-14 weeks after cycle 1 if the following criteria are fulfilled:

- No Grade 2 or higher platelet toxicity
- No other grade 3 or 4 hematologic toxicity
- < 40% increase of serum creatinine/decrease of creatinine clearance
- Other grade 3 or 4 toxicity possibly related to ^{177}Lu-DOTA-JR11 therapy

The second treatment cycle can be postponed for up to 12 weeks for grade 3 toxicities to resolve to a level that meets the criteria shown above. If the toxicities have not resolved by this time, the patient is considered as having excessive toxicity and will not receive a second cycle of ^{177}Lu-DOTA-JR11 therapy.

Treatment will be administered as for cycle 1 with the possibility of a revised activity of ^{177}Lu-DOTA-JR11, depending on the doses calculated for the previous cycle. Infusion of renal protectant solution will be administered as described for treatment cycle 1. The

same set of imaging, blood sampling, and radiation dose calculations will be performed. Patients will be monitored for adverse events. Between the two therapy cycles, bi-weekly tests of CBC, creatinine, and liver enzymes will be collected for three months. Within 10 (+/- 5) days before administration of the second cycle, patients will be assessed for progression by history, clinical examination and repeat imaging studies (using the same imaging modality as for the pre-therapeutic imaging study). Patients with disease progression according to RECIST 1.1 will not receive a second cycle of ^{177}Lu-DOTA-JR11.

Patients with progression of disease between cycle 1 and 2 will be replaced. The activity of ^{177}Lu-DOTA-JR11 administered per cycle will not exceed 200 mCi (7.4 GBq) independent from the radiation dose to the kidneys and/or red marrow.

9.4 Follow-up

For each patient the same imaging modality (completed after cycle 1) will then be used for all follow-up imaging studies every 12 weeks.

Patients will be monitored through bi-weekly tests of CBC, creatinine, and liver enzymes for three months after the second cycle and four to six weeks until all treatment-related toxicities have resolved, returned to baseline, or been deemed irreversible, whichever is longest.

Urinalysis and LDH will be performed once every month to rule out thrombotic microangiopathy, and haptoglobin will be performed once every 2 months.

Patients will then be followed by history and physical examination every 12 weeks with CT scan or MRI imaging (as is routine for metastatic NET patients at MSK). Uniform assessment of response will be provided for each patient, i.e. one patient may be followed by either MRI or triphasic CT, but not both. NET patients are infrequently lost to follow-up. However, should there be relocation, or if a patient chooses to be followed by their primary oncologist after the completion of the study, every effort will be made to identify the follow-up evaluation and ensure that all notes are sent to MSK. Patients will be contacted by telephone for at least one year (every three months) to determine disease-free survival and overall survival, and the investigators will obtain appropriate source documentation from external providers to corroborate these assessments. Every effort will be made to follow all patients for survival every three months until death, or the cut-off date for the last protocol-mandated analysis, whichever occurs first. Any patients deemed lost to follow up, proceed with another treatment or pass away while on-study, they will be taken off-study at that time.

Patients removed from the study for unacceptable adverse events will be followed until resolution as well as for progression of disease.

Patients receiving any portion of the therapeutic dose will be included in the assessment of response.

9.5 Stopping Rules

A 5% probability of excessive toxicities is considered acceptable and a 20% probability as unacceptable. Excessive toxicities are defined as treatment related toxicities leading to an unacceptable delay in completing the 2 cycles of therapy as well as any delayed or irreversible grade 3 or 4 toxicities. If we observe more than 1 excessive toxicity within the first 10 patients, we will stop the study. If not, we accrue 10 more patients for a total of 20 patients. If we see more than 2 within the 20 (cumulative, including the 1 you might have seen among the first 10) we will also stop the study for excessive toxicity. If the true probability of toxicity is 5% then the probability of stopping for toxicity is 12%. If the true probability of toxicity is 20% then the probability of stopping for toxicity is 83%.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Schedule of Assessments

	Screening[1]		PET/CT	Dosimetry	Treatment[2]			Follow-up Every 3-4 months
	Within 4 weeks	Within 2 weeks	Day 1	Day 2-28	Cycle 1	Cycle 2	At end of each cycle	
Informed consent	X							
Medical history	X							X
Physical exam	X				X[3]	X[3]		X
Adverse event monitoring			X[16]	X[16]	X	X	X	
Concomitant medications	X				X[3]	X[3]		
ECOG/Karnofsky status	X				X[3]	X[3]		
Laboratory assessment		X			X[3]	X[3]		
CBC, creatinine, and liver enzymes, urine analysis[4]		X					X	
Pregnancy test if applicable		X		X	X	X		
EKG	X							
Urinalysis		X					X[13]	
Vital Signs	X		X[5]	X[5]	X[5]	X[5]		
^{111}In-Octreotide SPECT[6]	X							
MRI/CT scan	X				X[15]			X[15]
^{68}Ga-DOTA-JR11 injection			X					
^{99m}DTPA with filtration rate		X				X[11]		X[12]
^{68}Ga-DOTA-JR11 PET/CT scan			X					
^{177}Lu-DOTA-JR11 injection[7]				X	X	X		
Whole body imaging[8]				X	X	X		
SPECT/CT[9]				X	X	X		
Research blood draw[10]				X	X	X		
Endocrine Monitoring	X					X		X[14]
Assessment for delayed toxicity (red bone marrow, renal and hepatic functions)								X[14]

1. To be completed prior to study entry, i.e. patient registration.
2. Treatment with ^{177}Lu-DOTA-JR11 will begin within 6 weeks of completion of dosimetrystudy; Cycle 1 and 2 will be performed 10-14 weeks apart.
3. PE, ConMed review, performance status, and bloods (CBC, Comprehensive and LDH only) will be completed 7 -14 days prior to start of each cycle.
4. Bi-weekly tests of CBC, creatinine, and liver enzymes for three months after each cycle.
5. Vitals will be obtained prior to injections.
6. Octreotide scan must be within 8 weeks prior to study entry.
7. ^{177}Lu-DOTA-JR11 injection will be given on Day 1.
8. Whole body planar imaging will be obtained at nominal times of approximately1 -5 hours (i.e. day 1), 18-30 (i.e. day 2), 66-120 (i.e. day 4-6), and 144-192 (i.e. day 7-9) hours post injection. Less than 20 min
9. SPECT/CT will be obtained at 18-30 (day 2) hours post injection. Less than 40 min
10. Research blood samples will be drawn at 5-10 min, 15-20 min, 30-40 min, 60-90 min, 120-150 min, and 4-6 hours post-injection and, subsequently, at the times of imaging.
11. Within 2 weeks of cycle 2.
12. Within 10-14 weeks after cycle 2 and within 11-13 months after the dosimetrystudy.
13. Urinalysis and LDH will be performed every month. Haptoglobin will be performed every2 months.
14. Within 11-13 months after the dosimetrystudy.
15. The first imaging study(post-treatment baseline) will be performed within 10 (+/-5) days before start of cycle 2. In each patient the same imaging modality(CT or MRI) will be used for all follow-up imaging to ensure uniform response assessment. The first assessment of progression/response after completion of treatment will be performed 12 weeks after

the post-treatment baseline studyand subsequent assessments will again be performed at 12 week intervals, i.e. 12, 24, 36, … weeks after the post-treatment baseline study.
16. Please see section 11 for description of safety assessments.

11.0 TOXICITIES/SIDE EFFECTS

Detection and Treatment of Infusion Reactions

The following measures will be taken to detect and treat an infusion reaction:

Nurses or physicians will monitor patients for the duration of the PET/CT, dosimetry and treatment periods. EKG and pulse oximetry will be continually monitored, and blood pressure measurements will be performed every 15-20 min. For dosimetry and treatment monitoring will start with the infusion of the renal protectant solution and will be continued for total of approximately 4 h. Body temperature and blood glucose levels will be measured before the start of the infusion and approximately 4 h later. For the PET/CT study these measurements will be performed before injection and after completion of the imaging studies.

To our knowledge, hypersensitivity reactions to somatostatin agonist or antagonists have not been reported in the literature. If the event of symptoms of a hypersensitivity reaction the patient will be treated the same way as an acute reaction to radiologic contrast media according to the guidelines of the Department of Radiology (https://one.mskcc.org/sites/pub/radiology/Documents/Contrast%20Reaction%20policy.pdf). Briefly, mild to moderate reactions will be treated with diphenhydramine 25-50 mg PO or IV. Patients with a severe reaction will receive epinephrine 0.3 mg IM or 0.1-0.3 mg slowly IV. Patients will also receive oxygen via nasal cannula or face mask.

In the unlikely event that the microdose of [^{68}Ga] or [^{177}Lu]-DOTA-JR11 causes a carcinoid syndrome, patients will be treated with octreotide and ranitidine. In the case of hypoglycemia in patients with an insulin secreting neuroendocrine tumor, glucose will be administered intravenously. All these drugs will be readily available at the time of radiopeptide therapy.

Toxicity to Endocrine Glands

Although somatostatin receptors are expressed by various endocrine glands, previous studies have not shown clinically significant effects after treatment with a cumulative dose of up to 800 mCi ^{177}Lu-DOTA-TATE (31). In order to detect and monitor endocrine toxicities by ^{177}Lu-DOTA-JR11 the following parameters will be determined before the dosimetry study, before the second treatment cycle, and 1 year after the dosimetry study: Serum gonadotropins (LH, FSH), estradiol, testosterone, free thyroxine (FT4), triiodothyronine (T3), thyroid-stimulating hormone (TSH), glycosylated hemoglobin (HBA_{1C}) and ACTH as previously described for ^{177}Lu-DOTA-TATE (31). $HBA1_{1C}$ will not be measured in patients who are diabetic at the time of inclusion into the study. An endocrinologist is an investigator of this study and any abnormalities will be discussed with the endocrinologist. Supplementation and/or management of the endocrine abnormalities (if any) will be under the discretion of the study endocrinologist. Since it is unlikely that alterations will be significant, no dose reductions are built into the protocol at the present time. Should we find consistent and/or significant abnormalities, we will inform our IRB, FDA and amend the protocol accordingly.

Assessment for Delayed Toxicity

Delayed toxicity assessment at one year will be conducted. Delayed effects on red bone marrow, renal and hepatic functions will be assessed (11-13 months after the dosimetry study) by patients' interim history, physical examination, complete blood counts (white blood cell count with differential, hemoglobin, MCV, hematocrit, platelet count), serum creatinine and creatinine clearance with Cockcroft Gault formula, BUN, uric acid, albumin, bilirubin, AST, ALT, GGT, ALP, LDH, sodium potassium, calcium, glucose, and urinalysis).

Risks

^{68}Ga-DOTA-JR11 PET/CT Scans

As part of this scan, radiation is delivered both from the ^{68}Ga and from the low-dose CT scan, which is performed as part of the PET/CT for attenuation correction and co-registration. Although any exposure to ionizing radiation has the potential to cause some harm to tissue, the radiation exposures in this study are comparable to the low-level exposures associated with common diagnostic procedures such as CT scanning. There remains a low theoretical risk of developing a cancer at some point later in life as a result of the radiation exposure received in this study. This risk is much smaller than the clinical risks posed by the patient's current cancer. In general the radiation doses from the ^{68}Ga-DOTA-JR11 PET/CT scan are much less (typically < 1%) of those from ^{177}Lu-DOTA-JR11 therapy.

^{177}Lu-DOTA-JR11 Therapy

Because of the low injected mass of the peptide (<= 100 µg), which is 1,000 times less than the therapeutic dose of somatostatin analogs (21), we do not expect pharmacologic effects by the peptide scaffold of DOTA-JR11. However, side effects may occur as a consequence of the beta and gamma radiation emitted by ^{177}Lu. The toxicity of ^{177}Lu-labeled DOTA-TATE, which has a similar biodistribution to ^{177}Lu-DOTA-JR11 (10), has been studied in 504 patients with neuroendocrine tumors (3). Patients received up to 27.8-29.6 GBq (750 to 800 mCi), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. Hematologic toxicity grade 3 or 4 occurred after 3.6% of administrations. 62% of patients experienced grade 1 (i.e. minimal, per WHO criteria) temporary hair loss. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in three patients and temporary, nonfatal liver toxicity in two patients. There were two cases of renal insufficiency, but both were considered by the investigators to be unrelated to ^{177}Lu-DOTA-TATE therapy. One patient with extensive liver metastases died of hepatic failure after five weeks of therapy. Because this patient experienced a similar deterioration due to rapid tumor growth after his previous course of chemotherapy, the liver failure was considered more likely tumor growth-related rather than radiation-induced. Two other patients, both of whom had multiple liver metastases, had temporary rises in serum ALT, AST, and bilirubin concentrations. In both patients, this condition resolved without causative treatment, and both resumed treatment at half doses uneventfully. Lastly, myelodysplastic syndrome (MDS) occurred in four patients. In one patient, previous chemotherapy with alkylating agents was the more likely cause of MDS. In the other three patients, MDS was diagnosed two to three years after the last treatment and was considered as probably treatment-related (3).

A higher rate of side effects has been observed in patients treated with the somatostatin analog ^{90}Y-DOTA-TOC (2). A total of 1,109 patients were treated with two to four cycles of 3.7 GBq/m^2 of ^{90}Y-DOTA-TOC. Grade 3 or 4 hematologic toxicity was observed in 12.8% of the patients (n = 142). Leucopenia was observed in 67 patients, while anemia was observed in 11 patients, and thrombocytopenia in 64 patients. Of the total sample, 2 developed myeloproliferative syndromes, and 1 experienced acute myeloid leukemia. Another 2 patients developed tumor lysis syndrome directly after treatment with reversible kidney failure, and 102 patients (9.2%) experienced permanent renal toxicity (67 patients grade 4; 35 patients grade 5). The higher rate of renal toxicity is probably related to the higher energy of beta radiation emitted by ^{90}Y, which leads to a higher radiation dose to the glomeruli (31).

In the planned study, the risk of side effects will be minimized by performing detailed dosimetric studies for kidney and red marrow before and during therapy and by co-infusion of amino acids to decrease renal uptake of the JR11 (25). In a study of 90 patients treated with ^{90}Y-DOTA-TOC (co-infused with Aminosyn II amino acid solution containing approximately 28 g of both lysine and arginine), temporary grade III/IV renal toxicity was observed in 3 patients. No significant change in creatinine levels were observed at one year after the start of therapy (27). The amino acid infusion may cause nausea and vomiting. Other side effects are unlikely in the selected patient population with adequate renal and hepatic function.

JR11

Preclinical Toxicology

In mice, intravenous injection of 2,000 µg/kg did not cause death, a significant change in body weight, or pathologic findings on necropsy 15 days post-injection.

Clinical Toxicology

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Reference Values
Age (yr)	77	74	44	74	
Sex	F	M	F	F	
Diagnosis	Neuroendocrine Carcinoma (Bladder)	Neuroendocrine Tumor (Lung)	Neuroendocrine Tumor (Ileum)	Neuroendocrine Tumor (Ileum)	
Tumor grade	G3	G1	G2	G2	
Staging	pT3b pN1 pM1	cT2 cN2 cM1	pT4 pN1 pM1	pT4 cN1 pM1	
First diagnosed	5 months ago	3 years ago	5 years ago	11 months ago	
Treatment before recruitment					
Surgery	Yes	No	Yes	Yes	
Somatostatin analogues	Yes	No	Yes	Yes	
Others	No	No	Yes*	No	
Pre-treatment evaluation					
Date	10.11.2010	12.07.2011	01.07.2011	16.01.2012	
ECOG performance status†	2	0	1	0	
Remission status (CT scan)‡	PD	PD	PD	PD	
Somatostatin receptor scan	Positive	Positive	Positive	Positive	
Serum chromogranin A	387	1505	385	180	< 100
Serum creatinine	1.12 mg/dl	1.16 mg/dl	1.23 mg/dl	1.10 mg/dl	0.5 – 1 mg/dl
Creatinine clearance	54 ml/min/1.73 m^2	50 ml/min/1.73 m^2	87 ml/min/1.73 m^2	77 ml/min/1.73 m^2	90 – 170 ml/min/1.73 m^2
MAG3 clearance‖	127 ml/min/1.73 m^2	164 ml/min/1.73 m^2	125 ml/min/1.73 m^2	145 ml/min/1.73 m^2	> 150 ml/min/1.73 m^2
^{177}Lu-DOTA-JR11 treatment (2.2 GBq/m2 per treatment cycle, 2 – 3 treamtent cycles)					
Total treatment activity	6.1 GBq	15.2 GBq	5.9 GBq	13.7 GBq	
Post-treatment evaluation (3 months post-treatment outcomes)					
Date	18.03.2011	17.02.2012	25.01.2012	15.06.2012	
Remission status (CT scan)‡	Mixed response	PR	SD	PR	
Serum chromogranin A	752	857	368	288	< 100
Serum creatinine	1.40 mg/dl	1.30 mg/dl	1.34 mg/dl	1.20 mg/dl	0.5 – 1 mg/dl
Creatinine clearance	37 ml/min/1.73 m^2	57 ml/min/1.73 m^2	NA	55 ml/min/1.73 m^2	90 – 170 ml/min/1.73 m^2
MAG3 clearance‖	111 ml/min/1.73 m^2	138 ml/min/173 m^2	119 ml/min/173 m^2	134 ml/min/173 m^2	> 150 ml/min/1.73 m^2
Post-treatment evaluation (7 – 13 months post-treatment outcomes)					
Date	dead 12.05.2011	22.10.2012	23.11.2012	18.10.2012	
Serum chromogranin A	NA	NA	406	188	< 100
Serum creatinine	NA	1.50 mg/dl	1.30 mg/dl	1.38 mg/dl	0.5 – 1 mg/dl
Adverse events (follow-up 3 - 13 months)					
Anemia (reversible or preexisting)	Grade 1	Grade 1	Grade 2	Grade 2	
Leukopenia (reversible)	Grade 2	Grade 1	Grade 2	Grade 0	
Thrombocytopenia (reversible)	Grade 0	Grade 3	Grade 0	Grade 0	
Chronic kidney disease (preexisting)	Grade 3	Grade 3	Grade 2	Grade 3	

Table 6. Hematologic and clinical chemical parameters before and after treatment with ^{177}Lu-DOTA-JR11 in four patients with metastatic neuroendocrine tumors (10).

Four patients have so far been treated with ^{177}Lu-DOTA-JR11 at a peptide mass of 160-200 µg per injection and an activity of 5.9-13.7 GBq. The activity was delivered with two to three injections per patient. One patient had one episode of flush after injection of ^{177}Lu-DOTA-TATE, which resolved spontaneously. No other clinical side effects were observed. One episode of grade 3 thrombocytopenia resolved within eight weeks after injection. Renal function showed no significant change during follow-

Radiation dosimetry

The radiation exposure after injection of ^{177}Lu-DOTA-JR11 has been measured in four patients with metastatic NETs (10) and is summarized in Table 5. Table 7 shows total radiation dose projections for the proposed study. The dose estimates used for ^{68}Ga-DOTA-JR11 were generated by weighting published human radiation doses for ^{68}Ga-DOTA-TATE (32) with the ratio of ^{68}Ga-DOTA-JR11 to ^{68}Ga-DOTA-TATE tissue uptake in mice (7) .

^{68}Ga/^{177}Lu-DOTA-JR11 Patient Dosimetry including CT						
Total Activity of ^{68}Ga-DOTA-JR11			185	MBq in 1 admin =	5	mCi
Total Activity of ^{177}Lu-DOTA-JR11			12.74	GBq in 3 admin =	344[1]	mCi
PET/CT Attenuation scan@ 80mA			0.9	cGy x 1		
SPECT/CT Attenuation scan@ 80mA			0.9	cGy x 3		
Absorbed Dose Projections						
	^{68}Ga-DOTA-JR11[2]		^{177}Lu-DOTA-JR11[3]		Dose from CT	TOTAL
Target Organ	mGy/MBq	cGy	mGy/MBq	cGy	cGy	cGy
Kidney	0.215	3.98	1.80	2292	3.6	2300
Liver	0.057	1.05	0.33	420	3.6	425
Spleen	0.097	1.79	3.00	3821	3.6	3826
Adrenal gland	0.067	1.24	0.11	140	3.6	145
Lungs	0.002	0.04	0.11	140	3.6	144
Urinary bladder wall	0.100	1.85	0.37	471	3.6	477
Red marrow	0.022	0.41	0.10	127	3.6	131
Total body	0.013	0.24	0.13	166	3.6	169
Effective dose (rem)	0.019	0.35	0.20	255	3.6	259

[1] Please not that this is a typical activity. The exact administered activity will depend on the radiation dose calcluation as described in the text
[2] based on data for ^{68}Ga-DOTATATE (Sandstrom et al, J Nucl Med, 54, 1755-59, 2012)
[3] Wild et al. J Nucl Med, 55, 1248-52, 2014

Table 7. Projected radiation dosimetry for the proposed clinical study.

Reduction of the risk of radiation exposure to patient's family member, the general public and health care workers

Radiation dose rates measured in previous MSKCC pilot studies for patients administered ^{177}Lu labeled compounds have shown average dose rates within an hour after administration to be 0.23 mR/h/mCi (range 0.16-0.30) on contact and 0.011 mR/h/mCi (range 0.007-0.018) at a distance of 1 m. Patient-specific instructions indicating how many days to implement radioactive precautions will be determined according to the limits of 10 CFR Part 35 (US Nuclear Regulatory Commission) using the methodology of NUREG-1556, Vol. 9, Appendix U (US Nuclear Regulatory Commission), and guidance in NCRP Report #155 (National Council on Radiation Protection and Measurements). MSKCC Radiation Safety staff will perform regulatory-required patient dose rate monitoring for each patient following administration and will prepare and provide patient-specific radioactive precautions

in written and verbal form to each patient and the healthcare providers associated with the patient's care. Patients will be required to acknowledge receipt of these instructions. The instructions will specify how long patients should sleep in a separate bed, when they are able to return work, how long to maximize distance from other adults, pregnant women and children, and how long to avoid extended time in public places. While in the medical facility, lead shielding (either permanent or portable) will be provided as required based on dose rate measurements to maintain dose rates at 1 m from the patients to < 2 mR/h.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Tumor response will be monitored by CT and MR studies acquired as part of routine standard clinical care of patients approximately three and six months after the last treatment cycle. Tumor response will be classified according to RECIST 1.1. Confirmatory scans for partial response will not be performed. Changes in tumor diameters for all lesions that can be well identified on the SPECT/CT images of the dosimetry study will be recorded and correlated with the calculated radiation doses.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will go off-study if any of the following criteria are met:

- Any treatment related CTCAE grade 4 toxicity
- Unacceptable treatment delay due to delayed or irreversible toxicity
- Patient request

No replacement of patients discontinued for excessive toxicity is allowed.

Participation in the study is strictly voluntary, and patients will have the right to withdraw from the study at any time. If a patient chooses to withdraw, he or she must inform the investigator immediately. In addition, the investigator has the right to terminate participation of any patient at any time if it is deemed in the patient's best interest. Patients will be replaced if they are removed from the study and data obtained are inevaluable. The reason and circumstances for premature discontinuation will be documented in the patient's medical records. Possible examples for reasons of premature withdrawal include withdrawal of consent, SAE or intolerable AE, progression of disease, or any other medical illness at the investigator's discretion. If a patient progresses between cycle 1 and 2, patient will be removed from the study.

14.0 BIOSTATISTICS

Primary Objectives

This is a first-in-man study of ^{68}Ga-DOTA-JR11; there are only limited human data on the dosimetry of ^{177}Lu-DOTA-JR11. The main goal is therefore to ensure safety and tolerability, and characterize the adverse event profile. In addition descriptive data on the diagnostic accuracy of ^{68}Ga-DOTA-

JR11 and the tumor and normal organ doses after administration of ^{177}Lu-DOTA-JR11 will be obtained. We expect an accrual rate of 1-2 patients per month.

The safety, tolerability, and AE will be summarized using descriptive statistics. With 20 patients treated adverse event rates can be estimated to within +/- 10%, assuming the true rate is 25%, although estimation based on the observed data will use exact binomial confidence intervals and the length of confidence intervals will vary. All patients receiving a therapeutic dose of ^{177}Lu-DOTA-JR11 will be included in the safety data analysis. We will also capture those patients who do not receive a second therapeutic dose of ^{177}Lu-DOTA-JR11 of and record the reasons for not proceeding to cycle 2.

Assessment of biodistribution will be descriptive by calculating the standardized uptake values and areas under the time activity curves for the two radiopharmaceuticals.

Sensitivity of PET with ^{68}Ga-DOTA-JR11 to stage metastatic NETs in comparison to the clinically used sstr agonist ^{111}In-DTPA-octreotide will be assessed on a lesion basis. Reference standard will be determined by a consensus of the clinical investigators and systemic analysis of all available imaging studies and follow-up. Sensitivity will be estimated using the observed proportion of positive for a given modality using a variance inflation factor to adjust for multiple lesions in the same patient to compute the confidence intervals With an anticipated 4 lesions per patient and a putative intrapatient correlation of 0.1 these sensitivity can be estimated to within +/- 10%.

^{177}Lu-DOTA-JR11 dosimetry is described in Section 9.2.

Secondary Objectives

For estimation of radiation doses after administration of ^{177}Lu-DOTA-JR11, we are assuming a standard deviation of 8.2 Gy/GBq for the tumor dose after the administration of ^{177}Lu-DOTA-JR11 and a standard deviation of 0.8 Gy/GBq for the kidney dose (as observed in our pilot study). Under these assumptions, we should be able to determine the tumor dose with a standard error of the mean of 1.83 Gy/GBq as well as the kidney dose with a standard error of the mean of 0.18 Gy/GBq. We consider these as sufficiently accurate for the planning of larger clinical studies.

The correlation between tumor uptake of ^{68}Ga-DOTA-JR11 and tumor dose of ^{177}Lu-DOTA-JR11 will be estimated using rank-based methods (e.g. Spearman correlation) and reported in a descriptive way.

Overall response rate (ORR) according to RECIST 1.1 and median progression-free and overall survival will be estimated and reported with 95% confidence intervals. As a measure of tumor response we will report the ORR at 6 months after administration of the second treatment cycle.

We will generate Kaplan-Meier curves to describe and calculate the progression-free survival (PFS), which is defined as the period elapsing between the date of initiation of therapy and the date of either disease progression or date of death, whichever is earlier. This applies even if a given patient is withdrawn from treatment due to toxicity or discontinues treatment and is withdrawn prior to documentation of progression; all patients will be included in this statistic. We will also perform Kaplan-Meier curves to describe and calculate the overall survival (OS), defined as the interval between the time of initiation of therapy and the date of death from any cause. Patients who are

alive at the time of study completion will be censored at the time the patient was last known to be alive.

Duration of stable disease (SD) will be summarized and measured from the start of treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. All patients will be included in this analysis. A subset analysis of patients with stable disease at the initiation of therapy will be performed.

Patients who progress between cycles 1 and 2 will be replaced. This is to ensure that we will be able to study toxicity and tolerability in 20 patients who finish full course of therapy. Patients who are replaced due to progression will still be included in the analysis of secondary endpoints (ORR, PFS and OS) so the sample size for some of the analyses may exceed 20. We expect progression during therapy to be rare. In a study of metastatic GEP-NETs treated with ^{177}Lu-DOTA-TATE, progression during therapy occurred in only 37 out of 458 patients (8%) (3).

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

Not applicable.

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of the CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the protocol study team's activities.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

Study personnel will record clinical data in each patient's source documents (i.e., the patient's medical record).

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the data stored in the database used for data collection. Records will be retained and securely stored for a minimum of two years after the completion of all study activities.

Data will be entered throughout the duration of the trial as patients are enrolled. Accrual is expected to last 24 months.

16.2 Quality Assurance

Regularly scheduled registration reports will be generated to monitor patient accruals and the completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and the extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period, and potential problems will be brought to the attention of the principal investigator for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team at least once a year, and more frequently if indicated.

16.3 Data and Safety Monitoring

The data and safety monitoring (DSM) plans at MSK were approved by the National Cancer Institute (NCI) in September 2001. The plans address the policies set forth by the NCI in the document entitled *Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials*, which can be found at http://cancertrials.nci.nih.gov/clinicaltrials. The DSM plans at MSK were established and are monitored by the Office of Clinical Research. The MSK DSM plans can be found on the MSK Intranet at: https://one.mskcc.org/sites/pub/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety, and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research quality assurance) and departmental procedures for quality control, and two institutional committees are responsible for monitoring the activities of our clinical trials programs. The committees are as follows: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials; both of which report to the MSK Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH-sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed, and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, GCP guidelines established by the International Conference on Harmonization, and the ethical standards set forth in the Declaration of Helsinki 2004 (available at: www.laakariliitto.fi/e/ethics/helsinki.html).

The PET/CT scan with ^{68}Ga-DOTA-JR11 is diagnostic in nature and, based on our extensive clinical experience with diagnostic radiotracers in general and diagnostic radiolabeled peptides in particular, will involve administration of the labeled peptide at mass and activity levels far below those that would induce any toxic or other pharmacological effects. However, as with any exposure to radiation, even at the diagnostic levels to be used in this study, there is a very low, theoretical risk of radiation-induced cancer at some later point in life. The projected normal-organ radiation doses to subjects in this study are determined and included in our protocols and are well in the range of typical diagnostic imaging tests for cancer patients, such as CT. The risk of subsequent radiation- induced cancer is explicitly included in the Informed Consent forms for the studies included in this protocol. In addition, the subjects who will be enrolled in this clinical investigation will be exclusively patients with metastatic neuroendocrine cancers. The additional radiation doses associated with the PET/CT scans involved in this study will typically represent a small increment in their "lifetime" exposures by diagnostic tests, and more importantly radiopeptide therapy.

For the therapeutic part of the study, we also do not expect pharmacologic effects because the amount of peptide is again very low when compared to the therapeutic dose of somatostatin analogs (<= 100 µg every 3 months vs. 120 mg every 4 months). However, the therapeutic beta radiation presents a risk. Lutetium-177 has been extensively used for radiopeptide therapy of neuroendocrine tumors after coupling to the somatostatin agonist DOTA-TATE. Since the biodistribution and dosimetry of ^{177}Lu-DOTA-JR11 is similar to ^{177}Lu-DOTA-TATE (10) (Table 5), we therefore expect the same radiation exposure.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatning adverse event
- An adverse eent that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital adminssion for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

17.2.1

This protocol will have an IND. SAE will also be reported to the FDA through the IND office and the report will include the FDA-assigned IND number and name.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain the full details of the protocol and study procedures, as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and MSK's Institutional Review Board/Privacy Board. The consent form will include the following:

1. The nature and objectives, potential risks, and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies).
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Not applicable.