Diagnosis and staging of neuroendocrine tumors (NETs) utilizing ^{68}Ga-DOTATOC PET-CT scan

Document Date: 7/20/2016

NCT03136328

Protocol ID: 15-06-274

Principal Investigator:	**Charito Love, M.D.**
Biostatistician:	**Mimi Kim, Sc.D.**
Study Site:	**Montefiore Medical Park** **1695A Eastchester Road** **Bronx, NY 10461**

Version Amendment 1, dated 07.20.2016

Table of Contents

1.0 Objectives

1.1 Main objective:

The primary goal of the analysis is to estimate the diagnostic accuracy of 68Ga-DOTATOC PET-CT for detecting NET compared to conventional imaging techniques.

1.2 Secondary objectives:

We will assess the safety and tolerability of 68Ga-DOTATOC PET-CT by measuring the number of adverse events in patients receiving 68Ga-DOTATOC PET-CT.

2.0 Background and Rationale

Neuroendocrine tumors (NETs) are a heterogeneous group of rare neoplasms that originate from neuroendocrine cells. According to analysis of the National Cancer Institute Surveillance, Epidemiology and End Results data between 2003 to 2007, the incidence of NET is 3.56 cases per 100,000 (1). Compare this with incidence of colon and rectal cancer at 42.4 cases per 100,000. These neoplasms are generally small in size and occur mostly in the gastrointestinal tract and pancreas (so called Gastro-entero-pancreatic NET), but can also occur in other tissues including thymus, lung, and other uncommon sites such as ovaries, heart and ear. These neoplasms can present as multiple primary tumors located in variable sites. Regardless of their primary site, NETs share histological, immunohistochemical and ultrastrucural features. NETs retain multi-potent differentiation capacities including the ability to produce and secrete a variety of metabolically active substances including amines, peptides and prostaglandins following activation from somatostatin, a naturally occuring hormone in the body responsible for controlling neuroendocrine cells. Symptoms of NETs are usually vague, nonspecific and vary by the affected organ. Non-functional NETs are not associated with any specific hormonal syndrome, instead, their clinical manifestations are similar to most solid tumours, i.e. causing mass-effect either inside the organ where the tumor is growing or pressuring adjacent organs and structures (2).

The endocrine-related characteristics of NETs arise from the enterochromaffin and enterochromaffin-like cells of the gut. Pancreatic, enteric and unknown origins account for most NETs (>85%). Glucagonomas, VIPomas, and somatostinomas (pancreatic) are the rarest, the combined incidence accounting for only 2% of NETs (2-3).

Imaging plays an important role in diagnosing and localization of NETs. The information generated by imaging can guide therapy, which includes medications (somatostatin analogues), chemotherapy and/or surgery (2-3). Surgery remains the first choice for therapy but in many cases, additional therapy is needed as many patients have metastatic disease by the time diagnosis is made.

In nuclear medicine, imaging entails localization of a radiopharmaceutical, which is the agent that allows visualization of a normal or abnormal process, on imaging with using detectors. In the case of NETs, because they overexpressed multiple somatostatin receptors on their surfaces, imaging has been performed using a somatostatin analogue. The natural somatostatin has a half-life of 2-3 minutes while a somatostatin analogue consisting of an 8 amino acid protein that represents the part of the naturally occurring somatostatin hormone that localizes to the somatostatin receptor (SSTR) has a half-life of 90 minutes. Thus, it is amenable for imaging. This analogue is attached to a radiopharamaceutical and upon localization to a somatostatin receptor on the surface of a

NET; the images obtained allow detection and localization of the NET (3-5). This 8-amino acid analogue is called Octreotide and has been attached to In-111, a gamma emitting radiopharmaceutical through a DTPA linker. The resulting agent is called In-111 Octreotide. In-111 Octreotide is imageable on gamma camera available in many nuclear medicine facilities; this technique is widely known as Octreoscan. It has been approved for use in USA since 1989 (3-6). In-111, the radiopharmaceutical, has a long half-life of 2.8 days. There are advantages to a radiopharmaceutical with such long half-life in that it allows delayed imaging. Currently, imaging is accomplished by acquiring whole body images 4 hours after injection of In-111 Octreotide during which time there is normally no bowel activity and may allow detection of abnormal activity in the abdomen. The patient comes back 24 hours later whereby delayed whole body images and single photon emission tomography (SPECT) is performed. Because of the normal excretion of the agent into the bowel after 4 hours, it is often necessary to repeat the SPECT at 48-72 hours later to confirm that bowel activity moved. The availability of hybrid SPECT/CT has facilitated the distinction of normal bowel activity and abnormal tumor activity in some cases but not in all cases. This imaging procedure often requires multiple trips to the nuclear medicine imaging suite over few days (6).

There are important disadvantages as well to a radiopharmaceutical with long half-life. The long half-life involves higher radiation exposure to the patient. To circumvent this, only a very small amount of the radiopharmaceutical can be used often resulting in less than optimal images. Additionally, one can only use a small amount of the somatostatin analogue for the allowable amount of radiopharmaceutical contributing further to poor images. Another factor in poor detection of somatostatin receptors by In-111 Octreotide is the variable sensitivity of this agent to various forms of the receptors. Somatostatin receptor (SSTR) has 5 subtypes: 1-5. In-111-Octreotide has high affinity to SSTR subtype 2 but has no affinity for SSTR 1 and SSTR 4, and low affinity to SSTR 3 and SSTR 5. Thus, the primary tumor is not identified in 20-50% of NETs. Additional reasons for the relatively high failure rate of detecting NETs include low sensitivity of gamma camera imaging technology so visualization of deep or small lesions can be impaired. Secondly, most somatostatin receptor-positive tumors express multiple SSTR subtypes simultaneously. Thirdly, even in the same patient, the SSTR expression is heterogeneous. Lastly, In-111 Octreotide only has 10 ug of the somatostatin analogue available for receptor localization (6). Thus, In-111 Octreotide may not always successfully demonstrate NETs.

Combined positron emission tomography (PET) with CT (PET/CT) technology has proved its utility with F-18 FDG PET/CT imaging of more well-known or more common carcinomas such as lymphoma, breast, colon or lung cancers. The images obtained with a positron emitter using PET/CT technology provides exquisite resolution giving rise to better visualization and more accurate localization of a tumor and allows semiquantitative analysis of a molecular event in a tumor (7). In Europe, investigators found a way to optimize the use of somatostatin analogue by labeling it with a positron emitting radiopharmaceutical, Ga-68, which proved easy to perform. Because of the prior experience with Octreotide, Ga-68 dota-Octreotide was the first agent used (8, 9). This is the same somatostatin analogue in In-111 Octreotide. Ga-68 has a half-life of 68 minutes (F-18 FDG, the more common radiopharmaceutical used for many carcinomas, has a half-life of 110 minutes). Following injection, imaging can be performed 60-120 minutes later during which time no bowel activity is seen to confound the evaluation of images. Thus, any tumor within the gut is easily visualized. The shorter half-life decreases the radiation dose to the patient and also allows higher dose of the somatostatin analogue to be incorporated with the radiopharmaceutical: ≤ 50 ug. The shorter half-life of the radiopharmaceutical also means that imaging is completed within 3 hours or less instead of days as in the case of In-111 Octreotide (6).

In one of the earliest study consisting of 8 patients with biopsy proven neuroendocrine tumor, all lesions, defined by CT and MRI, were detected by Ga-68 DOTATOC (100%) while In-111 Octreotide missed 30% of the lesions. Arterial blood analysis at 4 hours after Ga-68 DOTATOC injection showed no detectable radioactivity in the serum confirming the short half-life of Ga-68 (8). Two other forms of Octreotide namely dota-Octreotate (DOTATATE) and dotan-Octreotide (DOTANOC) were also labeled with Ga-68. In addition to European countries, Japan and other Asian countries have also started to use Ga-68 Octreotide preparations for imaging (9).

Human dosimetry has shown that the highest absorbed organ doses for the Ga-68 labeled somatostatin analogues were seen in the spleen, uroepithelium of the bladder, kidneys, adrenal glands and liver (6, 10). Relative radiation dose (effective dose) for Ga-68 is 0.023 mSv/MBq dose. For comparative purposes of radiation exposure measurement, the table below illustrates the effective doses Ga-68 labeled Octreotide preparations versus In-111 Octreotide and F-18 FDG (10):

	Ga68-DOTATATE	Ga68-DOTATOC	Ga68-DOTANOC	In-111 Octreotide	F18-FDG
MBq injected activity	185	185	185	74 (222)*	370
Equivalent mCi injected activity	5	5	5	2 (6)*	10
Effective dose (mSv)	4.8	4.8	4.8	5.9 (17.7)*	7.0

*Standard dose of In-111 Octreotide injected in USA is 6 mCi (222 MBq), equivalent MBq and ED for this amount in parenthesis.

The low dose CT for PET/CT imaging incurs about 7-10 mSv. For a dose of 100-185 MBq Ga-68 PET/ CT, the total radiation dose comes to 10-14.3 mSv which is equivalent to 3.3 to 4.8 years of natural background radiation. Clearly, Ga-68 labeled somatostatin analogues are associated with much lower radiation dose compared with currently available In-111 Octreotide, which is injected as a 6 mCi dose in USA.

As far as the ability to detect the primary NET is concerned, many studies as shown Section 2.2 have shown the superiority of Ga-68 labeled somatostatin analogues. For example, in a prospective clinical investigation with 19 consecutive patients, the following results were obtained (11):

	Sensitivity	Specificity	Accuracy
Ga-68 DOTATATE	0.96	0.97	0.97
Tc-99m Octreotide	0.60	0.99	0.86
MRI	0.73	1.0	0.91

In another study that reviewed a total of 123 patients with unknown primary NET in their institution; 15 of 52 (45.5%) patients evaluated with Ga-68 DOTATOC had their primary tumors localized. Only 4 of the 71 (8%) patients who underwent In-111 Octreotide scan had their primary tumor visualized. Seventeen patients underwent both imaging modalities: both In-111 Octreotide and Ga-68 DOTATOC identified the primary tumor in two patients; Ga-68 detected an additional lesion in one of these patients. In-111 Octreotide failed to detect the primary tumor in 15 patients, whereas Ga-68 DOTATOC localized the tumor in 7 of these patients (12). Other experiences with

Ga-68 labeled somatostatin analogues can be found in Section 2.2.

While the number of patients included in many of the clinical investigations using Ga-68 products described in this protocol is small compared to the usual number of patients in many oncologic investigations, it should be noted that NETs are rare and multicentre trials have not been performed.

In August 2013, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) submitted an application to the Federal Drug Administration to designate Ga-68 DOTATOC as orphan drug to allow its availability for clinical use in the USA since it has already been shown by many investigators from various countries to be efficacious and safe for human use. In September 2013, FDA granted Ga-68 DOTATOC its orphan drug designation and allowed its use in the USA as investigational new agent/drug without the traditional preclinical and Phase I clinical studies. With this new orphan drug designation, Ga68-DOTATOC is directed down a unique pathway within the FDA on its road to approval.

SSTR imaging is important for diagnosing, staging and for follow up of patients with NETs. It is even more important now given the availability of a very effective protein radionuclide radiotherapy (PRRT) using the same somatostatin analogue, Octreotide, labeled with another radiopharmaceutical that is useful for therapy such as Lu-177 or Y90 has been has been very helpful in metastatic disease and in resistant NET with reported at least 30% decrease in tumor size (13). For PRRT to be effective, confirmation of SSRT receptor status is required. Indeed, somatostatin analogues have been used for diagnosis and for therapy with encouraging results (9, 13-16). There are currently very few institutions in USA that have a specialized NET program. One such institution is located in Vanderbilt University Hospital in Tennessee and another hospital in Iowa. There is no established program in the East Coast at the moment. The availability of PRRT for patients with inoperable, advanced or recalcitrant NET will provide a much needed option for these patients (14-16).

2.1 Characteristics of ^{68}Ga-DOTATOC

^{68}Ga-DOTATOC has 3 main components, namely the somatostatin analogue (DOTA^{0}-Phe^{1}-Tyr^{3}) octreotide (commonly referred as DOTATOC), the chemical linker DOTA (tetraxetan) and the positron emitter ^{68}Gallium. These entire three components have been previously used in human subjects and in medical research. Approximately 50 micrograms of DOTATOC will be used for labeling with ^{68}Ga to manufacture PET/CT agent.

DOTA is a well-established bifunctional chelating agent first used in the 1970s (7,8,17), with chemical formula 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, a 12 member tetraaza macrocycle, essentially a cyclen skeleton that has been modified with acetate side arms to form a polyamino carboxylic acid. At the time of its discovery DOTA was demonstrated to have the largest known formation constant for the complexation Ca^{2+} and Gd^{3+} ions. A modified version of DOTA C-functionalized to act as a bifunctional chelate agent was first reported in 1988. DOTA is the most frequently used moiety for elemental labelling, typically metal isotopes to proteins (antibodies and peptides). There are several derivatives of DOTA also being used in medicine, such as DOTATOC ((DOTA (0)-Phe (1)-Tyr (3)) octreotide) or edotreotide) and DOTATATE ((DOTA (0), Phe1, Tyr3)-octreotate), however, all of these compounds have so far no marketing authorisation.

Gallium is a metallic element, which in nitrate form is used intravenously to treat hypercalcaemia due to bone tumors. Isotopes of Gallium (^{67}Ga, ^{68}Ga) are used as radiopharmaceuticals in

different forms and salts. The body handles Gallium similarly to Iron, and thus it is bound (and concentrates) in areas of inflammation, such as infection, and also areas of rapid cell division. ^{68}Gallium, a positron emitter with a short half-life (68min) is used as a diagnostic radiopharmaceutical for PET-CT when linked to pharmaceutical preparations such as ^{68}Ga-DOTATATE or DOTATOC all of which are somatostatin analogues being researched for the diagnosis of neuroendocrine tumours. Ga-68 linked with DOTA has allowed simpler radiolabeling procedure for different peptides.

2.2 Previous Human Exposure

There is substantial previous clinical experience with Octreotate from therapeutic trials and diagnostic use of ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC. Following is a list of few peer-reviewed publications related to use of somatostatin analogues for diagnostic as well as therapeutic purposes.

2.3 Clinical studies with use of somatostatin analogues as ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE and ^{177}Lu-DOTATOC

1. **Henze M, Schuhmacher J, Hipp P. et al: PET imaging of somatostatin receptors using [68Ga]DOTA-D-Phe-Tyr-Octreotide: first results in patients meneingiomas. J Nucl Med 2001;42:1053-1056.**

   This earlier study included 3 patients with 8 meningiomas who underwent brain imaging with Ga-68 DOTATOC. All menigiomas, including small sized lesions, were detected with very high target to background ratio. No adverse reaction was noted in the patients. Investigators concluded that Ga-68 DOTATOC can be used in small lesions.

2. **Kowalski J, Henze M, Schuhmacher J, et al: Evaluation of positron tomography imaging using [68Ga]-DOTA-D Phe(1)-Tyr(3)-Octreotide in comparison to [111In]DTPAOC SPECT. First results in patients with neuroendocrine tumors. Molec Imaging and Biology. 2003; 5:42-48.**

   4 patients were evaluated using In-111 Octreotide and Ga-68 Octreotide. The investigators found Ga-68 B DOTATOC to be superior to In-111 Octreotide especially in small tumors or tumors bearing only a low density of SSTRs. No adverse side effects reported following injection of Ga-68 DOTATOC.

3. **Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Guggenberg E, Bale R, and Virgolini IJ. ^{68}Ga-DOTA-Tyr3-Octreotide PET in Neuroendocrine Tumors: Comparison with Somatostatin Receptor Scintigraphy and CT. *J Nucl Med* 48, 508-518 (2007).**

   Study Design: 84 patients (48 men, 36 women; age range, 28–79 y; mean age ± SD, 58.2 ± 12.2 y) were prospectively studied. For analysis, patients were divided into 3 groups: detection of unknown primary tumor in the presence of clinical or biochemical suspicion of neuroendocrine malignancy (n =13 patients), initial tumor staging (n = 36 patients), and follow-up after therapy (n = 35 patients). Each patient received 100–150 MBq ^{68}Ga-DOTA-TOC. The gold standard for defining true-positive (TP), true-negative

(TN), false-positive (FP), and false-negative (FN) results was based on all available histologic, imaging, and follow-up findings.

Results: PET was TP in 69 patients, TN in 12 patients, FP in 1 patient, and FN in 2 patients, indicating a sensitivity of 97%, a specificity of 92%, and an accuracy of 96%. The FP finding was caused by enhanced tracer accumulation in the pancreatic head, and the FN results were obtained in patients with a tumor of the gastrointestinal tract displaying liver metastases. ^{68}Ga-DOTA-TOC showed higher diagnostic efficacy compared with SPECT (TP in 37 patients, TN in 12 patients, FP in 1 patient, and FN in 34 patients) and diagnostic CT (TP in 41 patients, TN in 12 patients, FP in 5 patients, and FN in 26 patients). This difference was of statistical significance ($P< 0.001$). However, the combined use of PET and CT showed the highest overall accuracy.

Discrepancies with Ga-68 DOTATOC PET and In-111 Octreotide SPECT were in 32 patients (32%) all of whom were TP with PET and FN with SPECT. In this group of patients, 10 liver metastases, 22 small nodal metastases in 15 patients and carcinoid tumors in 2 patients with peritoneal deposits were missed on SPECT. A total of 32 bone lesions were only seen on Ga-68 PET images, not visualized on In-111 Octreotide scan or on bone scan.

Discrepancies with Ga-68 PET and diagnostic CT were found in 34 patients (40.5%): 2 TP, 1 TN, 5 FP, 26 FN findings with CT. FP findings on CT were caused small nodular lung lesions in 2 patients, enlarged nodes in another 2 patients and one patient with leiomyoma in a jejunal wall lesion. Ga-68 PET provided information on 9 patients with unsuspected bone metastases on CT. In 5 patients, the primary or residual NET was missed on CT and detected on Ga-68 PET.

Intravenous injection of Ga-68 DOTATOC was well tolerated by all 84 patients with side effects observed. The optimal time of imaging in this study was determined to be 100 minutes after injection.

Conclusion: ^{68}Ga-DOTA-TOC PET shows a significantly higher detection rate compared with conventional somatostatin receptor scintigraphy (Octreoscan) and diagnostic CT with clinical impact in a considerable number of patients.

4. **Buchmann I, Henze M, Engelbrecht S, Eisenhut M, Runz A, Schäfer M, Schilling T, Haufe S, Herrmann T, Haberkorn U. Comparison of ^{68}Ga-DOTATOC PET and ^{111}In-DTPAOC (Octreoscan) SPECT in patients with neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 34, 1617-1626 (2007).**

Study Design: 27 NET patients were prospectively examined. ^{68}Ga-DOTATOC PET and ^{111}In-DTPAOCTREOTIDE SPECT were performed using standard techniques. Treatment was not applied in between. Mean and maximum standardized uptake values (SUVs) were calculated for PET findings. Tumor/non-tumor ratios were calculated for SPECT findings. Findings were compared by a region-by-region analysis and verified with histopathology, CT and MRI within 21 days.

Results: SUVs of positive lesions on ^{68}Ga-DOTATOC PET ranged from 0.7 to 29.3 (mean SUV) and from 0.9 to 34.4 (maximum SUV). Tumor/non-tumor ratios on ^{111}In-DTPAOC SPECT ranged from 1.8 to 7.3. In imaging lung and skeletal manifestations, ^{68}Ga-DOTATOC PET was more efficient than ^{111}In-DTPAOC SPECT. All discrepant lung findings and 77.8% of discrepant osseous findings were verified as true positive PET interpretations. In regional comparison of liver and brain, ^{68}Ga-DOTATOC PET

and ^{111}In-DTPAOC SPECT were identical. In lymph nodes, the pancreas and the gastro-intestinal system, different values of the two techniques were not indicated in regional analyses. In a single patient, surgical interventions were changed on the basis of ^{68}Ga-DOTATOC PET findings.

Conclusion: ^{68}Ga-DOTATOC PET is superior to ^{111}In-DTPAOC SPECT in the detection of NET manifestations in the lung and skeleton and similar for the detection of NET manifestations in the liver and brain. ^{68}Ga-DOTATOC PET is advantageous in guiding the clinical management.

5. **Srirajaskanthan R, Kayani I, Quigley AM, Soh J, Caplin ME, and Bomanji J. The Role of ^{68}Ga-DOTATATE PET in Patients with Neuroendocrine Tumors and Negative or Equivocal Findings on 111In-DTPA-Octreotide Scintigraphy. *J Nucl Med.* 51, 876-882 (2010).**

   Study Design: Fifty-one patients with a histologically confirmed diagnosis of neuroendocrine tumors were included. Of the 51 patients, 35 who were negative and 16 equivocal for uptake on ^{111}In-DTPA-octreotide scintigraphy underwent ^{68}Ga-DOTATATE PET. Findings were compared using a region-by-region analysis. All findings were verified with CT or MRI. After ^{68}Ga-DOTATATE PET, all cases were reviewed to determine whether the ^{68}Ga-DOTATATE PET findings resulted in any alteration in management, in terms of suitability for peptide receptor therapy, somatostatin analogs, and surgery.

   Results: Of the 51 patients, 47 had evidence of disease on cross-sectional imaging or biochemically. ^{68}Ga-DOTATATE PET was positive in 41 of these 47 patients (87.2%). No false positive lesions were identified. ^{68}Ga-DOTATATE PET detected 168 of the 226 lesions (74.3%) that were identified with cross-sectional imaging. ^{68}Ga-DOTATATE PET identified significantly more lesions than ^{111}In-DTPA-octreotide scintigraphy ($P < 0.001$). There was no correlation between ^{68}Ga-DOTATATE uptake and histologic grade of neuroendocrine tumors. ^{68}Ga-DOTATATE imaging changed management in 36 patients (70.6%), who were subsequently deemed suitable for peptide receptor– targeted therapy.

   Conclusion: In patients with negative or equivocal ^{111}In-DTPA-octreotide findings, ^{68}Ga-DOTATATE PET identifies additional lesions and may alter management in most cases.

6. **Hofman MS, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol.* 56, 40-47 (2012).**

   Study Design: Fifty-nine GaTate PET/CT studies were performed over an 18-month period (52 proven or suspected gastro-entero-pancreatic or bronchial neuroendocrine tumors and seven neural crest/mesenchymal tumors). A retrospective blinded review was performed on the number of abnormalities (1, 2-5 or >5) within defined regions with comparison to conventional imaging to assess incremental diagnostic information. Subsequent management impact (high, moderate or low) was determined by clinical review and follow up to assess pre-PET stage, treatment intent and post-PET management change.

Results: Eighty-eight percent of GaTate studies were abnormal. Compared with conventional and In-111 octreotide imaging, additional information was provided by GaTate PET/CT in 68 and 83% of patients, respectively. Management impact was high (inter-modality change) in 47%, moderate (intra-modality change) in 10% and low in 41% (not assessable in 2%). High management impact included directing patients to curative surgery by identifying a primary site and directing patients with multiple metastases to systemic therapy.

Conclusion: GaTate PET/CT imaging provides additional diagnostic information in a high proportion of patients with consequent high management impact. GaTate PET/CT could replace In-111 Octreotide scintigraphy at centers where it is available given its superior accuracy, faster acquisition and lower radiation exposure. Rapid implementation could be achieved by allowing institutional funding in the Medicare Benefit Schedule.

7. **Poeppel TD, Binse I, Petersenn S, Lahner H, Schott M, Antoch G, Brandau W, Bockisch A, Boy C. ^{68}Ga-DOTATOC versus ^{68}Ga-DOTATATE PET/CT in functional imaging of neuroendocrine tumors. *J Nucl Med.* 52, 1864-1870 (2011).**

Study Design: Forty patients with metastatic NETs underwent ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE PET/CT as part of the work-up before prospective peptide receptor radionuclide therapy. The performance of both imaging methods was analyzed and compared for the detection of individual lesions per patient and for 8 defined body regions. A region was regarded positive if at least 1 lesion was detected in that region. In addition, radiopeptide uptake in terms of the maximal standardized uptake value (SUVmax) was compared for concordant lesions and renal parenchyma.

Results: Seventy-eight regions were found positive with ^{68}Ga-DOTATATE versus 79 regions with ^{68}Ga-DOTATOC (not significant). Overall, however, significantly fewer lesions were detected with ^{68}Ga-DOTATATE than with ^{68}Ga-DOTATOC (254 vs. 262, $P < 0.05$). Mean ^{68}Ga-DOTATATE SUVmax across all lesions was significantly lower than ^{68}Ga-DOTATOC (16.0 ± 10.8 vs. 20.4 ± 14.7, $P < 0.01$). Mean SUVmax for renal parenchyma was not significantly different between ^{68}Ga-DOTATATE and ^{68}Ga-DOTATOC (12.7 ± 3.0 vs. 13.2 ± 3.3).

Conclusion: ^{68}Ga-DOTATOC and ^{68}Ga-DOTATATE possess a comparable diagnostic accuracy for the detection of NET lesions, with ^{68}Ga-DOTATOC having a potential advantage. The approximately 10-fold higher affinity for the sst2 of ^{68}Ga-DOTATATE does not prove to be clinically relevant. Quite unexpectedly, SUVmax of ^{68}Ga-DOTATOC scans tended to be higher than their ^{68}Ga-DOTATATE counterparts.

8. **Velikyan I, Sundin A, Sorensen J, et al: Quantitative and qualitative intrapatient comparison of 68Ga-DOTATOC and 68Ga- DOTATATE: net uptake rate for accurate quantification. J Nulc Med 2014;55:204.210.**

Quantitative imaging and dosimetry are crucial for individualized treatment during PRRT. In this investigation, 68 Ga-DOTATOC and 68 Ga –DOTATATE were used for diagnostic imaging and 177Lu-DOTATATE for therapy.

Study Design: Ten patients with metastatic neuroendocrinetumors underwent one 45-min dynamic and 3 whole-body PET/CTexaminations at 1, 2, and 3 h after injection with both tracers. The number of detected lesions, SUVs in lesions and normal tissue, total functional tumor volume, and SSTR volume (functional tumor volume multiplied

by mean SUV) were investigated for each time point. Net uptake rate (Ki) was calculated according to the Patlak method for 3 tumors per patient.

Results: There were no significant differences in lesion count, lesion SUV, Ki, functional tumor volume, or SSTR volume between 68Ga-DOTATOC and 68Ga-DOTATATE at any time point. The detection rate was similar, although with differences for single lesions in occasional patients. For healthy organs, marginally higher uptake of 68Ga-DOTATATE was observed in kidneys, bone marrow, and liver at 1 h. 68Ga-DOTATOC uptake was higher in mediastinal blood pool at the 1-h time point (P 5 0.018). The tumor-to liver ratio was marginally higher for 68Ga-DOTATOC at the 3-h time point (P 5 0.037). Blood clearance was fast and similar for both tracers. SUV did not correlate with Ki linearly and achieved saturation for a Ki of greater than 0.2 mL/cm3/min, corresponding to an SUV of more than 25.

Conclusion: 68Ga-DOTATOC and 68Ga-DOTATATE are suited equally well for staging and patient selection for PRRT with 177Lu-DOTATATE. However, the slight difference in the healthy organ distribution and excretion may render 68Ga-DOTATATE preferable. SUV did not correlate linearly with Ki and thus may not reflect the SSTR density accurately at its higher values, whereas Ki might be the outcome measure of choice for quantification of SSTR density and assessment of treatment outcome.

9. **Kayani I, Conry BG, Groves AM, Win T, Dickson J, Caplin M, Bomanji JB. A comparison of ^{68}Ga-DOTATATE and ^{18}F-FDG PET/CT in pulmonary neuroendocrine tumors. *J Nucl Med.* 50, 1927-1932 (2009).**

Study Design: Twenty SRS were included in the study. Patients' age (n = 20) ranged from 25 to 75 years (mean 55.4 ± 12.7 years). There were eight patients with well-differentiated neuroendocrine tumor (WDNET) grade1, eight patients with WDNET grade 2, one patient with poorly differentiated neuroendocrine carcinoma (PDNEC) grade 3 and one patient with mixed adenoneuroendocrine tumour (MANEC). All patients had two consecutive PET studies with ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC. All images were evaluated visually and maximum standardized uptake values (SUV (max)) were also calculated for quantitative evaluation.

Results: On visual evaluation both tracers produced equally excellent image quality and similar body distribution. The physiological uptake sites of pituitary and salivary glands showed higher uptake in ^{68}Ga-DOTATATE images. Liver and spleen uptake values were evaluated as equal. Both ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC were negative in 6 (30 %) patients and positive in 14 (70 %) patients. In ^{68}Ga-DOTANOC images only 116 of 130 (89 %) lesions could be defined and 14 lesions were missed because of lack of any uptake. SUV (max) values of lesions were significantly higher on ^{68}Ga-DOTATATE images.

Conclusion: This study demonstrated that the images obtained by ^{68}Ga-DOTATATE and ^{68}Ga-DOTANOC have comparable diagnostic accuracy. However, ^{68}Ga-DOTATATE seems to have a higher lesion uptake and may have a potential advantage.

10. **Forrer, F., Uusijarvi, H., Storch, D., Maecke, H.R. & Mueller-Brand, J. Treatment with ^{177}Lu-DOTATOC of patients with relapse of neuroendocrine tumors after treatment with 90Y-DOTATOC. *J Nucl Med* 46, 1310-6 (2005).**

Study Design: Twenty seven patients with metastatic NETs who had previously received treatment with ^{90}Y-DOTATOC received a single fixed dose of 7.4 GBq (200 mCi) ^{177}Lu-DOTATOC at a median of 15.4 months after the last cycle of ^{90}Y therapy. Restaging was performed after 8-12 weeks. Patients with hematological toxicities after ^{90}Y therapy (grade 1 or 2 WHO criteria) were included. Infusion of amino acids (Ringers lactated Hartmann solution, Proteinsterile HEPA *% MG5-Sulfat) was given 30 min prior to and up to 3 h after treatment for kidney protection.

Results:. The mean absorbed doses were 413±159mGy for the whole body, 3.1±1.5 mGy for the kidneys and 61±5 mGy for the red marrow. After restaging, a partial response was found in 2 patients (7%), Minor response in 5 patients (18%), stable disease in 12 patients (44%) and progressive disease in 8 patients (29.6%).

Conclusions: ^{177}Lu-DOTATOC treatment is feasible, safe and efficacious. No serious adverse events occurred.

11. **Haug AR, Auernhammer AJ, Wangler B, Schmidt GP, Uebleis C, Goke B, Cumming P, Bartenstein P, Tiling R, and HackerM. ^{68}Ga-DOTATATE PET/CT for the early prediction of response to somatostatin receptor- mediated Radionuclide therapy in patients with well-Differentiated nueroendocrine tumors. *J Nucl Med.* 51, 1349-1356 (2010).**

    Study Design: 32 patients (22 male and 11 female; mean age ± SD, 57.8 ± 12.1 y) were investigated at baseline and again 3 month after initiation of the first cycle of PRRT. ^{68}Ga-DOTATATE receptor expression was assessed using 2 measures of standardized uptake value (SUV)

    Results: The 23 of 31 patients with decreased SUVT/S after the first PRRT cycle had longer progression-free survival than did the 8 of 31 patients with stable or increased scores. For the 18 of 33 patients showing a reduction in SUVmax, there was no significant difference in progression-free survival. Multivariate regression analysis identified.

    Conclusion: Decreased ^{68}Ga-DOTATATE uptake in tumors after the first cycle of PRRT predicted time to progression and correlated with an improvement in clinical symptoms among patients with well differentiated neuroendocrine tumors.

12. **Gabriel M, Oberauer A, Dobrozemsky G, Decristoforo C, Putzer D, Kendler D, Uprimny C, Kovacs P, Bale R, Virgolini IJ. ^{68}Ga-DOTA-Tyr3-octreotide PET for assessing response to somatostatin-receptor-mediated radionuclide therapy. *J Nucl Med.* 50, 1427-1434 (2009).**

    Study Design: Forty-six patients (29 men, 17 women; age range, 34-84 y) with advanced neuroendocrine tumors were investigated before and after 2-7 cycles of radionuclide therapy. Long-acting somatostatin analogs were not applied for at least 6 wk preceding the follow-up. Data were acquired with a dedicated PET scanner. Emission image sets were acquired at 90-100 min after injection. ^{68}Ga-DOTA-TOC PET images were visually interpreted by 2 experienced nuclear medicine physicians. For comparison, multislice helical CT scans and 1.5-T MRI scans were obtained. Attenuation-corrected PET images were used to determine SUVs. Repeated CT evaluation and other imaging modalities, for example, (18)F-FDG, were used as the reference standard.

Results: According to the reference standard, ^{68}Ga-DOTA-TOC PET and CT showed a concordant result in 32 patients (70%). In the remaining 14 patients (30%), discrepancies were observed, with a final outcome of progressive disease in 9 patients and remission in 5 patients. ^{68}Ga-DOTA-TOC PET was correct in 10 patients (21.7%), including 5 patients with progressive disease. In these patients, metastatic spread was detected with the follow-up whole-body PET but was missed when concomitant CT was used. On the other hand, CT confirmed small pulmonary metastases not detected on ^{68}Ga-DOTA-TOC in 1 patient and progressive liver disease not detected on ^{68}Ga-DOTA-TOC in 3 patients. Quantitative SUV analysis of individual tumor lesions showed a large range of variability.

Conclusion: ^{68}Ga-DOTA-TOC PET shows no advantage over conventional anatomic imaging for assessing response to therapy when all CT information obtained during follow-up is compared. Only the development of new metastases during therapy was detected earlier in some cases when whole-body PET was used. SUV analysis of individual lesions is of no additional value in predicting individual responses to therapy.

2.4 Diagnostic Agent

Ga-68 DOTATOC has been officially added to MMC's formulary lists having been cleared by both the Radiology and MMC's Pharmacy and Therapeutics committees, the radiation safety committees as well as the NYC Bureau of Radiological Health. Its use as investigational new agent is now possible pending clearance from the institution's regulatory committees for clinical trials.

The chemistry, manufacturing and controls (CMC) for the study agent are described in the Quality module included with the IND submission (appendix a). The following sections are a brief overview of the product.

2.5 Chemical Identity:

The proposed study medication is "Gallium" (^{68}Ga)-DOTATOC, where ^{68}Ga (the tracer) is a positron-emitter, Octreotide (the peptide) is a somatostatin analogue, and DOTA (chelator) is a chemical chelator used to link ^{68}Ga to Octreotide.

Chemical name of Octreotide: L-Cysteinamide,N-[[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-N-[(1R,2R)-2-hydroxy-1-(hydroxymethyl)propyl]-, cyclic (2→7)-disulfide

Molecular weight: 1421.6g/mol (DOTATOC).

Route of administration: intravenous route.

Composition: Each batch preparation of ^{68}Ga-DOTATOC contains the following

^{68}Gallium	10-45 mCi in 4 mL	Drug Substance precursor

DOTATOC in 0.25 M Acetate buffer(pH=5.5)	50 ± 5 µg in 1.2 mL	Drug Substance precursor
Sterile Water for injection	7.4 ± 1 mL	Excipient
Phosphate buffer solution	0.4 ± 0.1 mL	Excipient

^{68}Gallium is a short-lived (half-life: 68min) positron-emitting isotope generated from decay of the parent isotope ^{68}Germanium (half-life: 271 days) in a ^{68}Ga-generator. ^{68}Ga decays by electron capture to form Zinc (^{68}Zn), which is a stable nuclide. The main advantage of ^{68}Ga-generator is its cyclotron-independent availability, which is important for smaller hospitals by providing less expensive and convenient alternative to cyclotron-generated isotopes. Furthermore, the non-halogenated and non-volatile chemical properties of ^{68}Ga make this isotope ideal as PET tracer. Other key radiochemical characteristics of ^{68}Ga are summarised in the table below.

^{68}Ga physical half-life T½	**Decay product**	**Maximum positron energy**	**Maximum linear range**	**Medium linear range**
68min	^{68}Zn	1.89MeV	9.1mm	1.9mm

A new ^{68}Ga/^{68}Ge generator will be fully dedicated to this IND approved clinical investigation.

2.6 Production of ^{68}Ga-DOTATOC:

Due to its short half-life (68min), on-site generation of ^{68}Ga-labelled radiopharmaceuticals is mandatory. Generation is relatively simple, consisting of the ^{68}Ga/^{68}Ge-generator being eluted initially with hydrochloric acid. The eluate is submitted to a peptide buffer solution for labeling.

^{68}Ga-DOTATOC is labeled according to Current Good Manufacturing Practice (cGMP) per U.S. Food and Drug Administration (FDA) guidelines. Production will be performed at the cGMP suite of 390 Concord Avenue Bronx, New York 10454. After sterile filtration of the reaction mixture, the product undergoes radiopharmaceutical quality control.

The quality control of the 68Ga-DOTATOC injection solution will be performed by NCM USA Bronx, LLC 390 Concord Ave. Bronx, NY 10454 Phone: 718-362-8028 Fax: (718) 362-8029. Appearance, volume, yield, radiochemical purity -HPLC, radioactivity measurements, filter integrity, pH, residual solvent testing, radionuclide identity, radionuclide purity and endotoxin. These tests will be performed before product release, and test results will be documented on the Certificate of Analysis. Additional QC steps, including sterility testing, and Germanium breakthrough. These tests will be performed after product release, and the test results will be included on the Certificate of Analysis.

The Drug Product Ga-68-DOTATOC Injection Solution contains Ga-68-DOTATOC as Drug substance (API) filled in a 25 mL glass vial, closed with a coated (FluoroTec™) butyl rubber stopper secured with an aluminum crimp seal. The bottle is shipped from the NCM LLC to the site of administration in a box with lead shielding.

3.0 Inclusion Criteria

3.1 Signed informed consent.
3.2 Patients of either gender, aged ≥18 years.
3.3 Karnofsky status ≥60.
3.4 Life expectancy of at least 12 weeks.
3.5 Histologically and/or clinically confirmed and/or suspicious of NET.
3.6 A diagnostic CT or MRI of the tumour region or suspected area within the previous 4-6 months prior to dosing day is available.

3.7 Recent Blood test results up to 4-6 weeks as follows:

3.7.1 WBC: $\geq 2*10^9$/L
3.7.2 Haemoglobin: ≥8.0g/Dl
3.7.3 Platelets: $\geq 50x10^9$/L
3.87.4 ALT, AST, AP: ≤5 times ULN
3.7.5 Bilirubin: ≤3 times ULN

3.8 Serum creatinine: within normal range or <120μmol/L for patients aged 60 years or older.
3.9 Negative pregnancy test in women capable of child-bearing.

4.0 Exclusion Criteria

4.1 Known hypersensitivity to DOTA, to ^{68}Gallium, to DOTATOC or to any of the excipients of ^{68}Ga-DOTATOC.
4.2 Therapeutic use of any somatostatin analogue, including Sandostatin® LAR (within 21 days) and Sandostatin® (within 2 days) prior to study imaging. It can be stopped for shorter period, depending on the PIs discretion.
4.3 Pregnant or breast-feeding women.
4.4 Current somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study.

5.0 Study design

This is a prospective, Phase 2, single center study in a total of 40 subjects with Neuroendocrine Tumors (NETs). Study participants will receive 68Ga-DOTATOC and undergo a PET/CT imaging study, to investigate its suitability as a PET imaging agent for NETs. The radiation (imaging) dose will be 111–185 MBq (3 - 5 mCi) ± 25%. All doses after labeling will be presented in buffered solution for intravenous injection. Imaging will start 90 ±30 minutes after injection.

About 40 patients with histologically and/or clinically confirmed and/or suspected NET are anticipated to be enrolled during 3 years from initiating the study.

Patients will be recruited at Montefiore Medical Park where there is a medical group specialised in the diagnosis and treatment of NETs. Each patient will undergo a screening visit within 14 days prior to receiving study medication.

The primary goal of the analysis is to estimate the diagnostic accuracy of 68Ga-DOTATOC PET-CT for detecting NET compared to conventional imaging techniques.

The patients will be followed up by a telephone call 24 hour after administration of test drug (^{68}Ga-DOTATOC) to assess if patients have experienced any adverse event. This information will be captured in the CRF for further assessment.

5.1 Image Acquisition:

5.1.1 PET imaging

^{68}Ga-DOTATOC PET images will be acquired 90 ±30 minutes after injection of 111–185 MBq (3-5 mCi) ±25% of ^{68}Ga-DOTATOC. Any adverse effects will be documented after the injection of ^{68}Ga-DOTATOC. Imaging will be performed with patients in supine position using the Philips Gemini TF time-of-flight (TOF) PET/CT scanner (Philips Medical Systems, Cleveland, Ohio) with a spatial resolution of 5 mm in the center of the field of view, with emission scan acquired for 1 min 40 sec. per frame in 3D acquisition mode. Proprietary vendor-provided software will be used for image reconstruction with LISTMODE OS-EM reconstruction algorithm (33 subsets, 3 iterations). The low-dose CT (LDCT) scan will be used for non-uniform attenuation correction. Both scatter and random corrections will be performed by embedded program provided by the vendor.

5.1.2 CT Scan

CT scan will be performed using the CT exposure factors for all examinations of 140 kVp and 80-100 mA in 0.8 s. With patient position maintained, a whole-body PET emission scan will be performed covering an area identical to that covered by CT; scans will be performed in 3-dimensional mode. All PET acquisitions will be carried out in 3- dimensional mode (5 min per bed position), in an approximately 40-min scanning time. PET images will be reconstructed using CT for attenuation correction and using ordered-subsets expectation maximization with 2 iterations and 24 subsets.

5.1.3 PET/CT Images

The images from ^{68}Ga-DOTATOC PET/CT will be reported by experienced nuclear medicine physicians. Areas of abnormal focal uptake will be documented. These areas of abnormal uptake will be compared with any prior cross-sectional imaging (CT or MRI) within 12 weeks to confirm the presence of lesions.

5.2. Interpretation of Data

The number of lesions that could be identified clearly as single focus will be determined for each patient. To enable a methodic and consistent approach to lesion identification, we will create 3 categories of lesion sites: organs (Head and Neck, lungs, breast, liver, pancreas, gastrointestinal tract, kidney, spleen, and pelvis/ovaries), nodal regions (Axillary, thoracic, mesenteric, abdominal, and pelvic [excluding mesenteric], and inguinal regions), and musculoskeletal system (vertebrae, bony thorax, bony pelvis, and limb bones). Because of confluence and inability to clearly delineate single liver lesions in some cases, liver metastases will be classified as 1 organ metastasis, independent of the number of liver metastases present. Lymph nodes smaller than 1 cm on CT or MRI and showing marked avidity for ^{68}Ga-DOTATOC will be labeled as positive for

disease. In cases where images from ^{111}In-Octreotide are available for comparison, the same imaging parameters will be applied. The presence of lesions will be confirmed by cross-sectional imaging of all patients with CT or MRI. As there may be lesion/s that can show abnormal focal activity on Ga-68 PET images but not on morphologic images, such lesion/s will be considered positive NET.

Each scan (^{68}Ga-DOTATOC) will be read by two independent, board certified nuclear medicine physicians blinded to the results of other scan. A third independent nuclear medicine physician will then review both the results (independent reviews) and clinical information to reach to a consensus.

5.3 Population characteristics

We will collect demographic information and medical history as provided by patients.

5.4 Statistical Analysis

The primary goal of the analysis is to estimate the diagnostic accuracy of 68Ga-DOTATOC PET-CT for detecting NET compared to conventional imaging techniques. Analyses will be performed with both patient and lesion as the unit of observation. Since all patients are expected to have at least one NET lesion, only sensitivity can be estimated in the analysis by patient, whereas both sensitivity and specificity will be estimated in the lesion based analysis. We will compute the relevant proportions and corresponding 95% confidence intervals, with adjustment for correlated data from the same patient. Results from pathology reports available from previous biopsy or surgical specimens will be considered the gold standard. In the absence of pathology reports, initial and follow up diagnostic CT or MRI scan following nonsurgical therapy including chemotherapy will be considered the gold standard.

Kappa statistics will be computed and McNemar's test will be performed to compare the sensitivity and specificity between ^{68}Ga-DOTATOC PET-CT with SPECT and diagnostic CT for detecting NET. All analyses will be performed in SAS and p-values < 0.05 will be considered statistically significant.

5.4 Justification of Sample Size

We project that it will be feasible to recruit a total of 40 patients with histologically and/or clinically confirmed and/or suspected NET into the study. Each subject is expected to have on average 2 lesions and among the 80 total lesions; we project that 60% will be positive for NET. To evaluate the adequacy of the sample size (i.e., number of lesions), we computed the precision, as measured by the width of the 95% CI, with which the sensitivity and specificity of 68Ga-DOTATOC PET-CT scan can be estimated. The width of the 95% CI will be no greater than +/- 14% for sensitivity and +/- 17% for specificity in the lesion-based analysis. For the patient-based analysis, the precision with which sensitivity can be estimated is +/- 15%.

6.0 Criteria for Study Termination

The IND/study will be stopped if any adverse reaction >grade 1 is observed during the trial. A full assessment of adverse reaction will be conducted to determine if it is drug related or not drug related. If the adverse reaction is not related to the drug, the study will be resumed and further

patients will be recruited. If the adverse reaction is found to be drug related, it will be reported to the IRB and FDA according to respective schedule.

The toxicity/adverse event will be evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, published by NIH. The scale of toxicity is 1 to 5, with 1 being mild adverse event and 5 being death. The details of the scale can be found at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf , which is specified in the CRF.

7.0 Monitoring and Quality Control / Assurance

This study will be monitored at all stages by the clinical research personnel designated by the physician. Monitoring will include personal visits and telephone communication to ensure that the investigation is conducted according to the Protocol and complies with GCP guidelines and applicable regulatory requirements. On-site review of CRFs will include a review of forms for completeness and clarity, and consistency with source documents available for each patient.

Any data recorded directly in the CRF, for which no other written or electronic record will be maintained in the patient's medical record, will be considered source data and should be signed by the Investigator (e.g. results of physical examinations, vital signs testing, or the investigational product administration procedure). During monitoring visits the data recorded in the CRFs, source documents, and other study-related records will be compared against each other in order to ensure accurate data that reflect the actual experience of the patient in the study, i.e. source data verification. The Investigator must ensure that the clinical notes will be available for direct verification of source data.

To this end, the Investigator agrees to allow regular visits (frequency depending on recruitment, but estimated as four-weekly) by the study monitors and to ensure they have a suitable area in which to work (e.g. a desk) and adequate access to study personnel and documents.

Medical monitors and clinical research associates (CRAs) or assistants may request to witness patient evaluations occurring as part of this Protocol. The Investigator and appropriate personnel will be periodically requested to attend meetings/workshops to ensure acceptable Protocol execution, if deemed necessary.

The study may be audited or inspected by the Regulatory or Health Authority or IEC/IRB. If such an audit or inspection occurs, the Investigator must agree to allow access to the study site, required patient records and study documents. By signing this Protocol, the Investigator grants permission to personnel mentioned in this protocol and appropriate Regulatory Authorities for on-site monitoring of all appropriate study documentation, as well as on-site review of the procedures employed in the CRF generation, where clinically appropriate. The Investigator will be informed about the outcome of the audit.

The following activities will be undertaken to ensure the quality of trial-related activities:

- adherence to the trial site standard operating procedures to maintain accurate and consistent practices and procedures
- conduct of a site initiation visit to ensure the Investigator and all personnel involved in the trial understand the Protocol, including the study procedures and their responsibilities
- completion of a standard CRF in accordance with GCP requirements to ensure accurate and reliable data

- Periodic monitoring to ensure the trial data are accurate, complete and verifiable from source documents, and that the Protocol is being followed.

8.0 Patient Consent and Peer Review

Informed consent will be obtained for each patient prior to being placed on this study. Approval by the institutional review board is necessary before beginning this protocol. Please find appendix (b) for a copy of patient consent.

9.0 Data Safety and Monitoring Boards

This trial will be monitored by the Albert Einstein Cancer Center Data Safety Monitoring Committee (AECC DSMC). A copy of the monitoring plan is maintained at the CPDMU. The DSMC as part of its function performs quarterly reviews of Clinical Trials Compliance Audits, monthly reviews Adverse Events Reports, and monthly reviews of internally monitored Phase I/Phase II trials for accrual and response. Other monitoring activities are established as necessary in a protocol specific manner.

The details of the monitoring are outlined in the AECC Data and Safety Monitoring Plan policy document.

9.1 Trial Monitoring

This trial will be monitored by the Albert Einstein Cancer Center Data Safety Monitoring Committee (AECC DSMC). A copy of the monitoring plan is maintained at the CPDMU. The DSMC as part of its function performs quarterly reviews of Clinical Trials Compliance Audits, monthly reviews Adverse Events Reports, and monthly reviews of internally monitored Phase I/Phase II trials for accrual and response. Other monitoring activities are established as necessary in a protocol specific manner.

This trial will be part of the monthly Quality Assurance Audits. Each patient will be evaluated within 8 weeks of registration. This permits evaluation of consent, eligibility, and treatment/dose modification/Adverse Event (AE) reporting, and data quality for the first cycle (or month) of treatment.

This trial may also be eligible for quarterly Quality Enhancement Audit. Each audit consists of a review of regulatory documents, pharmacy drug accountability (if applicable) and patient case review, confirming eligibility, protocol compliance and source documentation

The results of the audit will be presented at the following month's DSMC meeting. The DSMC has the authority to close trial to patient accrual should the risk to patients be excessive or results require a corrective plan from the Principal Investigator. All study suspensions and closures will be forwarded to the IRB and study sponsor. All audit reports are forwarded to the DSMC and presented to the DSMC by the Audit Committee Coordinator.

10.0 Bibliography

1. Lawrence B, Gustafsson BI, Chan A, et al. The epidemiology of gastroenterohepatic neuroendocrine tumors. Endocrinol Metabb Clin N Am 2011 ;20 :1-18.
2. Hande KR: Neuroendocrine tumors and the carcinoid syndrome. In: Goldman L, Schafer AI (eds). Goldman-Cecil Medicine, 25th edition, Philadelphia, PA, Elsevier Saunders, 2016; 1556-1560.
3. Frilling A, Akerstrom G, Falconi M , et al : Neuroendocrine tumor disease: an evolving landscape. Endocrine-Related Cancer 2012; 19 :R163-R185.
4. Teunissen JJM, Kwekkeboom DJ, Valkema R : Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocrine-Related Cancer 2011; 18:S27-S51.
5. Rust E, Hubele F, Marzano E, et al : Nuclear Medicine imaging of gastro-entero-pancreatic neuroendocrine tumors, The key role of cellular differentiation and tumor grade : from theory to clinical picture. Cancer Imaging 2012;12:173-184.
6. Hofman MS, Lau WFE, Hicks RJ. Somatostatin receptor imaging with GaDOTATE PET/CT : clinical utility, normal patterns, pearls, and pitfalls in interpretation. RadioGraphics 2015;35: 500-516.
7. Velikyan I : Prospective of ^{68}Ga-Radiopharmaceutical development. Theranostics 2014; 4:47-80.
8. Hofmann M, Maecke H, Borner R, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med Mol Imaging. 2001; 28: 1751-7.
9. Wang L, Tang K, Zhang Q, et al: Somatostatin receptor-based molecular imaging and therapy for neuroendocrine tumors. Biomed Res International 2013; Article ID 102891:11 pages.
10. Walker RC, Smith GT, Liu E, et al: Measured human dosimetry of ^{68}Ga-DOTATATE, J Nucl Med: 2013: 54:855-860.
11. De Camargo Etchebehere ECS, de Oliveira Santos A, Gumz B. et al : ^{68}Ga-DOTATATE 99mTc-HYNIC-Octreotide SPECT/CT, and whole-body MR imaging in detection of neuroendocrine tumors : a Proespective trial. J Nucle Med 2014 ;55 :1598-1604.
12. Schreiter NF, Bartels AM, Froeling V, et al: Searching for primaries in patients with neuroendocrine tumors (NET) of unknown primary and clinically suspected NET : Evaluation of Ga-68 DOTATOC PET/CT and In-111 DTPA octreotide SPECT/CT. Radiol Oncol 2014; 48:339-347.
13. Van der Zwan WA, Bodie L, Mueller-Brand J, et al: Radionuclide therapy in neuroendocrine tumors. Euro J Endocrinol 2015;172:R1-R8.
14. Baum RP and Kulkarni HR : Theranostics : From molecular imaging using Ga-68 labeled tracers and PET/CT to personalized radionculide therapy- the Bad Berka experience. Theranostics 2012 ;2 :437-447.
15. Bodei L, Kidd M, Baum R, et al : PRRT : Defining the paradigm shift to achieve standardization and individualization. J Nucl Med 2014;55:1753-1756.
16. Ilan E, Sandstrom M, Wassberg C, et al : Dose response of pancreatic neuroendocrine tumors treates with pepetide receptor radionuclide therapy using 177 Lu-DOTATATE. J Nucl Med 2015 :56 :177-182.

17. Stetter H & Frank W: Complex Formation with Tetraazacycloalkane-N,N′,N″,N‴-tetraacetic Acids as a Function of Ring Size. Angewandte Chemie International Edition in English. 1976;15:686-689.

11.0 Signature Page

Principle Investigator:

Charito Love MD _____