Phase II,
Dosimetry-Guided, Peptide Receptor Radiotherapy (PRRT) with ^{90}Y-DOTA-tyr^{3}-Octreotide (^{90}Y-DOTATOC) in Children and Adults with Neuroendocrine and other Somatostatin Receptor Expressing Tumors

Dosimetry guided PRRT with ^{90}Y-DOTATOC

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Document type: PROTOCOL FOR IND #61,907
Version number: 5
IRB# 201708778
Date: August 19, 2019

Project Goals

Demonstrate safety and efficacy of dosimetry-guided peptide receptor radiotherapy using ^{90}Y-DOTA-tyr^{3}-Octreotide in patients with neuroendocrine and other somatostatin receptor expressing tumors.

Monitor all adverse events associated with peptide receptor radiotherapy using ^{90}Y-DOTATOC.

Schema

Phase II,
Dosimetry-Guided, Peptide Receptor Radiotherapy (PRRT) with
^{90}Y-DOTA-tyr^{3}-Octreotide (^{90}Y-DOTATOC) in Children and Adults
with Neuroendocrine and other Somatostatin Receptor Expressing Tumors

Screening period		Pathology diagnosis of Neuroendocrine Tumor with slides available High resolution, contrast enhanced CT or MRI within 120 days of Cycle 1 ^{68}Ga-DOTATATE PET/CT within 6 months of Cycle 1 No treatment other than Sandostatin or Lanreotide between CT (MRI) and ^{68}Ga-DOTATATE PET and Cycle 1			
Treatment Cycles and Followup		**Imaging and Treatment Schedule**	**Initial ^{90}Y-DOTATOC Dose**	**Cumulative ^{90}Y-DOTATOC Dose**	**Cumulative Renal Radiation**
Cycle 1 Week 1	Day 1	Physical exam with height, weight, vitals, labs, med list, GFR, pregnancy test; QOL questionnaire Start 18 hrs IV/PO fluids			
	Day 2	^{90}Y-DOTATOC + IV amino acids Continue IV/PO fluids for 48 hrs	50 mCi/m^2 in children; 120 mCi in adults	120 mCi maximum	
	Day 4	^{90}Y-DOTATOC PET/CT			
Cycle 2 Week 7-9	Day1	Physical exam with height, weight, vitals, labs, med list, GFR, pregnancy test Start 18 hrs IV/PO fluids			
	Day2	^{90}Y-DOTATOC + IV amino acids Continue IV/PO fluids for 48 hrs	Dosimetry determined	270 mCi maximum	
	Day4	^{90}Y-DOTATOC PET/CT			
Cycle 3 Week 13-17	Day 1	Physical exam with height, weight, vitals, labs, list, GFR, pregnancy test Start 18 hrs IV/PO fluids			
	Days 2-3	^{90}Y-DOTATOC + IV amino acids Continue IV/PO fluids for 48 hrs	Dosimetry determined	420 mCi maximum	≤ 23 Gy
FU	3 months after treatment	Physical exam with height, weight, vitals, labs, med list, GFR; QOL questionnaire, CT (MRI)			
	6-9 month after treatment	Physical exam with height, weight, vitals, labs, med list, GFR; diagnostic CT (MRI) ^{68}Ga-DOTATOC PET/CT;			

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1.0 Background and Rationale

1.1 Somatostatin Receptor Positive Tumors

Neuroendocrine tumors are solid malignant tumors that arise from dispersed neuroendocrine cells found throughout the body. Gastroenteropancreatic neuroendocrine tumors (NETs) can be divided into two groups: Carcinoid tumors that may arise from the lungs, stomach, small bowel or colon and pancreatic neuroendocrine tumors (also known as pancreatic islet cell tumors). The clinical behavior of NETs is extremely variable; some may cause hormone hypersecretion and others may not, the majority of them are slow-growing tumors (well-differentiated NETs), whereas some NETs are highly aggressive (poorly differentiated NETs). The incidence of NETs is increasing, from 1.1/100,000 per year in 1973 to 5.3/100,000 per year in 2004[1]. Among NETs, 25% have distant metastases and 25% have regional involvement at the time of initial diagnosis[1]. Other tumors that express high levels of somatostatin receptors include neuroblastoma and medulloblastoma[2-4].

The radiological detection and staging of these tumors is challenging and requires a multimodality approach. Somatostatin receptor imaging with In-111 Pentetreotide (OctreoScan) and multiphase CT are the most commonly used modalities although the use of endoscopic ultrasound and MRI is rapidly increasing. Surgery is the only curative option for NETs. However, curative surgery in malignant NET is possible in less than 30% of patients with recurrence identified in the majority of patients as late as 15 years after initial surgery. Treatment with somatostatin analogs, which include the short acting subcutaneous and long acting release (LAR) octreotide as well as long acting lanreotide, are effective in stabilizing NETs and have been recently demonstrated to prolong the time to progression of disease[5,6]. Chemotherapy is generally not effective in low grade NETs, but it may be helpful in high grade and pancreatic NETs. On the other hand, neuroblastoma and medulloblastoma are initially responsive to chemotherapy, but relapses are common and salvage therapies are not very effective, resulting in <30% overall survival at 5 years[7-9].

1.2 Somatostatin Receptor Targeted Imaging

Tumors that express somatostatin receptors can be targeted with radiolabeled somatostatin analogues for imaging and treatment (Figure 1), making theranostics using peptide analogs of somatostatin feasible by labeling with one radionuclide for imaging and the same or a different radionuclide for therapy.

Somatostatin receptor gamma camera imaging with In-111 DTPA-octreotide (OctreoScan) targeting somatostatin receptor 2 (SSTR2), is used routinely for imaging of neuroendocrine tumors with a detection rate >90% for well-differentiated carcinoid tumors and majority of pancreatic NETs, but only a 50% detection rate for insulinomas, which may show a weaker expression of SSTR2[10]. Over 90% of neuroblastoma tumors express somatostatin receptors[11]; they can be imaged with Octreoscan and they respond to ^{90}Y-DOTATOC therapy[12,13]. Medulloblastoma has recently been categorized into four genetic categories, each one of which includes tumors which express somatostatin receptors, but no category is 100% positive for somatostatin receptor expression[14-16]. We have also imaged medulloblastoma using Octreoscan[12].

More recently, positron emission tomography (PET) radiopharmaceuticals have been developed that can be labeled with Gallium-68 (Ga-68). Gallium-68 is a generator product with a half-life of 68 min (compared to 67 hours for In-111 in OctreoScan). The parent nuclide of Ga-68 is Germanium-68, which has a half-life of 270.8 days. Ga-68 decays by 89% through positron emission and 11% by electron capture. Another advancement has been the identification of DOTA as a superior chelator compared to DTPA, increasing the stability and receptor targeting of somatostatin analogues[17].

A number of Ga-68 DOTA-conjugated peptides have been introduced, including ^{68}Ga-DOTATOC, Ga-68 DOTA^0-1Nal^3-octreotide (^{68}Ga-DOTANOC) and Ga-68 DOTA^0-Tyr^3-octreotate (^{68}Ga-DOTATATE). All of these radiolabeled peptides bind to sstr2, although DOTANOC also binds to sstr3 and sstr5, and DOTATOC to sstr5[18]. The primary advantage of Ga-68 based somatostatin receptor PET imaging over OctreoScan SPECT is the higher imaging resolution and accurate quantification of uptake due to robust attenuation correction. The improved resolution and quantification of uptake obtained with ^{68}Ga-DOTATOC PET should provide a more accurate assessment of somatostatin receptor density, which will lead to a more accurate prediction of treatment response to somatostatin analogues. A recent study from Europe comparing ^{68}Ga-DOTATOC with Octreoscan found ^{68}Ga-DOTATOC to be superior in detection of skeletal and pulmonary involvement of neuroendocrine tumors[19]. We have now published a study of the reproducibility of ^{68}Ga-DOTATOC PET in our institution.

1.3 ^{68}Ga-DOTATOC PET in staging disease for patients with metastatic neuroendocrine tumors.

Given the clinical efficacy of peptide analogs of somatostatin as a diagnostic agent, studies to test if therapeutic radiation could be targeted to tumors in a similar manner was a logical next step. Attempts to utilize In-111 DTPA Octreotide as a therapeutic agent have been minimally effective due to the short range of auger electrons utilized in this therapy. The efficacy of sstr2 targeted treatment was improved with the development of somatostatin analogues labeled with beta emitting radioisotopes.

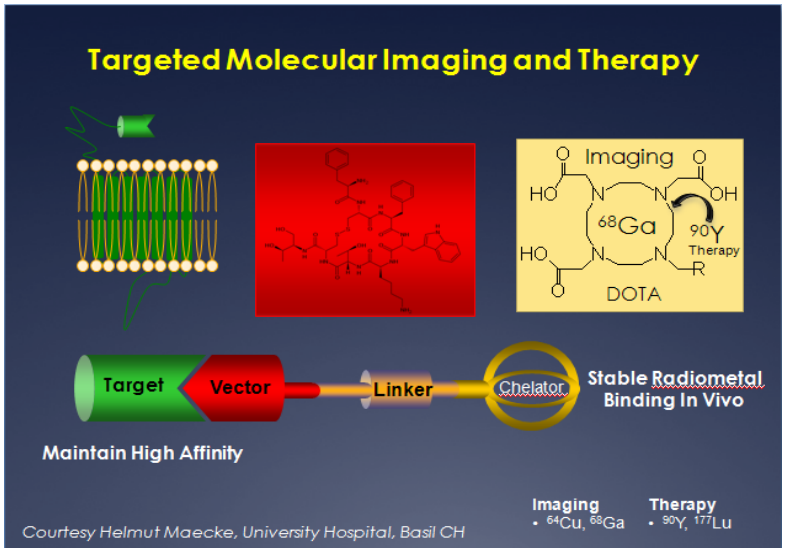

Figure 1: Conceptual representation of targeted molecular imaging and therapy of cancerous tumors. A cell surface receptor is identified that is upregulated in cancerous tumor cell relative to normal surrounding tissue and organs. A peptide vector is developed that binds with high affinity and specificity to the molecular target. A chelator is added to the targeting vector via a molecular linker. The chelator can be used to couple a positron emitter as the reporter signal for PET, or with a beta emitting radionuclide (e.g., 90Y) for molecular therapy. To be effective, the high binding affinity of the vector for the target antigen and the stable high specific activity radiometallation must be maintained after placement of the chemical linker.

^{90}Yttrium-DOTA complexes are extremely stable; the dissociation constant for this complex is approximately 10^{-25} M. The high stability of the ^{90}Y-DOTA chelated complex is a major advantage. Additionally, ^{90}Yttrium is a high-energy beta minus particle-emitter with a physical half-life of 64.1 h and a mean range of 5 mm in tissue, permitting effective treatment of tumors with heterogeneous sstr2 expression due to bystander effects. ^{90}Yttrium is commercially available in sufficient amounts and in a no-carrier-added form that allows the preparation of a radioligand with high specific activity.

There is now a large clinical experience with ^{90}Y-DOTATOC peptide radioreceptor therapy (PRRT) in Europe, primarily in adults with neuroendocrine tumors[20]. An international Phase II clinical trial then followed and included several trial sites in the United States, notably the University of Iowa; we entered 40 subjects[21]. With its low toxicity profile, the significant improvement in symptoms and quality of life and the lack of effective alternative therapies, PRRT has been suggested as possible first-line therapy in adult patients with neuroendocrine tumors. Recent data have also demonstrated a significant survival benefit with PRRT compared to historical controls in this population[21]. We have now conducted a Phase I trial of ^{90}Y-DOTATOC in children and young adults at the University of Iowa, which also shows promise of efficacy of this treatment in pediatric patient population[13].

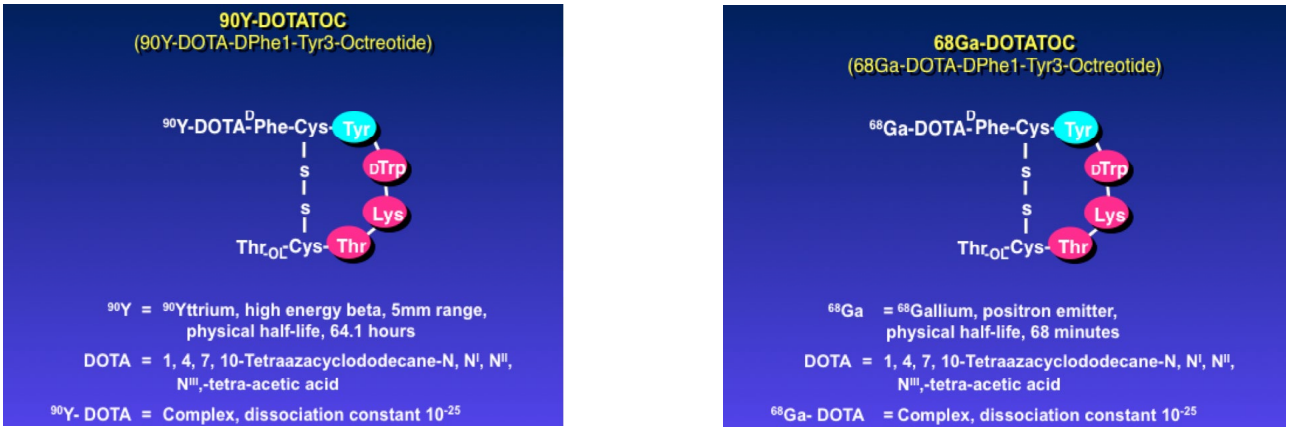

Figure 2. Chemical identity of ^{90}Y- DOTATOC and ^{68}Ga-DOTATOC

1.4 Somatostatin Receptor Targeted Therapy

Known as peptide receptor radionuclide therapy (PRRT), this molecularly targeted internal radiation has been utilized in Europe for nearly 20 years. The two main radiopharmaceutical agents are ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE, both targeting sstr2. The response rates are very similar with very few complete responses, 20-30% partial responses, and greater than 50% stable disease among patients who have progressed on other therapies[22,23]. The time to progression following PRRT, for these patients with progressive metastatic neuroendocrine tumors has been 36-48 months compared to 5-7 months with everolimus or sunitinib[24,25].

The normal organ at greatest risk for toxicity with ^{90}Y-DOTATOC is the kidney[21,23,26,27]. In our previous Phase II trial in adults and our Phase I trial in children, we were able to decrease renal toxicity with amino acid infusion and hydration[13,21,28]. This trial is designed to utilize dosimetry to maximize radiation dose to tumor while minimizing renal toxicity.

1.5 Study design

This is a Phase 2 peptide receptor radionuclide therapy trial of ^{90}Y-DOTATOC in patients with somatostatin receptor positive tumors. The somatostatin receptor targeting of the therapeutic will be checked with ^{68}Ga-DOTATOC PET-CT imaging prior to therapy. Treatment consists of 3 cycles, 6-8 weeks apart. Cycle 1 dose is fixed with Cycles 2 and 3 doses to be determined by dosimetry-based calculation of renal doses from previous cycles not to exceed 23 Gy for the total renal dose.

^{68}Ga-DOTATOC PET imaging and ^{90}Y-DOTATOC peptide receptor radionuclide therapy (PRRT) are readily available in Europe, but neither radiopharmaceutical is approved for use in the United States. We are presently conducting a safety and efficacy trial of ^{68}Ga-DOTATOC PET in adults and children under IND# 114,398, that to date has included over 220 subjects with no serious adverse events. We have conducted a single institution Phase I trial of ^{90}Y-DOTATOC therapy in children and young adults under IND# 61,907 with no serious adverse events[13], and we have participated in a Phase II trial of ^{90}Y-DOTATOC PRRT in adults, also with no dose limiting toxicities[21].

The total radiation dose to kidneys with PRRT using ^{90}Y-DOTATOC is currently limited to ≤ 23 Gy for both children and adults. Several reports, including dosimetry performed on children in our Phase I trial, have suggested that this dose limit can safely be raised to as high as 35 Gy to kidneys when performing individualized dosimetry measurements to guide therapeutic dosing of ^{90}Y-DOTATOC [26,29,30]. We have considerable expertise in the development of theoretical models for dosimetry[31], as well as experience in performing dosimetry in individual patients[13,32]. These studies demonstrated a wide variation in renal dose, both between patients and between cycles in any given individual. In this Phase II therapeutic trial, we therefore propose to perform dosimetry for each patient during the first and second cycles of therapy. The method for performing the dosimetry will take advantage of a positron decay component of Yttrium-90 that will allow quantification of radiation dose using PET imaging to measure rate of 90Y-DOTATOC into kidneys, coupled with semi-quantitative measurement of bremsstrahlung energy using single photon emission tomography (SPECT) to follow the body clearance of ^{90}Y-DOTATOC over 72 hrs after injection of the therapeutic dose.

We are currently conducting an imaging trial at the request of the FDA, to compare the efficacy of ^{68}Ga-DOTATOC PET + a low dose CT with ^{111}In-DTPA-tyr^3-Octreotide (Octreoscan) SPECT/CT + a high resolution, contrast enhanced CT (or MRI). There are 3 major advantages of ^{68}Ga-DOTATOC PET/CT over Octreoscan SPECT/CT: 1) lower dose of radiation using Gallium-68 (T½=68 min) versus Indium-11 (T½=2.8 day); 2) greater sensitivity of PET compared to SPECT imaging; and 3) ^{68}Ga-DOTATOC PET/CT can be completed in a single, 3-hr visit whereas Octreoscan requires 2 visits over a 24 hr period. We now propose to utilize ^{68}Ga-DOTATOC (or ^{68}Ga-DOTATATE) and ^{90}Y-DOTATOC in a dosimetry-guided theranostics trial for both children and adults with neuroendocrine and other somatostatin receptor positive tumors.

2.0 Project Goals

2.1 Demonstrate safety and efficacy of renal uptake dosimetry-guided peptide receptor radiotherapy (PRRT) using ^{90}Y-DOTA-tyr^{3}-Octreotide (^{90}Y-DOTATOC) in patients with neuroendocrine and other somatostatin receptor expressing tumors.

2.2 Monitor all adverse events associated with peptide receptor radiotherapy using ^{90}Y-DOTATOC.

2.3 Establish ^{68}Ga-DOTA-tyr^{3}-Octreotide (^{68}Ga-DOTATOC) or ^{68}Ga-DOTATATE PET/CT as an accurate technique for diagnosis, staging, treatment targeting, and monitoring response to ^{90}Y-DOTATOC therapy.

3.0 Hypotheses

3.1 Hypotheses:

1. We hypothesize that dosimetry-guided, individual dosing of ^{90}Y-DOTATOC will provide excellent tumor response.
2. We hypothesize that individual, dosimetry-guided dosing of ^{90}Y-DOTATOC will provide maximum safe dose to tumor and minimize renal toxicity while limiting renal radiation dose to ≤ 23 Gy.
3. We hypothesize that ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE PET/CT will accurately stage extent of disease at study entry and accurately measure response to therapy at six months following last ^{90}Y-DOTATOC treatment.
4. We hypothesize that both quantitative PCR and semi-quantitative immunohistochemical analysis of somatostatin receptor 2 (sstr2) expression on the first diagnostic biopsy of neuroendocrine tumor will positively correlate with standard uptake value (SUV) of that subject's first ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE PET scan at study entry.

4.0 Objectives

4.1 Primary Objectives

1. Quantify number of CR, PR, MR, SD and progressions in response to dosimetry-guided PRRT utilizing RECIST 1.1 criteria and ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE PET to evaluate efficacy of ^{90}Y-DOTATOC therapy in children and adults with neuroendocrine and other somatostatin receptor positive tumors.
2. Monitor renal, hematologic, and clinical toxicities associated with dosimetry-guided ^{90}Y-DOTATOC PRRT while maximizing total tumor dose and limiting total renal dose of ^{90}Y-DOTATOC to ≤ 23 Gy.

4.2 Secondary Objectives

1. For those subjects who participated in the Comparator study of ^{68}Ga-DOTATOC versus Octreoscan + conventional imaging using high-resolution, contrast-enhanced CT or MRI (IRB# 201212736), the intent is to determine response to therapy of lesions identified by ^{68}Ga-DOTATOC PET/CT but not identified on Octreoscan as a confirmatory measure of true positivity of the Ga-68 DOTATOC avid lesion.
2. Determine if Standard Uptake Value (SUV) on initial ^{68}Ga-DOTATOC/TATE PET imaging correlates with SSTR2 expression as measured by quantitative messenger RNA (qPCR) or immunohistochemistry (IHC) on the diagnostic biopsy specimen.

5.0 Eligibility Criteria

5.1 Inclusion Criteria

1. Disease not amenable to standard treatment (nonresectable or disease present after one or more surgeries and/or Sandostatin treatment) or subject has failed existing first line chemotherapy, biologic therapy, targeted agent therapy or radiation therapy.
2. Participation in Iowa Neuroendocrine Tumor Registry.

3. A pathologically confirmed (histology or cytology) malignant neoplasm with at least one target lesion that is confirmed by conventional imaging and is determined to express somatostatin receptors by ^{68}Ga-DOTATOC (TATE) PET within 6 months prior to treatment with ^{90}Y-DOTATOC.
4. The target lesion is one that either has never received external beam radiation or has been previously irradiated and has since demonstrated progression. Any local irradiation of the target lesion or any non-target lesions via external beam, conformal or stereotactic radiation treatments must have occurred more than 4 weeks prior to study drug administration. Any full cranial-spinal radiation, whether or not a target lesion is included in the field, must have occurred more than 3 months prior to study drug administration.
5. Life expectancy $\geq$ 2 months at the time of study drug administration.
6. Archival tissue from a previous biopsy will be required.
7. Age ≥ 6 months-90 years at the time of study drug administration.
8. Performance status as determined by Karnofsky $\geq$ 60 or Lansky Play Scale $\geq$ 60% at the time of study drug administration.
9. Completion of Norfolk Quality of Life Questionnaire.

10. Within 7-10 days of study drug administration, patients must have normal organ and marrow function as defined below:

–	absolute neutrophil count	$\geq$1000/mm^3
–	Platelets	$\geq$90,000/mm^3
–	total bilirubin	<3X ULN for age
–	AST(SGOT) & ALT(SGPT)	$\leq$10X institutional upper limit of normal for age
–	Urinalysis	no greater than 1+ hematuria or proteinuria
–	Renal function*	Adults(age18 or >): Serum creatinine ≤ 1.2 mg/dl; if serum creatinine is >1.2 mg/dL, nuclear GFR will be measured. GFR will need to be ≥ 80 ml/min/1.73m^2 for subjects ≤40 years old, ≥ 70 ml/min/1.73m^2 for subjects between 41-50; ≥ 60 ml/min/1.73m^2 for subjects between 51-60; ≥ 50 ml/min/1.73m^2 for subjects > 60 years old. Children(age <18): nuclear GFR ≥ 80 mL/min/1.73 m^2

* Renal function criteria based on our previous experience with 90Y-DOTATOC therapy and known changes in GFR with age[13,21,33-35]

11. The effects of ^{90}Y-DOTA-tyr^3-Octreotide on the developing human fetus are unknown. For this reason and because Class C agents are known to be teratogenic, women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
12. Ability to understand and the willingness to sign a written informed consent document.

5.2 Exclusion Criteria

1. Pregnant women are excluded from this study because ^{90}Y-DOTATOC is a *Class C* agent with potential teratogenic or abortifacient effects.
2. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ^{90}Y-DOTATOC, breastfeeding should be discontinued until 6 weeks after the last administration of study drug.
3. Surgery within 4 weeks of study drug administration.
4. External beam radiation to both kidneys (scatter doses of <500 cGy to a single kidney or radiation to < 50% of a single kidney is acceptable).

5. Prior PRRT with ^{90}Y-DOTATOC (TATE) or ^{177}Lu-DOTATOC (TATE) or ^{131}I-MIBG therapy for this malignancy.
6. Another investigational drug within 4 weeks of study drug administration.
7. Concurrent, malignant disease for which patient is on active therapy.
8. Another significant medical, psychiatric, or surgical condition which is currently uncontrolled by treatment and which would likely affect the subject's ability to complete this protocol.
9. Any subject for whom, in the opinion of their physician, a 12-hour discontinuation of somatostatin analogue therapy represents a health risk. Also subjects who have received SandostatinLAR in the past 28 days or long-acting lanreotide within the past 8 weeks are excluded. Subjects may be maintained on short acting octreotide during the time from last injection of long-acting somatostatin analogue until 12 hrs prior to injection of study drug. Known antibodies to Octreotide, Lanreotide, or DOTATOC or history of allergic reactions attributed to compounds of similar chemical or biologic composition to ^{90}Y-DOTATOC.
10. Patients who have had chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) of study drug administration or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
11. Uncontrolled 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.
12. Subject weighs more than 450 pounds. (Subjects who weigh more than 450 pounds will not be able to fit inside the imaging machines.)
13. Inability to lie still for the entire imaging time (due to cough, severe arthritis, etc.)

5.3 Inclusion of Women and Minorities

Both male and female children and adults as well as members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below.

Race and Ethnicity of Children and Adults with Neuroendocrine or other Somatostatin Receptor Positive Tumors Referred to UIHC Specialty Clinics						
Year	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Solid Tumors	40	38	61	41	45	Pending
Male	29	20	32	16	21	
Female	11	18	29	25	24	
Hispanic Ethnicity	2	1	3	4	3	
African American	2	2	2	1	6	
American Indian	0	0	0	0	0	
Pacific Islander	0	0	0	0	3	
White	36	35	55	36	33	
Other*		1	1	0	1	

The 2010 US Census reports the following minorities living in Iowa: 3.2% African-American, 0.1% Native Hawaiian/Pacific Islanders, 0.5% American Indian/Alaskan native, 2.0% Asian, and 5.3% Hispanic.

6.0 Imaging and Treatment Plan

Phase II, Dosimetry-Guided, Peptide Receptor Radiotherapy (PRRT) with ^{90}Y-DOTA-tyr^{3}-Octreotide (^{90}Y-DOTATOC) in Children and Adults with Neuroendocrine and other Somatostatin Receptor Expressing Tumors					
Treatment Cycles and Followup		**Imaging and Treatment Schedule**	**Initial ^{90}Y-DOTATOC Dose**	**Cumulative ^{90}Y-DOTATOC Dose**	**Cumulative Renal Radiation**
Cycle 1 Week 1	Day 1	Physical exam with height, weight, vitals, labs, list, GFR, pregnancy test; QOL questionnaire Start 18 hrs IV/PO fluids			
	Day 2	^{90}Y-DOTATOC + IV amino acids Continue IV/PO fluids for 48 hrs	50 mCi/m^2 in children; 120 mCi in adults	120 mCi maximum	
	Day 4	^{90}Y-DOTATOC PET/CT			
Cycle 2 Week 7-9	Day 1	Physical exam with height, weight, vitals, labs, med list, GFR, pregnancy test Start 18 hrs IV/PO fluids			
	Day 2	^{90}Y-DOTATOC + IV amino acids Continue IV/PO fluids for 48 hrs	Dosimetry determined	270 mCi maximum	
	Day 4	^{90}Y-DOTATOC PET/CT			
Cycle 3 Week 13-17	Day 1	Physical exam with height, weight, vitals, labs, list, GFR, pregnancy test Start 18 hrs IV/PO fluids			
	Days 2-3	^{90}Y-DOTATOC + IV amino acids Continue IV/PO fluids for 48 hrs	Dosimetry determined	420 mCi maximum	≤ 23 Gy
FU	3 months after treatment 3	Physical exam with height, weight, vitals, labs, med list, GFR; QOL questionnaire, diagnostic CT (MRI)			
	6-9 months after treatment 3	Physical exam with height, weight, vitals, labs, med list, GFR; diagnostic CT (MRI) ^{68}Ga-DOTATOC PET/CT;			

Treatment consists of 3 cycles, 6-8 weeks apart. Cycle 1 dose is fixed. Cycles 2 and 3 doses will be determined by dosimetry-based calculation of renal doses from previous cycles; total renal dose ≤ 23Gy.

6.1 Delivery of Therapeutic Infusion

^{90}Y-DOTA-tyr^{3}-Octreotide and amino acid infusions will be administered on Day 2 of each treatment cycle. A large IV, either 20 gauge peripheral IV or a PICC line, will be inserted to provide free flow of the hyperosmolar amino acid solution, thus avoiding local inflammation with risk of blistering. Amino acid infusion will begin 30 min prior to infusion of ^{90}Y-DOTATOC and continue 3.5 hrs after infusion of radiotherapeutic drug. If rate of amino acid infusion is decreased due to nausea, the length of infusion

may be longer than 3.5 hrs. There will be rescue Sandostatin available (subcutaneous bolus of 200 µgm (200 µgm/mL)) in case of carcinoid crisis after ^{90}Y-DOTATOC infusion has been completed.

6.2 Methods for Dosimetry Estimates

Renal dosimetry: Each subject will have renal ^{90}Y-DOTATOC time-of-flight (TOF) PET/CT images taken within approximately 48 hours (40-56 hours) after the administration of ^{90}Y-DOTATOC.

Bone Marrow dosimetry: Blood dosimetry will be performed as a surrogate of bone marrow dosimetry. Blood samples will be obtained prior to start of Amino Acid infusion, again within 1-4 hours after administration of ^{90}Y-DOTATOC and at 48 hrs (40-56 hrs).

6.3 Measurement of Renal Dose

The following information is required to estimate the dose to the kidneys:
a) An estimate of the radioactivity accumulated in the kidneys,
b) The kinetics of the radioactivity, and
c) The size (mass) of the kidneys.

The renal accumulation of the radiopharmaceutical will be measured with Y-90 DOTATOC time-of-flight PET-CT imaging. A standard of Y-90 will be also imaged. PET images will be reconstructed with an OSEM iterative algorithm that incorporates the time of flight information. The kidney mass will be obtained from CT images.

The methods of kinetic analysis of the renal clearance of Y-90 DOTATOC is modified based on our previous experience. Our analysis of 47 prior administrations demonstrate that the renal clearance of Y-90 DOTATOC follows a biexponential pattern with the majority of the radiation exposure to the kidneys coming from the slow (long) component of clearance after the initial fast elimination. The rate constant of the slow component was gaussian distributed with a standard deviation less than 30% of the mean. This allows us to use a population based rate constant for slow clearance adjusted based on the uptake at 48 hours. The estimated renal radiation dose using this approach shows excellent correlation with the measured radiation dose (See *Appendix 1t: Single Timepoint Dose Estimate for Exponential Clearance*) and allows for a clinically feasible personalized treatment dosimetry with one follow-up visit after 48 hours of treatment administration. The information on renal uptake, renal mass and residence time will be entered into OLINDA software to calculate the radiation dose.

The Phase II studies of ^{90}Y-DOTA-tyr^3-Octreotide administered to adults suggest that the safe range of $\leq$23 Gy for radiation to kidneys delivered by external beam radiation, is more likely 30-35 Gy when delivered as divided doses of targeted internal radiation[58]. Furthermore, there were no dose limiting renal toxicity events in children or young adults enrolled in the Phase I study. Nevertheless, because of the young age of pediatric subjects described in Aim 1, we limited the total dose to kidneys, including any previous external beam radiation to $\leq$ 23 Gy. The dose to kidneys measured in Cycles 1 and 2 will be summated for each subject. If this total dose is <23 Gy, the remaining allowable body activity for that subject will be calculated according to the following formula:

1000 x (23 Gy – summed renal dose (Gy))/renal dose per activity (mGy/MBq).

All subjects will receive a concomitant amino acid infusion as renal protectant[13]. A parenteral amino acid solution which supplies $\geq$27 g each of lysine and arginine in 2 liters of normal saline ($\leq$ 800 mOsm/L) will be administered IV at a max of 8.3 mL/kg/hour (max 450 mL/hr) for 4 hours to begin 30 minutes prior to infusion of ^{90}Y-DOTATOC. Initial infusion rate should be 300mL/hr or less; if tolerated for initial 30 min, rate may be increased to max rate. The total minimum volume which shall be infused is 1600 mL. This will constitute an off-label use of these approved amino acid solutions due to the higher than recommended volume infused. Any further information regarding dosing should be obtained from the manufacturer's instructions.

Patients will be pre-medicated with EMEND and Lorazepam, and/or another anti-emetic, 30 minutes prior to the Amino Acid infusion.

7.0 Calendar of Tests and Procedures

Calendar of Tests and Procedures									
Test	**Base line[6]**	**C1D1[7]**	**C1D2**	**C2 D1**	**C2D2**	**C3D1**	**C3D2**	**3-4 Month Followup[8, 11]**	**6–9 Month Followup**
Physical Exam	X	X		X		X		X	X
Medical history/treat-ment history	X	X							
Vital signs[1]	X	X	X	X	X	X	X	X	X
Medication list	X	X		X		X		X	X
GFR if indicated[2]	X	X		X		X		X[12]	X
Blood Tests[3]	X	X	X[14]	X	X[14]	X	X[14]	X	X
QOL questionnaire	X	X						X[13]	
Pregnancy Test[4]	X	X[9]	X[9]	X	X[9]	X	X[9]		
^{68}Ga-DOTATOC (TATE) PET/CT	X								X
Diagnostic CT or MRI	X							X	X
^{90}Y-DOTATOC Therapy (& Amino Acids)			X		X		X		
Skin assessment[15]			X		X		X		
Dosimetry (blood & imaging)			X		X		X		
Adverse Event Assessment	X[5]	X	X	X		X		X	X
Fluid diary[11]		X	X	X	X	X	X		

1. temp, pulse, respirs, b/p, weight. Height at baseline only. Weight at baseline and Day 1 of each cycle.

2. required for children(<18 years). Required for adults (18 and older) if serum creatinine >1.2mg/dl. If required at baseline for patient, then all subsequent time points require nuclear GFR also.

3. blood tests include: CBC/diff, AST, ALT, creatinine, plus urinalysis at baseline only and T.Bili at baseline only.

4. required for females of child bearing potential only

5. Documentation of baseline symptoms

6. All baseline evaluations within 30 days of first ^{90}Y-DOTATOC dose except blood tests need to be within 10 days and ^{68}Ga-DOTATOC/TATE PET/CT needs to be within 6 months of first ^{90}Y-DOTATOC infusion. The diagnostic scans need to be within 120 days of the first ^{90}Y-DOTATOC infusion.

7. events only repeated prior to treatment 1 if they fall outside of the baseline windows noted in footnote 6.

8. Patients who discontinue dosing of ^{90} Y-DOTATOC early and who have received at least 1 dose of ^{90}Y-DOTATOC are also required to complete follow up appointments per calendar

9. repeat testing can be point of care urine pregnancy test done in Nuclear Medicine.

10. Patients will be instructed to have fluid intake of 1.5 liters Day 1 and 2 liters/day on Days 3 & 4.

11. 3-4 month follow up procedures may be performed by patient's local MD.

12. If GFR is indicated, patients will be required to return to UIHC.

13. If patient does not return to UIHC for F/U, QOL may be mailed or e-mailed to patient.

14. Electrolytes will be drawn during the last hour of amino acid infusion.

15. The skin at the site of the infusion will be assessed by clinic visit or phone at 3-5 days following each infusion of amino acids.

8.0 Duration of Therapy and Stopping Rules

8.1 Stopping Rules for individual subject

In the absence of treatment delays due to adverse events, treatment may continue for 3 cycles or until one of the following criteria applies:

- Cumulative renal radiation dose exceeds 23 Gy.
- Intercurrent illness prevents further administration of treatment.
- Unacceptable adverse event(s) such as irreversible renal or hematopoietic toxicity.
- Initiation of another tumor specific therapy.
- Patient decides to withdraw from the study.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

Other causes of discontinuation from study:

- Termination of study by Sponsor.
- Subject's condition no longer requires study drug.

* Note: Disease progression alone does not mandate discontinuation of ^{90} Y treatment.*

Disease progression per RECIST 1.1 criteria during the follow up period will warrant removal from study.

8.2 Stopping Rules for Trial

Enrollment will proceed according to a Simon two-stage study design. Thirty-five subjects will be enrolled in the first stage; if 5 or fewer patients respond (Stable, PR or CR) as determined by ^{68}Ga-DOTATOC PET/CT and diagnostic CT or MRI (RECIST 1.1 criteria), the study will be closed and the treatment ruled clinically uninteresting. Otherwise, an additional 29 subjects will be enrolled. If 20 or more responses are observed in the total of 64 subjects, then the treatment will be ruled worthy of further study.

9.0 Regulatory and Reporting Requirements

The Data and Safety Monitoring Committee (DSMC) of the Holden Comprehensive Cancer Center will provide data and safety monitoring for this study. "The Data and Safety Monitoring Plan of the Holden Comprehensive Cancer Center" provides standard operating procedures to monitor all clinical cancer trials at the UIHC. All investigator-initiated trials are automatically monitored by the DSMC. The Data Safety and Monitoring Plan for this risk level 4 study is attached as Appendix 1.

9.1 Adverse Events List and Reporting Requirements

As with any new drug, this study may involve risks that are currently unforeseeable. The most frequent adverse events observed in adults treated with these drugs are listed below.
Severity of adverse events will be graded according to NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) which is available at http://ctep.cancer.gov/reporting//ctc.html.
Adverse events will be collected from time of consent until 30 days post ^{90}Y treatment. Labs will only be collected as adverse events if deemed clinically significant by the investigator. Serious Adverse Events (SAE's) that occur >30 days after the last ^{90}Y treatment will only be reported if at least possibly related to investigational product.

9.1.1 Routine Adverse Event Reporting Requirements to DSMC

An adverse event (AE) is defined in the *CTEP, NCI Guidelines* [2005] as "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure (attribution of unrelated, unlikely, possible, probably or definite)."

Routine adverse events will be reported by submission of an adverse events log to the DSMC at the time of DSMC review.

9.1.2 Expedited Adverse Event Reporting to DSMC

Serious adverse events occurring during study procedures with ^{90}Y-DOTATOC will require a notification to the DSMC as described in the Data and Safety Monitoring Plan (see appendix 1) below regardless of attribution to study intervention. The investigator will continue to follow or obtain documentation until the resolution of such an event until it is resolved (with or without sequelae)

9.1.3 Adverse Event Reporting Guidelines –

Documentation will begin after radiotracer injection and continue through 1 calendar day following imaging. This study will use the guidelines developed by the Cancer Therapy Evaluation Program (CTEP) for PET and/or SPECT IND agents. For purposes of the below table, it should be noted that the radioactive half-life for ^{90}Y is 64.1 hours. Therefore, 10 radioactive half-lives will be 27days for the purposes of adverse event reporting.

9.2 Expected Adverse Events Associated with ^{90}Y-DOTA-tyr^3-Octreotide (^{90}Y-DOTATOC)

Treatment involves administering a radioactive drug into the bloodstream from where it may attach to any cell (cancerous and healthy) that has somatostatin receptors on its surface and normally comes in contact with somatostatin. Therefore, healthy cells may potentially be killed or damaged by this drug. Healthy cells that contain somatostatin receptors are present in the pancreas, stomach, duodenum, small intestine, large intestine, pituitary, and ovaries. No damage to these organs has been seen in the adults who have taken this drug. Other healthy organs which do not contain somatostatin receptors but which normally come in contact with somatostatin include the bladder.

Kidney exposure is due to the renal clearance of this drug as well as the normal amino acid recirculation mechanism that operates to conserve amino acids and small peptides. The kidney contains somatostatin receptors and also comes in contact with ^{90}Y-DOTATOC as it is being excreted. This means the kidney usually receives the most radiation of any normal tissue in the body. Adult humans who have received ^{90}Y-DOTATOC have experienced some damage to the kidney. Some adults have experienced permanent decrease in kidney function, but no adults have required dialysis. **There is a risk that severe kidney damage could occur which may result in the need for permanent dialysis. Kidney damage may occur as a late effect, months after the last dose of ^{90}Y-DOTATOC.**

Adults and children have been treated with ^{90}Y-DOTATOC. Side effects that were observed include: bowel obstruction, diarrhea, weight loss, reduced red blood cells (anemia), reduced white blood cells (increased chance of infection), and reduced platelets (increased chance of uncontrolled bleeding). These effects depended on the dose of ^{90}Y-DOTATOC and occurred at higher doses tested. Most patients recovered from these effects after stopping ^{90}Y-DOTATOC; however, two patients (of a total of over 2500 patients treated as of 12/31/13) have developed myelodysplastic syndrome.

An unexpected allergic reaction following the administration of ^{90}Y-DOTATOC or the amino acids may consist of shortness of breath, wheezing, lowering of blood pressure, fever, chills, hives, itchiness or damage to the blood vessels. The amino acid solution is hyperosmolar and may cause local inflammation or in rare cases, blistering at the infusion site. A 20 gauge IV line or PICC line is recommended to avoid this inflammation. A phone call will be made to subjects 3-5 days following each infusion of amino acids to assess skin changes at the injection site. The long-term effects of ^{90}Y-DOTATOC are unknown. ^{90}Y-DOTATOC may cause radiation damage that may not surface until months or years later.

Participation in this study may be hazardous to a fetus or a nursing child. There is not enough information to determine whether there are significant risks to a nursing child or a fetus conceived or

carried by a subject who is participating in this study. Therefore, in order to participate, all females capable of becoming pregnant must have a negative pregnancy test within 7 days prior to the first ^{90}Y-DOTA-tyr^{3}-octreotide treatment. Female subjects must tell us if they may have become pregnant within the previous 14 days because the pregnancy test is unreliable during that time. All subjects capable of becoming pregnant must agree to practice a medically acceptable birth control measure (abstinence, birth control pills, intrauterine devices, vaginal diaphragm, vaginal sponge, or condom with spermicidal jelly) throughout the study and for eight months following the end of the last treatment. Any females who are nursing must refrain from nursing while on study and for three months following the end of the last treatment.

9.3 Expected Adverse Events Associated with Amino Acid Infusions:

Generalized flushing, fever, and nausea have been reported during infusions of amino acid solutions. Local reactions consisting of a warm sensation, redness, inflammation of the vein and blood clotting at the infusion site have also occurred. Low or high potassium and phosphate levels have been observed in some adult patients. These levels have not been clinically significant and have returned to within normal limits after completion of therapy except in one case out of more than 400 individual infusions of amino acids. To avoid this rare electrolyte disturbance, we will check heart rate and potassium level 60 min prior to end of amino acid infusion; if >6 meq/L and/or heart rate < 60 bpm, we will administer oral or IV $NaHCO_3$ and keep patient sitting or supine until heart rate >65 bpm.

9.4 Research radiation dose estimate

9.5 Risks of ^{90}Y-DOTATOC PET/CT Scan Procedure

Risks of Investigational PET/CT: Additional risks include radiation exposure from the investigational low dose CT scan and the inconvenience of the investigational PET/CT scan. Children may require sedation or anesthesia to remain still during the PET/CT scanning procedure. The risks of sedation include a reaction to the medication used for sedation or anesthesia. If anesthesia is required, there is a risk of injury to the throat or airways from insertion of the breathing tube.

10.0 Dosing Delays/Dose Modifications

10.1 Dosage Modifications

Dosimetry will be acquired following treatments1 & 2. The kidney dose/mCi will be calculated and the total target dose that will limit renal dose to ≤ 23 Gy. The target dose minus 120 mCi will then be divided into two equal doses for Cycles 2 and 3 with adjustments based on dosimetry. Regardless of the total dose to kidneys as determined by dosimetry, the maximum dose in Cycle 2 will be 150 mCi; Cycle 3 will be limited to ≤ Cycle 2.

Dose of ^{90}Y-DOTATOC will be decreased 25-50% for any subject in whom dosimetry measurement on first or second dose indicates probable total renal dose for three cycles will be >23 Gy. Dose may be increased on subsequent cycles so long as summation of dosimetry measurements limits total renal dose to $\leq$ 23 Gy.

Dose of ^{90}Y-DOTATOC will be increased 10-20% for any subject in whom dosimetry measurement on first or second dose indicates probable total renal dose for three cycles will be significantly <23 Gy. No subject will receive > 420 mCi total dose of ^{90}Y-DOTATOC.

Subjects who had a nuclear GFR measured at baseline will be followed for nephrotoxicity by nuclear GFR. If they demonstrate a $\geq$ 30% decrease in GFR as determined by nuclear GFR scan, their dose will be reduced by 50% on the next cycle. Full dose may then be given when GFR returns to 90% of baseline. Patients who experience $\geq$ 30% decrease in GFR will be placed on an age appropriate dose of captopril or other ACE inhibitor.

Also, patients that experience a rise in serum creatinine above 1.2 (who previously had normal levels) will be hydrated and have their serum creatinine repeated. If the creatinine level after hydration remains

elevated above 1.2, then nuclear GFR will be measured. If applicable, dose reductions will be implemented as described above.

Nephrotoxicity as demonstrated by ≥ 50% decrease in nuclear scan GFR will be considered a DLT if the resulting GFR is below normal for subject's age, height and weight. Subjects who experience a DLT are eligible to receive subsequent cycles of ^{90}Y-DOTA-tyr^3-Octreotide at a reduced dose if the DLT has returned to baseline value within 9 weeks of the untolerated ^{90}Y-DOTA-tyr^3-Octreotide dose. The subject's subsequent dose must be reduced to 50% of the untolerated dose.

10.2 Dose Delay

The time elapsed between the end of week 6 of a Cycle Study Period and Day 1 of the next Cycle Study Period should be ≤ 3 weeks. No further interruption between cycles should occur, except delays mandated by the protocol itself or regulatory requirements as in periods of enrollment locks or data review by health authorities. If a longer interruption does occur, the subject's continuation will be at the discretion of the Principal Investigator; approval will not be unreasonably withheld.

10.3 Concomitant Therapy

The subject may not receive any other approved or investigational anti-neoplastic therapies for the treatment of the refractory somatostatin-receptor positive tumor during the course of the study, excluding somatostatin analogues and bisphosphonates. However, all subjects on somatostatin analogue therapy will discontinue therapy from 12 hours prior to a) injection with ^{68}Ga-DOTATOC, and b) infusion with ^{90}Y-DOTA-tyr^3-Octreotide until 12 hours post administration. Subjects who have been on hormonal therapy (other than somatostatin analogues) for ≥ 2 months with SD or PD may continue to receive hormonal therapy during this study. Subjects who initiate another tumor-specific therapy will be discontinued from further treatment with ^{90}Y-DOTA-tyr^3-Octreotide. Patients may continue long acting Somatostatin analogues between cycles of ^{90}Y therapy. It should be administered as standard of care after completion of dosimetry imaging for Cycles 1 and 2. Following Cycle 3, it may be given on Day 3 or later. Patients on long acting Lanreotide should have this treatment held until after ^{90}Y treatment Cycle 3. Short acting somatostatin analogue can be used at the discretion of the treating physician to bridge the patient.

All subjects who have received at least one dose of ^{90}Y-DOTA-tyr^3-Octreotide must continue into the Long-Term Follow-up Study Period at the point of treatment discontinuation. This is necessary to determine any long-term effects of treatment with ^{90}Y-DOTA-tyr^3-Octreotide.

Subjects may receive, at the discretion of the investigator, appropriate medical treatment for medical problems that arise while on study.

11.0 Response Criteria/End of Study Assessments

11.1 Response criteria according to RECIST 1.1 include:

	Evaluation of Target Lesions
Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study
	Evaluation of Non-Target Lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

12.0 Data Analysis and Statistics:

12.1 Primary Objective 1

Treatment efficacy, defined as a complete response, partial response or stable disease (CR+PR+SD), is the primary endpoint of interest in this dosimetry-guided Phase II trial. Tumor response will be defined according to RECIST1.1 criteria applied on up to five target lesions (primary tumor if not surgically removed, up to two liver lesions, up to two nodal metastases, metastatic lesion in other organs, such as ovary, breast) that will be quantified and compared between pre-therapy and 3-9 months post-therapy high-resolution, contrast-enhanced CTs. Osseous metastases may be followed as non-target lesions. ^{90}Y-DOTATOC will be deemed worthy of further study if its associated response rate is ≥ 0.60, and clinically uninteresting if its rate is ≤ 0.40. Enrollment will proceed according to an optimal Simon two-stage study design. Sixteen (16) subjects will be enrolled in the first stage; if 7 or fewer patients respond, the arm will be closed and the treatment ruled clinically uninteresting. Otherwise, an additional 30 subjects will be enrolled. If 24 or more responses are observed in the total of 46 subjects, then the treatment will be ruled worthy of further study. The study design has a probability of early termination equal to 0.72. Power to detect efficacy is 0.80 with a type 1 error rate of

0.05.

Secondary analysis will focus on time to tumor progression and overall survival. The method of Kaplan- Meier will be used to estimate progression and survival rates. Subjects for whom the outcome of interest is not observed at the 6 month follow-up will be treated as censored observations in the survival analysis.

12.2 Primary Objective 2
Adverse events will be recorded and reported in tabular form by type and grade. If four or more subjects experience renal toxicity ≥ Grade 4, the radiopharmaceutical will be declared too toxic and the trial will be stopped. If any other irreversible Grade 4 toxicity is observed in four or more subjects, the treatment will be declared too toxic and will be stopped. Adverse events will be graded according to the most recent CTE guidelines.

12.3 Secondary Objective 1
For subjects who participated in the ^{68}Ga-DOTATOC Comparator trial (IRB # 201212736), the number, size, and location of discordant lesions between ^{68}Ga-DOTATOC PET/CT and Octreoscan will have been tabulated. This analysis will be updated using the results of post- therapy ^{68}Ga-DOTATOC PET/CT for those patients who participated in the comparator study, but only received the initial ^{68}Ga-DOTATOC PET/CT due to progression on the Octreoscan + high-resolution, contrast-enhanced CT. Lesions that were positive on PET, but negative on Octreoscan will be considered true positive if a response to PRRT is documented after either Cycle 1 or at 6-9 month followup following last ^{90}Y-DOTATOC infusion.
For subjects who did not participate in the ^{68}Ga-DOTATOC Comparator trial, all ^{68}Ga-DOTATOC PET/CT scans will be acquired as part of this study; number, size, and location of lesions will be analyzed between first and subsequent ^{68}Ga-DOTATOC PET/CTs.

12.4 Secondary Objective 2
Compare SUVmax between primary tumor, liver lesions, and extra-hepatic lesions with expression levels of sst2 using qRT-PCR and/or receptor IHC from fresh frozen or paraffin-embedded samples where available.

Compare maximum SUVs of primary tumor, liver lesions, and extra-hepatic lesions with expression level of sst2 RNA and IHC on fresh frozen tissue, or paraffin embedded samples (block(s) or 10 unstained slides) to determine whether or not any correlation exists between SUVmax, sst2 expression, or sst2 protein and response to PRRT. The study is expected to delineate whether measurement of sst2 expression by either qRT-PCT or immunohistochemistry at diagnosis can predict response to ^{90}Y-DOTATOC. We will construct a table tabulating SUVmax, level of RNA expression, and IHC level for all lesions biopsied. With 64 subjects the correlation between SUV max, RNA expression and IHC will be determined. Analysis of SUVmax compared with sst2 RNA and receptor protein expression on primary tumor and metastatic lesions will be considered worthy of further study if > 50% of lesions demonstrate a positive correlation. Tissue will be sent to 3080 Med Lab in University of Iowa Hospital and Clinics for analysis.

13.0 Study Drug

13.1 ^{90}Y-DOTA-tyr^3-Octreotide (^{90}Y-DOTATOC); IND# 61,907

13.1.1 Chemistry, Manufacturing and Control
Peptide Receptor Radionuclide Therapy (PRRT) requires a peptide conjugate that consists of the peptide receptor ligand as the targeting moiety and a chelator to bind the radionuclide as shown in Figures 1 and 2. [^{90}Y]Yttrium-DOTA-tyr^3-Octreotide (^{90}Y-DOTATOC) consists of the targeting peptide tyr^3-octreotide which is conjugated to the chelating moiety (DOTA) to bind the radionuclide ([^{90}Y]Yttrium). [^{90}Y]Yttrium-DOTA complexes are extremely stable[36].

The manufacture of ^{90}Y-DOTATOC will be conducted in the University of Iowa Nuclear Medicine Radiotherapeutics Laboratory. At least two technical personnel, one of whom has a postgraduate degree

(MS, PharmD, MD, or PhD) will be present during manufacture and quality control procedures to confirm adherence to standard operating procedures and release criteria. Reagents and supplies used for the preparation of ^{90}Y-DOTATOC are received and inspected per specification sheets and accepted or rejected. Accepted reagents and supplies are labeled with appropriate expiration dates, initialed, assigned identification numbers and then stored in specified locations in the Radiotherapeutics Laboratory.

Manufacture:
The starting material, DOTA-tyr^3-Octreotide (DOTATOC), is manufactured under GMP conditions and is obtained commercially with appropriate certificate of analysis documentation. Manufacturing of ^{90}Y-DOTATOC will be performed using a synthesis unit specifically designed for this purpose ModularLab PharmTracer from Eckert & Zeigler, Berlin, Germany. The system utilizes a purpose-built, disposable, GMP-certified (sterile, pyrogen-free) cassette that is snapped into place on the synthesis unit. Computer control manages the flow of reagents for radiolabeling, purification, and transfer of the product to the final product vial via a hydrophilic PVDF sterilizing 0.22 µm filter. A new cassette is used for each preparation and preparations are usually used for a single patient study.

The final product collection vial is labelled with the batch number and other relevant information (see section 13.1.2 Labeling). The vial is weighed, then prefilled under aseptic conditions with sterile isotonic saline for injection containing ascorbic acid. This solution acts as a diluent and the ascorbic acid as an agent to aid in prevention of radiolysis of the final product. Ascorbic acid 10-50 mg, typically 50 mg for the high radioactivity runs, is dissolved in 1 mL ultrapure water and this is added to a 100 mL bag of sterile isotonic saline. After thoroughly mixing, 84 mL is removed with a sterile syringe and passed through the sterilizing filter into the final product collection vial. When the reaction product is added later in the process (~ 16 mL solution) the solution will be close to 100 mL. This volume, in this vial, gives a finely defined geometry for accurate radioactivity dose measurement.

GMP grade [^{90}Y]Yttrium chloride, measured against a NIST standard, is purchased commercially (e.g., Perkin-Elmer) for each manufacturing procedure[37]. The received [^{90}Y]Yttrium chloride radioactivity (typically, 50 – 250 mCi) is calibrated to expected time of start of synthesis. Prior to synthesis the amount of received radioactivity is confirmed with the dose calibrator in the Radiotherapeutics Laboratory. The PharmTracer system transfers the [^{90}Y]Yttrium chloride using the ascorbate buffer (typically, 50 mg ascorbic acid in 1.5 mL ultrapure water) directly to a reaction vessel. The ascorbic acid serves not only as a buffer but also as an aid in prevention of radiolysis. The reaction vessel contains DOTATOC precursor dissolved in ultrapure water. To achieve maximum radiolabeling and high specific activity, the amount of precursor is restricted to the range 50-200 micrograms, typically 115 µg. The reaction mixture is heated to 95 °C for 25±5 minutes. The product is purified by passing the diluted solution (approximately 2-3 mL) through a solid phase extraction (SPE) C-18 cartridge, which retains the ^{90}Y-DOTATOC while allowing any remaining free [^{90}Y]Yttrium to pass through the column into the waste vial. The C-18 cartridge is rinsed with isotonic saline for injection to remove any residual free [^{90}Y]Yttrium, followed by elution of ^{90}Y-DOTATOC with 47.5% ethanol in water (2 mL), followed by isotonic saline (14 mL), directly through a sterile 0.22 micron membrane filter into the final product collection vial. The final product collection vial, containing ~100 mL of solution, is then agitated to give a homogenous solution of product suitable for quality control sampling and final release measurements.

Small aliquots (total 1.5 – 2 mL) are then taken for quality control testing and the product line and vent filter are removed. The final product collection vial is weighed and the contained radioactivity measured and recorded on the master batch sheet that then translates to the final product label. Radiochemical yields of >90% (uncorrected for decay) are routinely achieved. The final sterilization filter is retained for a QC pressure test to ensure filter integrity. The production process requires approximately 3 hours to complete.

Quality Control:
The QC process takes approximately 1.5 hours to complete. The quality control tests are performed and compared to release criteria prior to release of the final product as shown in Table 1 below.

Table 1. Analytical Specifications for ^{90}Y-DOTA-tyr^3-Octreotide (^{90}Y-DOTATOC)

Test	Release Criteria
Appearance	Clear and no visible impurities
Filter Test	>1 bar from 2 bar overpressure at 1 minute
pH	3.0 – 7.0
Radiochemical Purity	>90%
Endotoxin	Pass gel clot tests (sample & positive control)

Appearance: Any visible cloudiness or precipitate will disqualify the product for human use.

Filter Test: A filter pressure test is conducted by applying pressure to the sterilizing filter at 2 bar inert gas (nitrogen or argon) and monitoring the leak rate for 1 minute to ensure the integrity of the filter used for final product sterilization. The system pressure should be greater than 1 bar (100 kPa, 15 psi) above atmospheric pressure after 1 minute of terminating gas supply overpressure. In the unlikely event that the filter pressure test fails, the product may be re-filtered with a fresh sterile filter under aseptic conditions with all the quality control tests being conducted on samples of the newly filtered material.

pH: The pH of the final product is measured by spotting pH paper.

Radiochemical Purity: The radiochemical purity of the final product is determined on a reverse phase high pressure liquid chromatography (HPLC) system equipped with a radiation detector, using a C18 reverse phase column and mobile phase of 0.1% TFA in water (mobile phase A) and acetonitrile (mobile phase B). Using this column and mobile phase system, free Y-90 will elute with the void volume of the column while ^{90}Y-DOTATOC will be retained for a significant time on the column and the two species can be differentiated by their differences in retention time. Radiochemical purity is determined by integration of the 90Y-DOTATOC peak at a known retention time (7.8±0.5 min) and comparison to any peaks of trace free Y-90 and degradation peptides that may be present. This determination will be conducted by senior technical personnel.

Bacterial Endotoxins: Samples of final product will be tested using the limulus amebocyte lysate (LAL) gel-clot test. If either the positive control or product fails in the LAL gel-clot test, the entire test will be repeated in triplicate. Failure of any one of the triplicate gel clot tests will disqualify the product for human use.

Sterility: Tryptic Soy Broth (TSB) and Fluid Thioglycollate Media (FTM) are inoculated with a 0.25 mL sample each of final product, incubated (TSB at room temp, FTM at 32° C) and checked for growth during the following 14 days. At the completion of the sterility test, the batch record is completed and filed. This test will not be complete at the time of administration of the product. If any product fails this test after administration of the product to a patient, that patient will be contacted to ask about any symptoms and treated if clinically indicated. An investigation of the source of contamination will be conducted and further patient studies terminated until the source identified and rectified.

Expiration date: The product expires in 48 hrs. If product will be used later than 24 hours after production, a second small sample with be obtained from the product vial and re-examined by HPLC. If radiochemical purity is <90%, the product will be declared expired and will not be administered to any patient.

Table 2 demonstrates the Quality Control testing on three successive productions of ^{90}Y-DOTATOC at the University of Iowa. Each production was performed according to the standard operating procedure described herein using 115 µg DOTATOC and 200±10 mCi Y-90. Detailed batch records and HPLC chromatograms are attached in a separate Chemistry, Manufacturing and Control document.

Table 2. Quality Control Measurements on Three Successive Production Runs for 90Y-DOTATOC Manufactured at University of Iowa

	1/13/2015	1/15/2015	1/21/2015
Yield	180.8 mCi	192.8 mCi	205.0 mCi
Radiochemical Purity	97%@time zero	96%@time zero	100%@time zero
Appearance	Clear	Clear	Clear
pH	5.0	5.0	5.0
Sterility	Pass@14 days	Pass@14 days	Pass@14 days
Endotoxin	Pass	Pass	Pass
Expiration Date	Pass all release criteria @ 48 hrs	Pass all release criteria @ 48 hrs	Pass all release criteria @ 48 hrs

13.1.2 Labeling

Abiding by ALARA (as low as reasonably achievable) principles for handling radioactivity the actual final product vial (FPV) will not contain all the desired information. The FPV label will have the batch number, product name, and other limited information: for example

University of Iowa Hospitals and Clinics
Radiotherapeutics Laboratory, Nuc. Medicine
Department of Radiology
Radiopharmaceutical [Y-90]DOTATOC
Activity <300 mCi

Date
1/21/2015
Radionuclide [^{90}Y]
$T_{1/2}$ = 64.1 hours

Caution: New Drug
Limited by Federal (or United States) law to investigational use.

Active ingredient:
Y-90 DOTATOC
Inactive ingredients:
Ethanol,
Ascorbic Acid,
Sodium Chloride

x

Chemist(s) **01212015Y90DOTATOC01**

The shielded container of the FPV will be labeled with all relevant information: for example

University of Iowa Hospitals & Clinics	Batch #: 01212015Y90DOTATOC01	
Radiotherapeutics Lab Nuclear Medicine 200 Hawkins Drive Iowa City, IA 52242	Total Activity: 205.0mCi / 7.59GBq Ref. Date/Time: 1/21/15 11:28 Total Vol. (mL): 97.4 Conc. (mCi/mL): 2.106	Y-90, $T_{1/2}$ =64.1 hours Active ingredient: Yttrium-90 DOTATOC
"Caution: New Drug - limited by Federal (or United States) law to investigational use"	SA (MBq/nmole): ≥ 93.64 SA (Ci/μmole): ≥ 2.531 Exp Date/Time: 1/23/15 11:28	Inactive ingredients: Ethanol, Ascorbic Acid, Sodium Chloride Sterile for IV use only. Investigational use only.
Signatures:		Do not use if cloudy or contains particulates.
Chemist(s): S Kapoor BS ME Martin PhD GL Watkins PhD		1/21/2015

The values on these labels, including the batch number, are generated automatically from the master batch file. Each label is inspected for correctness prior to affixing to the appropriate container.

13.1.3 Environmental Assessment

We request a categorical exclusion for the Environmental Impact Statement requirement in section 21 CFR part 25 because this radiopharmaceutical meets the conditions stipulated in Section 25.24(c)(4). This material

is intended for in-house human clinical research only and any material not consumed for patient use will be treated and contained as low level radioactive waste. This waste is managed by the University of Iowa Radioactivity Protection Office / Environmental Protection Office. All waste generated during manufacture and dispensing is held for decay of radioactivity. Yttrium-90 decays to stable Zirconium-90. All waste is incinerated when activity levels are below acceptable limits. We anticipate doing 100 or less manufactures per year. We further expect to use 115 µg or less per run of precursor peptide, DOTATOC, which amounts to less than 10 mg total of peptide for the 100 runs per year. For comparison the unlabeled Octreotide is used therapeutically at 300 µg/dose subcutaneously 3 times daily up to 60 mg intramuscular (long-acting) Sandostatin LAR every 4 weeks.

13.3 Previous Human Experience with ^{90}Y-DOTATOC

^{90}Y-DOTATOC PRRT was also pioneered in Europe where it has been demonstrated to be the most effective therapy to date for patients with neuroendocrine tumors, with a mean time to disease progression is greater than 4 years[23,38]. University of Iowa investigators participated in an international Phase II study of ^{90}Y-DOTATOC PRRT and enrolled over 40 subjects. This clinical trial also demonstrated safety and efficacy of PRRT in humans when care is taken to protect the kidneys with concomitant amino acid infusion[21]. University of Iowa investigators also hold the only IND (#61,907) in the United States for this radiopharmaceutical and have completed the only Phase I trial of ^{90}Y-DOTATOC PRRT in children. University of Iowa investigators have treated 18 children and young adults as well as 40 older adults with ^{90}Y-DOTATOC PRRT; no irreversible renal toxicity has been experienced in these patients, primarily due to rigorous hydration prior to and after administration of the therapy as well as providing the total dose in 3 moderately sized doses rather than 2 higher doses. The major goal of this present study will be to determine if individualized, dosimetry-guided dosing of ^{90}Y-DOTATOC can successfully optimize dose to tumor while limiting renal toxicity for every patient.

13.4 Pharmacology and Toxicology Information

The above summary of human experience provides strong evidence that the amount of investigational drug (DOTATOC) in mass quantity and the amount of radiation (as also provided via our measured radiation dosimetry) are acceptable in terms of risk. The NOAEL level of DOTATOC has never been established in humans, despite studies reporting much larger mass quantity use than we propose, with some using multiple large doses[5]. The radiation toxicity from the investigational radioisotope is also, accordingly, within the acceptable range for patients with life-threatening malignancies whose treatment we believe will benefit from the use of the proposed investigational imaging procedure. Accordingly, we believe the risk/benefit of our proposed investigation to be justified.

13.5 Other Agents: Amino Acid Solution

The amino acid solution will be prepared in the University of Iowa Pharmacy. The solution used for these studies will contain a minimum of 27g each of arginine and lysine in a volume of 2 liters when diluted to $\leq$ 800 mOsm/liter will be administered at 8.3 mL/kg/hr with a maximum rate of 450 mL/hr to be administered starting 30 min prior to infusion of ^{90}Y-DOTATOC.

13.6 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form.

14.0 Data Reporting

Data for this study will be secured by entry into OnCore and EPIC. Both of these electronic medical record systems are maintained behind a firewall under the control of University of Iowa Hospitals and Clinics IT Department. Both systems are password protected and all computers on which data can be entered are secured in locked rooms when unattended. Any hard copies of data are secured in the Clinical Trials Support Services Office located at 11510 FPF.

The agent, DOTA-tyr^3-Octreotide utilized in the manufacture of ^{90}Y-DOTA-tyr^3-Octreotide for this study is provided to the investigators under a Clinical Trials Agreement (CTA) between Isotope Technologies Garching GmbH, Lichtenbergstr. 1, 85748 Garching, Germany (ITG) and the University of Iowa. Therefore, the following guidelines apply to the use of ^{90}Y-DOTA-tyr^3-Octreotide in this study:

1. ^{90}Y-DOTA-tyr^3-Octreotide may not be used for any purpose outside the scope of this protocol, nor can ^{90}Y-DOTA-tyr^3-Octreotide be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for ^{90}Y-DOTA-tyr^3-Octreotide are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators.
2. Clinical Trial Data and Results and Raw Data developed under a **Clinical Trials Agreement** (CTA) or **Cooperative Research and Development Agreement** (CRADA) will be made available exclusively to the University of Iowa investigators, the NCI, and the FDA, as appropriate.

15.0 References

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Appendix I

Single Timepoint Dose Estimate for Exponential Clearance

Introduction: Personalized dosimetry is highly desirable for many radionuclide therapy protocols in order to deliver the maximum tumor dose while sparing the critical organs. The determination of the total integrated activity (Ã) for radiation dose estimates generally requires measurements of tissue activity at multiple time points with a minimum of at least 2 time samples for each exponential component. This can add many additional days to the procedure creating a burden for both the patient and the clinic.

The aim of this paper is to demonstrate that in certain situations where the clearance of the radiotracer is described by a mono- or bi-exponential model and quantitative information about the long component is approximately known, it may be possible to obtain a useful estimate of **Ã** from a single time point measurement (**Ã***). This approach may prove to be accurate and simple enough to allow personalized dosimetry to more effectively manage radionuclide cancer treatments and thereby making personalized dosimetry feasible.

Single exponential derivation: We first derive the single point estimation approach for a single component exponential: $\mathbf{A(t) = A_0 \exp(-kt)}$ Eq. 1

Where $\mathbf{A_0}$ is the activity at t = 0 and **k** is the effective clearance rate constant.

The total number of decays associated with Eq. 1 is: $\mathbf{\tilde{A} = A_0/k}$ Eq. 2

If k is known and a quantitative activity measurement is made at time T, then is determined from:

$\mathbf{\tilde{A} = A(T) \exp(kT)/k}$ Eq. 3

Suppose we can accurately measure **A(T)** but only a population mean value is known for **k** (indicated by **k***). We hypothesize that **Ã** can be estimated from**:**

$\mathbf{\tilde{A}^* = A(T) \exp(k^*T)/k^*}$ Eq. 4

In Eq. 4, **A(T)** and **T** are measured and **k*** is known from either previous population measurements of from theoretical pharmacokinetic considerations.

Optimal sampling time: The time **T** where **Ã*** is exactly equal to **Ã** for all values of k can be determined by setting Eq. 2 equal to Eq. 3: $\mathbf{A_0/k = A(T)\ exp(k^*T)/k^* = A_0\ exp(-kT)\ exp(k^*T)/k^*}$. Solving this for T yields:

$\mathbf{T = \ln(k^*/k)/(k^*- k) = (1/k^*)\ \ln(k^*/k)/(1 - k/k^*) = \tau^*\ \ln(k^*/k)/(1 - k/k^*)}$, Eq. 5

where τ^* is the mean life of the estimated clearance rate. A plot of Eq 5 as a function of is shown in Figure 1

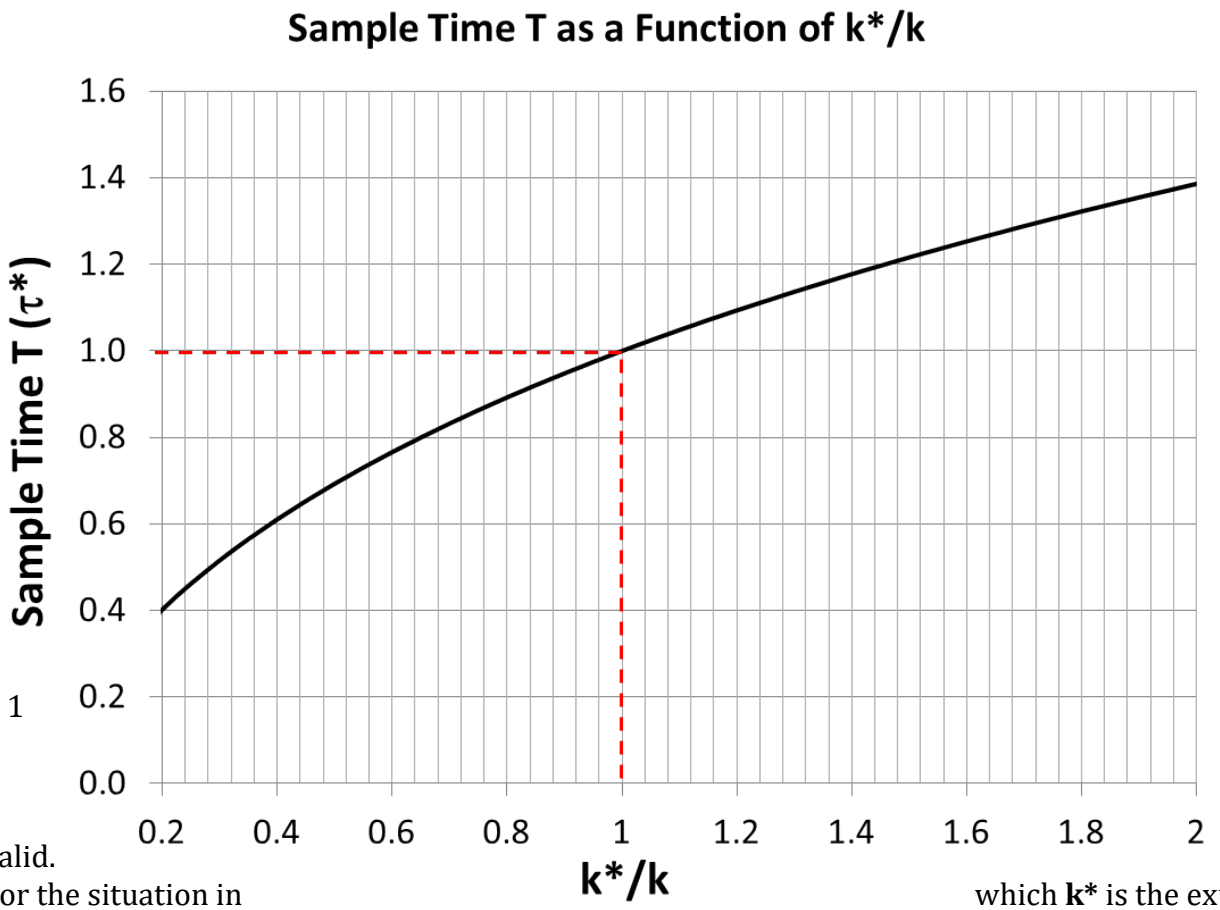


Figure 1. Plot of optimal sampling time as a function of k*/k. There is a singularity when k*/k = 1 since all sampling points are equally valid.

For the situation in which **k*** is the expectation value for the random variable **k**, the best sample time is therefore $\mathbf{T = \tau^*}$.

Validation of single exponential case: We hypothesize that Eq. 4 can be used to estimate the actual total number of decays without precisely knowing the actual clearance rate **k** if we know the expectation value **k***for a population of samples. As noted above, **k*** may have been determined from previous studies where sufficient samples were acquired to accurately determine individual **k** values or in some cases from prior knowledge about the tracer pharmacokinetics. To evaluate this hypothesis, a simulation using Excel was performed where values of **k** are randomly sampled for a set of initial activity levels ($\mathbf{A_0}$). Without any loss of generality, **k*** is assumed to equal 1/time (with arbitrary time units) and the values of **k** are selected from a random number generator with a gaussian distribution with a mean of 1 and a standard deviation of 0.18. In the 500 samples that were taken, **k** ranged from 0.42 to 1.58. The actual total number of decays **Ã** determined from Eq. 2 was compared against the estimated total number of decays **Ã*** determined from Eq. 4 as a function of sampling time T. Linear regressions were performed on the plots of **Ã** as a function of **Ã*** to determine the slope, intercept, correlation coefficient and the standard error of estimate.

Results of Single Exponential Simulation: The simulation result for the optimal sample time is shown in Figure 2, while the linear regression parameters as a function of sample time are given in Table 1.

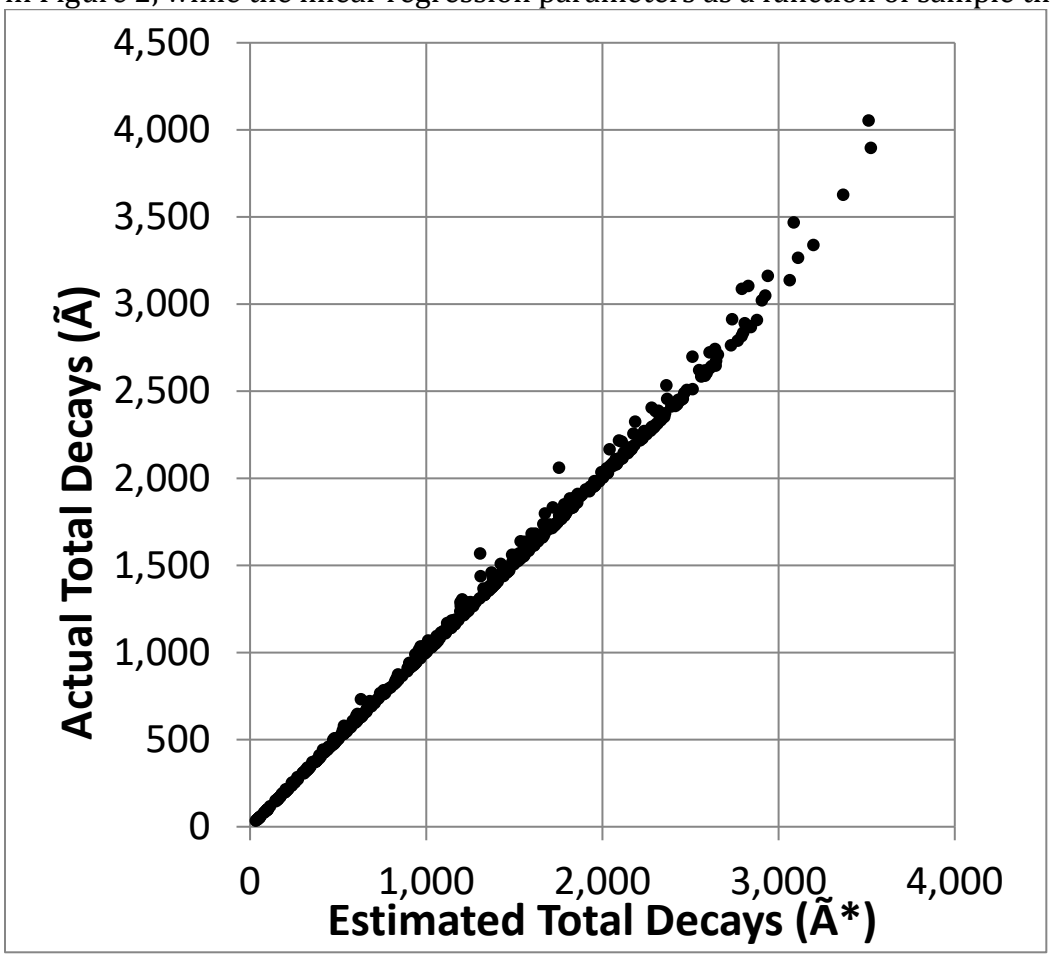


Figure 2. Single exponential simulation comparing actual decays with the single point time estimation.

Table 1 Linear Regression Results for **Ã** Comparison to **Ã***as a function of Sample Time

Sample Time T (τ)	Slope	Intercept	r^2	SEE
0.2	1.07	(43.7)	0.89	266.8
0.6	1.08	(60.7)	0.96	160.1
1.0	1.04	(23.3)	0.99	67.1
1.4	0.96	57.2	0.99	80.2
1.8	0.86	165.3	0.96	163.8

The plot of the simulation data shows an excellent correspondence between the estimated total decays calculated from a single time point sample and the actual total decays. Table 1 demonstrates that ideal sample time occurs at the mean life associated with k* as expected from the results given by Eq 5 and the plot shown in Figure 1.

Single exponential derivation: The derivation for bi-exponential clearance is similar to the mono-exponential derivation:

$$\mathbf{A(t) = A_1 \exp(-k_1 t) + A_2 \exp(-k_2 t)} \qquad \text{Eq 6}$$

The total decays are equal to: $\mathbf{\tilde{A} = A_1/k_1 + A_2/k_2}$ Eq 7

In most radionuclide therapy cases, the major portion of the radiation dose comes from the longer component (k2). Hence, Eqs 6 & 7 are rewritten in terms of $\mathbf{A_2}$ and $\mathbf{k_2}$.

Define $\mathbf{A_1/A_2 = c}$; $\mathbf{k_1/k_2 = a}$, then

$$\mathbf{A(t) = cA_2 \exp(-ak_2 t) + A_2 \exp(-k_2 t)} \qquad \text{Eq 8}$$

and $\mathbf{\tilde{A} = A_2/k_2\ (c/a + 1)}$ Eq 9

The activity at time t = **T** is: $\mathbf{A(T) = cA_2 \exp(-ak_2 T) + A_2 \exp(-k_2 T)}$

Solving for $\mathbf{A_2}$, $\mathbf{A_2 = A(T)/(c \exp(-ak_2 T) + \exp(-k_2 T))}$, thus:

$$\mathbf{\tilde{A} = \frac{A(T) \times (c/a + 1)}{[(c \exp(-ak_2 T) + \exp(-k_2 T)) \times k_2]}} \qquad \text{Eq 10}$$

Using a similar approach as with the single exponential case, the equation for the estimated total decays is written as:

$$\mathbf{\tilde{A}^* = \frac{A(T) \times (c^*/a^* + 1)}{[(c^* \exp(-a^* k_2^* T) + \exp(-k_2^* T)) \times k_2^*]}} \qquad \text{Eq 11}$$

As with the single exponential case, $\mathbf{k_2^*}$ is the effective clearance rate constant for the long component**,** but now there are 2 additional parameters that need to be included, **c*** and **a*.** At first glance, having this many parameters might seem to make the approach challenging and in the general case that is true. However, in instances that will be useful for radionuclide therapy, it will often be the case that $\mathbf{a^* > 10}$ and **c*** will be less than 2. When that is true, then:

$\mathbf{(c^*/a^* + 1) \approx 1}$ and $\mathbf{[(c^* \exp(-a^* k_2^* T) + \exp(-k_2^* T)) \times k_2^*] \approx \exp(-k_2^* T)) \times k_2^*}$,

Thus, $\mathbf{\tilde{A}^* \approx A(T) \exp(k_2^* T))/k_2^*}$ which is an approximation of the result obtained for the single exponential case in Eq 4.

Validation of the biexponential case: Using a similar approach as with the single exponential case, we hypothesize that Eq. 11 can be used to estimate the actual total number of decays without precisely knowing the actual biexponential parameters c, a, and k2 as long as we know their expectation values (**c*, a*, k_2*)** for a population of samples. To evaluate this hypothesis, a simulation using Excel was performed where values of **c, a** and **k_2** are randomly sampled for a set of initial activity levels (**A_2**). For this simulation, the values of c*, a* and k2* were determined from an actual clinical protocol that focused on the radiation dose to kidneys from Y-90 DOTATOC treatments. The parameters used in the simulation are given in Table 2. Note that while the standard deviation associated with k2* is relatively small, the standard deviations associated with c* and a* are large.

Table 2. Biexponential Simulation Parameters

	c*	**a***	**k_2***
mean	1.6	12.1	0.020
standard deviation	1.04	3.90	0.0036
maximum	4.2	19.0	0.034
minimum	0.03	5.4	0.009

The individual values of **k_2** are selected from a random number generator with a gaussian distribution while the distribution for **c** was triangular and the distribution for **a** was uniform. The maximum and minimum values for each of the parameters in the 500 samples that were generated show the large range over which **c** and **a** varied. The actual total number of decays **$\tilde{A}$** determined from Eq. 9 was compared against the estimated total number of decays **$\tilde{A}$*** determined from Eq. 11 as a function of sampling time T. Linear regressions were performed on the plots of **$\tilde{A}$** as a function of **$\tilde{A}$*** to determine the slope, intercept, correlation coefficient and the standard error of estimate.

Results of the biexponential simulation: The simulation result for the optimal sample time is shown in Figure 3, while the linear regression parameters as a function of sample time are given in Table 3. Although the correlation and standard error of estimate associated with the bi-exponential simulation are not as good as those obtained for the single exponential experiment, there still is a very strong correlation between the estimated and actual total decays. Table 3 shows the linear regression results as a function of the single sample time **T**, which is expressed in terms of the mean time associated with **k_2*** (τ_2).

Table 3. Biexponential simulation linear regression results as a function of sample time T

Sample Time T (τ_2)	**Slope**	**Intercept**	**r^2**	**SEE**
0.2	**0.93**	**41**	**0.91**	**134**
0.6	**1.05**	**-21**	**0.96**	**90**
1	**1.03**	**4**	**0.96**	**86**
1.4	**0.96**	**46**	**0.95**	**102**
1.8	**0.88**	**99**	**0.92**	**132**

As with the single exponential simulation results, the best sampling time in terms of the correlation and particularly the standard error of estimate is at **$T = \tau_2$**.

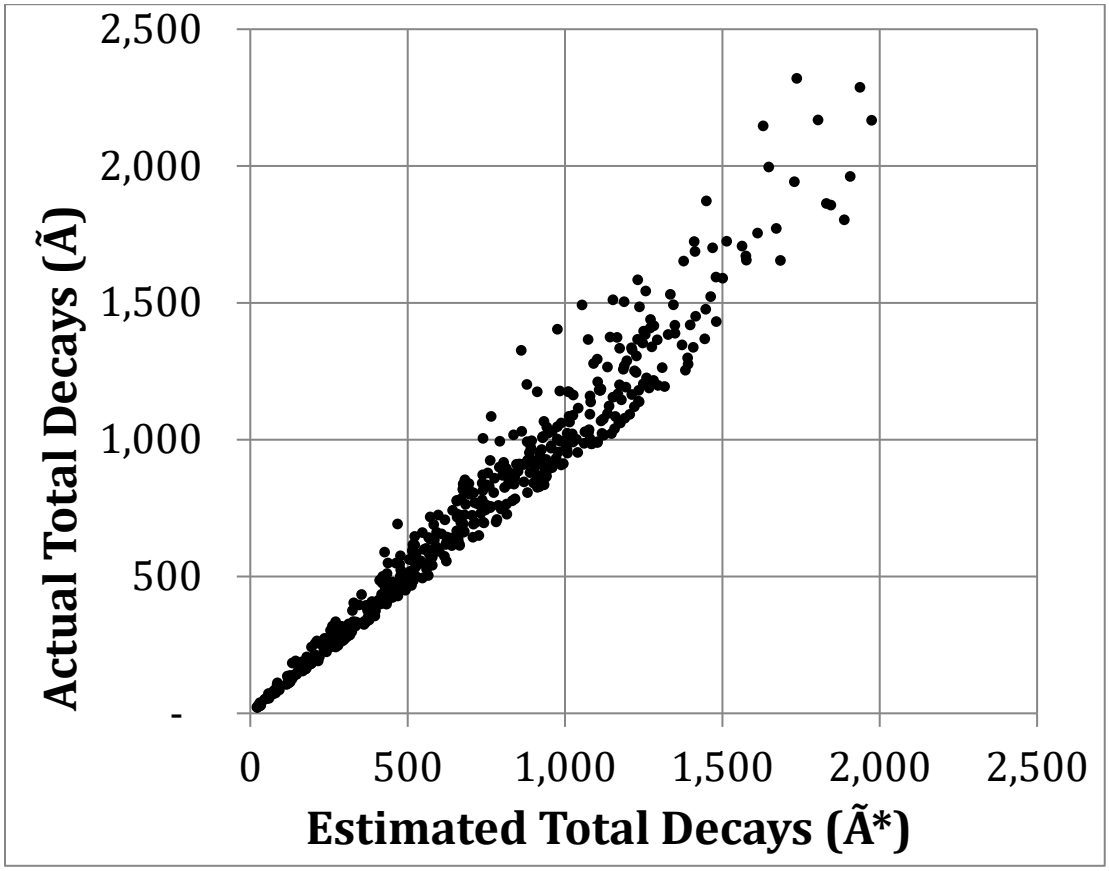


Figure 3. Biexponential simulation comparing actual decays with the single point time estimation.

Retrospective analysis of clinical study: There has been an ongoing clinical trial at the University of Iowa in which three cycles of Y-90 DOTATOC is used to treat patients with neuroendocrine cancer. The radiation dose to the kidneys from the first 2 cycles was determined using the following procedure. After administration of Y-90 DOTATOC and amino acids (~ 5 h), subjects were imaged with PET/CT to quantify kidney activity and then immediately imaged with bremsstrahlung SPECT/CT. Additional SPECT/CT was acquired at 24, 48 and 72 hours. Kidney dose was determined from the SPECT/CT clearance scaled by the PET/CT activity measurement.

The single time point approach was applied retrospectively to this data and used to calculate the kidney dose as a function of sampling time using the population means obtained for **c***, **a*** and $\mathbf{k_2}$ from the 47 patient studies which are given in Table 4. Figure 5 shows a plot of a comparison of the actual kidney dose and the estimated kidney dose at the best sampling time from our protocol (t = 48 hours). This is fairly close to the ideal sample time of 1/k2* = 50 hours.

Table 4. Mean values of c*, a*, and k2* from 47 patient samples.

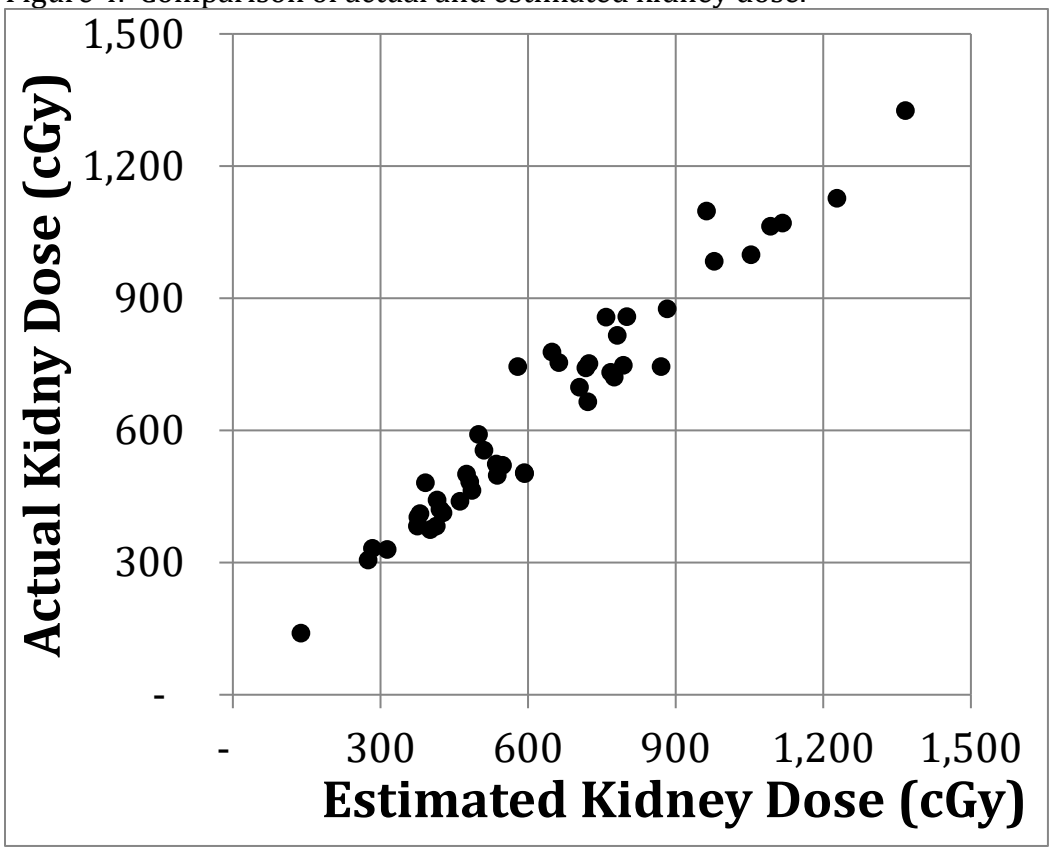
	c*	**a***	**k_2***
mean	1.11	12.3	0.020
standard deviation	1.06	7.3	0.005

Table 5. Retrospective analysis of clinical Y-90 DOTATOC data as a function of sample time.

Sample Time T (h)	**Slope**	**Intercept**	**r^2**	**SEE**
5	0.83	115.4	0.83	108.1
24	0.86	63.8	0.94	66.8
48	0.94	43.6	0.95	60.9

72	0.94	62.3	0.92	75.4

Figure 4. Comparison of actual and estimated kidney dose.



Discussion and conclusions: In this paper we have demonstrated that under conditions where there is exponential clearance of a radiotracer and some prior knowledge about the tracer kinetics is available, it is possible to accurately estimate the total numbers of decays (and thereby radiation dose) from a single time point measurement of activity. The simulations from both the single exponential and biexponential cases show excellent results for the estimations when the appropriate sample time is used. We have demonstrated that the best sample time is equal to the mean time associated with the rate constant k for a single exponential and k2 for the biexponential case. The simulations support this result since the minimum standard error of estimate is found when $T = \tau$. More importantly, the actual clinical results obtained by retrospectively applying the single time dose approach shows the same behavior. These results support the contention that the management of administered activity to patients undergoing radionuclide therapy can be determined with sufficient accuracy with a single time point activity measurement if information exists about population averages for the tracer kinetic parameters. The most favorable condition will be obtained when the rate constant of the long component ($\mathbf{k_2}$) is gaussian distributed with a standard deviation that is less than 30% of the mean. This does appear to be the case for Y-90 DOTATOC in the kidneys and is likely to be the case for other similar agents such as Lu-177 DOTATOC.

There is a straight forward way to predict whether this approach will work for a specific radiotherapeutic agent for which dosimetry data exists. One only needs to plot the actual total number of decays against one of the activity samples that was used to calculate the dose. If there is a strong linear relationship, then subsequent treatments could rely on the single time point method given in this paper. There is reason to believe that the application of this approach will substantially reduce the burden of both patients and the clinic through the reduction of imaging procedures over many days while still providing sufficient radiation dose information to guide the treatment of these patients.

Appendix II

HCCC Clinical Trial Data and Safety Monitoring Plan (DSMP)

Type of Clinical Trial:

- ☒ Investigator-initiated (UI/HCCC)
- ☒ Pilot study
- ☐ Phase I/II
- ☐ Phase III
- ☐ Interventional Treatment
- ☐ Interventional Treatment
- ☐ Investigator-initiated, participating site
- ☐ Phase I
- ☐ Phase II
- ☐ Compassionate-use drug protocol
- ☐ Interventional Non-Treatment

Study risk-level:

- ❑ Level 1—low risk of morbidity or death, * <1% of death or any adverse event
- ❑ Level 2—risk of death* <1% or any adverse event 1% – 5%
- ❑ Level 3—risk of death* 1% – 5% or grade 4 – 5 SAE 1% – 5%
- ☒ Level 4—risk of death* >5% or grade 4 – 5 SAE >5%
- ❑ Drugs being used on a "compassionate" basis

** Risk of death" refers specifically to 100-day treatment-related mortality*

Reporting and Monitoring Requirements:

All institutional investigator initiated trials (IITs), regardless of assigned risk level are subject to routine DSMC monitoring activities which may include but are not limited to review of signed consent documents, eligibility and adverse event reporting.

All institutional IITs have the following **reporting requirements** as part of their DSMP:

- Provide an annual progress report to the DSMC and PRMC
- Register subjects in HCCC's Clinical Trial Management System, OnCore
- Document Adverse Events
- Document protocol deviations

Selected monitoring strategy based on risk-level:

Risk Level 4

Interventional treatment trials involving investigational agents or devices with a risk of death* (>5% or grade 4 – 5 SAE >5%), e.g. all investigator initiated INDs, most Phase I/II trials, gene therapy, gene manipulation or viral vector systems high-risk clinical procedures if performed solely for research purposes. The use of a new chemical or drug for which there is limited or no available safety data in humans.

Study Safety Review

An independent study monitor and/or the DSMC Chair (or designee), will review study data (provided by the PI/available in OnCore) and communicate with the PI at least biannually. A copy of this communication will be forwarded to the DSMC and PRMC Chairs.

Additional Reporting Requirements:

- A scanned copy of the completed eligibility checklist, with screening information and signature from evaluating study team member, will be attached in OnCore for ongoing review by DSMC staff.
- Serious adverse events will be entered directly into an OnCore SAE report by the research team. OnCore will send an automatic notification to the DSMC Chair/acting Chair and staff for review.

- The DSMC utilizes a risk-based monitoring approach. The trial's research records will be monitored at minimum twice per year. Monitoring may be done more frequently depending on the protocol, risks to subjects, reported serious/adverse events, patient population and accrual rate. Records for a minimum of 25% of subjects will be monitored for the entire study.

  Monitoring will involve the following:

  - review eligibility of patients accrued to the study,
  - check for the presence of a signed informed consent,
  - determine compliance with protocol's study plan,
  - determine whether SAEs are being appropriately reported to internal and external regulatory agencies,
  - compare accuracy of data in the research record with the primary source documents,
  - review investigational drug processing and documentation,
  - assess cumulative AE/SAE reports for trends and compare to study stopping rules.

Routine Adverse Event Reporting

For non-serious Adverse Events, documentation will begin after radiotracer injection and continue through 1 calendar day following imaging. For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. [^{90}Y is 64.1 hours. Therefore, 10 radioactive half-lives will be 27days].

Collected information should be recorded in the electronic/Case Report Forms (eCRF/CRF) for that subject. A description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug (if a grade 3 or higher) should be included. Documentation should occur in real time.

Serious Adverse Event Reporting

For any experience or condition that meets the definition of a serious adverse event (SAE), recording of the event will begin after radiotracer injection and continue through 1 calendar day following imaging. For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. [^{90}Y is 64.1 hours. Therefore, 10 radioactive half-lives will be 27days]

Investigators must report to the DSMC any serious adverse events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64). SAEs must be reported via an OnCore SAE Report within 1 business of learning of the event.

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

1. Death
2. A life-threatening adverse event
3. An adverse event that results in inpatient hospitalization OR prolongation of existing hospitalization for ≥ 24 hours

4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. A congenital anomaly/birth defect.
6. 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

Data Monitoring and Management

All studies that undergo PRMC review and/or utilize HCCC Clinical Research Services (CRS) resources are required to register subjects in OnCore. Subject registration includes the following:

- Consent date and the IRB approved consent used
- Date of eligibility and eligibility status (eligible, not eligible)
- On study date and subject's disease site (and histology if applicable)
- On treatment date (if applicable)

If/when eCRFs are developed for this study, the following data monitoring strategy will be used:

Subject Data

In addition to the subject registration and subject status data entered in OnCore for all HCCC trials, research staff also enter the subject study data into electronic case report forms (eCRFs) for HCCC investigator initiated studies. eCRFs are approved by the PI and statistician prior to study activation to ensure the most effective data acquisition. All information on eCRFs will be traceable to the source documents which are generally maintained in the subject's file. eCRF data are expected to be entered into OnCore within 30 calendar days after a subject's study visit.

Forms Monitoring

OnCore eCRF data are monitored on a routine basis (dependent on accrual) to ensure all mandatory fields are entered completely, accurately and within time requirements. The assigned DSMC monitor manages the logistics associated with the data monitoring review. Once the clinical trial is identified for monitoring, the monitor arranges for a selection of cases to review from among the subjects registered in OnCore. As part of the forms monitoring process, the assigned monitor will issue queries within the eCRF to resolve missing, incomplete and/or incorrect information. A member of the research team is expected to respond to monitoring queries within 14 business days.

This process can often identify a misunderstanding or deficiency in protocol requirements early in the study and can improve data quality.

Final Reports

A summary of each subject's data record is continually available to the PI, research staff, and DSMC from OnCore's Biostat Console. The availability of this information is a valuable tool for the preparation of final reports and manuscripts as well as ongoing deficiency reports.

Appendix III – Data forms

IRB# 201708778

- Inclusion
- Exclusion
- Physical exam
- Data collection for ^{90}Y-DOTATOC PET/CT
- Karnofsky performance scale
- Lansky play scale
- QOL questionnaire
- Patient Home Going Instructions

University of Iowa Hospital and Clinics

Inclusion / Exclusion 90Y-DOTATOC Theranostics

Patient:_____

Inclusion Criteria

1 Y / N

Disease not amenable to standard treatment (nonresectable or disease present after one or more surgeries and/or Sandostatin treatment) or subject has failed existing first line chemotherapy, biologic therapy, targeted agent therapy or radiation therapy.

2 Y / N Participation in Iowa Neuroendocrine Tumor Registry (IRB 199911057)

3 Y / N

A pathologically confirmed (histology or cytology) malignant neoplasm with at least one target lesion that is confirmed by conventional imaging and is determined to express somatostatin receptors by ^{68}Ga-DOTATOC (TATE) PET within 6 months prior to treatment with ^{90}Y-DOTATOC.

Date of PET:_____

Date of Conventional Imaging:

4 Y / N

The target lesion is one that either has never received external beam radiation irradiated or has been previously irradiated and has since demonstrated progression. Any local irradiation of the target lesion or any non-target lesions via external beam, conformal or stereotactic radiation treatments must have occurred more than 4 weeks prior to study drug administration. Any full craniospinal radiation, whether or not a target lesion is included in the field, must have occurred more than 3 months prior to study drug administration.

External Beam: N/A // Date:_____//Progression Y / N

Craniospinal radiation: N/A // Date_____

5 Y / N

Life expectancy $\geq$ 2 months at the time of study drug administration.

6 Y / N

Archival tissue from a previous biopsy will be required.

7 Y / N

Age ≥ 6 months-90 years at the time of study drug administration. Age_____

8 Y / N Performance status as determined by Karnofsky ≥ 60% or Lansky Play Scale ≥ 60% at the time of study drug administration.

9 Y / N Completion of Norfolk Quality of Life Questionnaire.

10 Y / N Within 7-10 days of study drug administration, patients must have normal organ and marrow function as defined below:

absolute neutrophil count	$\geq$1000/mm^3
Platelets	$\geq$90,000/mm^3
total bilirubin	<3X ULN for age
AST(SGOT) & ALT(SGPT)	$\leq$10X institutional upper limit of normal for age
Urinalysis	no greater than 1+ hematuria or proteinuria
Renal function	Adults(age 18 or >): Serum creatinine ≤ 1.2 mg/dl; if serum creatinine is >1.2 mg/dL, GFR will need to be ≥ 80 ml/min/1.73m^2 for subjects ≤40 years old, ≥ 70 ml/min/1.73m^2 for subjects between 41-50; ≥ 60 ml/min/1.73m^2 for subjects between 51-60; ≥ 50 ml/min/1.73m^2 for subjects > 60 years old. Children(age <18): creatinine and nuclear GFR ≥ 80 mL/min/1.73 m^2

11 Y / N

Negative pregnancy test. The effects of ^{90}Y-DOTA-tyr^3-Octreotide on the developing human fetus are unknown. For this reason and because Class C agents are known to be teratogenic, women and men of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

12	Y / N	Ability to understand and the willingness to sign a written informed consent document.

Exclusion Criteria

1	Y / N	Pregnant women. Pregnancy status: male // female: premenarchal / >60y.o. / negative serum pregnancy / post menopausal x 12 M / ultrasound negative
2	Y / N	Breastfeeding women.
3	Y / N	Surgery within 4 weeks of study drug administration.
4	Y / N	External beam radiation to both kidneys (scatter doses of <500 cGy to a single kidney or radiation to < 50% of a single kidney is acceptable).
5	Y / N	Prior PRRT with ^{90}Y-DOTATOC (TATE) or ^{177}Lu-DOTATOC (TATE) or ^{131}I-MIBG therapy for this malignancy.
6	Y / N	Another investigational drug within 4 weeks of study drug administration.
7	Y / N	Concurrent, malignant disease for which patient is on active therapy.
8	Y / N	Another significant medical, psychiatric, or surgical condition which is currently uncontrolled by treatment and which would likely affect the subject's ability to complete this protocol.
9	Y / N	Any subject for whom, in the opinion of their physician, a 12-hour discontinuation of somatostatin analogue therapy represents a health risk. Also subjects who have received long-acting somatostatin analogue in the past 28 days or long-acting lanreotide within the past 16 weeks are excluded. Subjects may be maintained on short acting octreotide during the time from last injection of long-acting somatostatin analogue until 12 hrs prior to injection of study drug. Known antibodies to Octreotide, Lanreotide, or DOTATOC or history of allergic reactions attributed to compounds of similar chemical or biologic composition to ^{90}Y-DOTATOC. Last somatostatin therapy: long acting date and type:_____ short acting usage:_____
10	Y / N	Patients who have had chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) of study drug administration or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier. Date of last chemotherapy:_____
11	Y / N	Uncontrolled 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.
12	Y / N	Subject weighs more than 450 pounds. (Subjects who weigh more than 450 pounds will not be able to fit inside the imaging machines.)
13	Y / N	Inability to lie still for the entire imaging time (due to cough, severe arthritis, etc.)

Signature of Investigator: _____

Date:_____

University of Iowa Hospital
Patient:_____

Physical exam for ^{90}Y-DOTATOC

Subject Data

1) Limited Physical Exam:

a) HEENT (Circle or fill in blank): NORMAL **OR**_____

b) Chest (Circle or fill in blank): NORMAL **OR**_____

c) Cardiovascular (Circle or fill in blank): NORMAL **OR**_____

d) Abdomen (Circle or fill in blank): NORMAL **OR**_____

e) Integument (Circle or fill in blank): NORMAL **OR**_____

f) Musculoskeletal (Circle or fill in blank): NORMAL **OR**_____

g) Neurological (Circle or fill in blank): NORMAL **OR**_____

Investigator (Signature)_____ (Date) _____

University of Iowa Hospital
Patient:_____

Data Collection for ^{90}Y-DOTATOC PET/CT

This page will be completed in the PET Center: Date_____

1) Pregnancy test (urine) required? Y / N Results_____

2) ^{90}Y-DOTATOC Dose:_____mCi @ Injection Time_____:_____

3)PET Scan Uptake period _____min.

4) Vital Signs (supine) at PET Completion: P _____, BP _____/_____, RR_____ Temp _____ °C

5) Were any adverse events reported or observed since the ^{90}Y-DOTATOC injection?

☐ No ☐ Yes

If yes, provide a narrative of what the patient reported and/or what was observed.

_____

_____

_____

_____

_____

_____

Signature of PET staff: _____ Date / Time: _____

Patient:_____

Karnofsky Performance Scale

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Required occasional assistance, but is able to care for most of his personal needs.
	50	Required considerable assistance and frequent medical care.
Unable to care for self; required equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; required special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Signature:_____ Date:_____ Time:_____

Patient:_____

Lansky Play Scale

LANSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed	100	Fully active.
	90	Minor restriction in physically strenuous play.
	80	Restricted in strenuous play, tires more easily, otherwise active.
Mild to moderate restriction.	70	Both greater restrictions of, and less time spent in active play.
	60	Ambulatory up to 50% of time, limited active play with assistance/supervision.
	50	Considerable assistance required for any active play, fully able to engage in quiet play.
Moderate to severe restriction.	40	Able to initiate quiet activities.
	30	Needs considerable assistance for quiet activity.
	20	Limited to very passive activity initiated by others (e.g., TV).
	10	Completely disabled, not even passive play.
	0	Dead

Signature:_____ Date:_____ Time:_____

University of Iowa Hospital

Patient Diary

Patient name_____

Treatment # _____

Track the # of cups (8 oz each) of water you drink

Day prior to treatment **(18 hrs)** _____ glasses x .75 = _____glasses

Date:_____

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15

1st day after treatment drink _____ glasses

Date:_____

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15

2nd day after treatment drink _____ glasses

Date:_____

1	2	3	4	5
6	7	8	9	10
11	12	13	14	15

Signature_____ Date_____

Adult (≥18): 38 ml/kg=_____ml ÷ 1000=_____Liters x 4 =_____cups (8 oz each)

Pediatrics (< 18):

11-20 kg: (1000 ml + 50ml/kg for each kg over 10) x 1.5 = _____ml ÷ 1000 =_____Liters x 4 = _____cups (8 oz each)

Pediatrics (<18):

> 20 kg: (1500ml + 20 ml/kg for each kg over 20) x 1.5 = _____ml ÷ 1000 = _____Liters x 4 = _____cups (8 oz each)

UNIVERSITY OF IOWA HOSPITALS AND CLINICS
DEPARTMENT OF RADIOLOGY
DIVISION OF NUCLEAR MEDICINE

RADIATION PROTECTION PRECAUTIONS AFTER Y-90 DOTATOC THERAPY

Radiation from Y-90 DOTATOC does not penetrate outside the body, but a small amount of radiation may be present for about a week following treatment in body fluids, such as blood and urine. Certain precautions are suggested for one week after treatment to limit any potential radiation exposure to others. You should wash your hands thoroughly after urination and use a condom during sexual intercourse. In general, it is not necessary to avoid contact with friends or family during this time, and isolation is not required. You can usually return to work and your usual activities following treatment. Please follow the following instructions after treatment with Y-90 DOTATOC:

1. For 1 week after each treatment, clean up spilled urine and dispose of any body fluid-contaminated material to prevent it being handled (e.g., flush it down toilet or place it in plastic bag in household trash); Wash hands thoroughly after using toilet).

2. For 1 week after each therapy, use condoms for sexual relations.

3. There may be potential risks to the fetus from Y-90 DOTATOC radiation therapy. You should follow effective means of contraception throughout the therapy duration and for 1 year after the completion of the last cycle of treatment.

4. To further protect your kidneys, drink extra water or juice for the next 2 days after discharge. Please, for the sake of your kidneys, keep the fluid diary you have been given. This diary will help us determine if you need extra IV fluid.

If you have concerns after you leave the hospital, please contact Dr. Sue O'Dorisio at 319-356-3595 or

Dr. Yusuf Menda at 319-356-2000.

I have read this explanation or had it read to me and understand it.

_____ _____

Date **Signature**