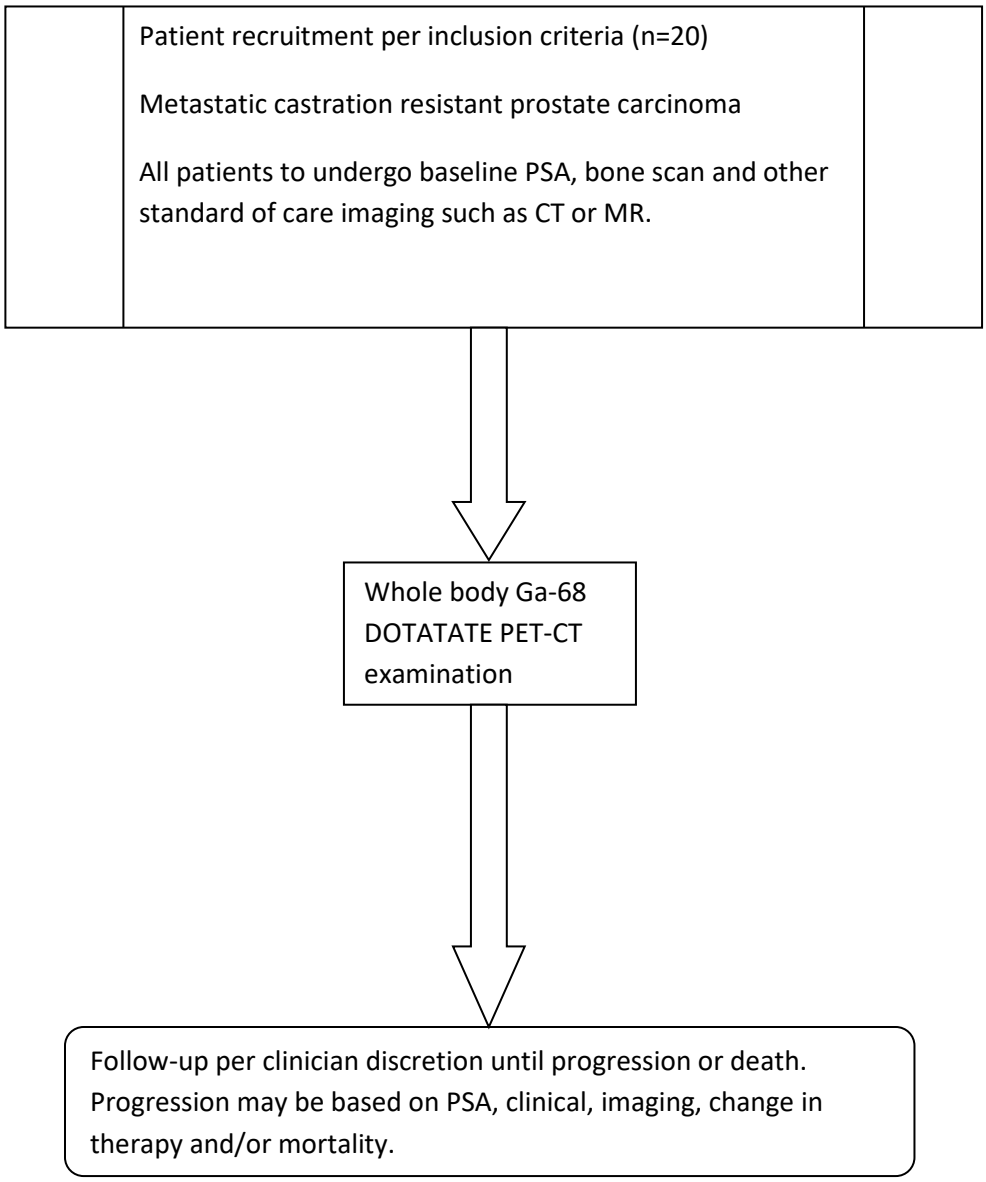
Study Title: Winship 4165-17: Molecular Imaging with Ga-68 DOTATATE PET to Investigate Neuroendocrine Differentiation in Prostate Cancer Patients

Principal Investigator: Mehmet Asim Bilen, M.D.
Emory University
Department of Hematology and Medical Oncology
Emory University School of Medicine, Atlanta, GA
Phone: (404) 778-3693
email: mbilen@emory.edu

Co-Investigator: Ephraim Parent, MD, PhD
Emory University
Department of Radiology and Imaging Science
Emory University School of Medicine, Atlanta, GA
Phone: (404) 712-4843
email: ephraim.parent@emoryhealthcare.org

Supplied Agent(s): **[Ga-68 DOTATATE & NETSPOT]**

Scheme 1:


Patient recruitment per inclusion criteria (n=20)
Metastatic castration resistant prostate carcinoma
All patients to undergo baseline PSA, bone scan and other standard of care imaging such as CT or MR.
Whole body Ga-68 DOTATATE PET-CT examination
Follow-up per clinician discretion until progression or death. Progression may be based on PSA, clinical, imaging, change in therapy and/or mortality.

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Precis/Abstract:

Neuroendocrine prostate cancer (NEPC) is an aggressive form of prostate cancer (PCa) that is usually diagnosed in later stages of the disease. Some patients with PCa that continue to progress while on androgen deprivation (AD) therapy have been shown to have increased risk of having undergone a transdifferentiation process resulting in a neuroendocrine phenotype. There is preliminary evidence that molecular positron emission tomography (PET) imaging with the somatostatin analog, ^{68}Ga-DOTATATE, may allow for whole body, non-invasive identification of NEPC in patients with known prostate cancer. This project will determine the feasibility of imaging with ^{68}Ga-DOTATATE PET/CT in men with PCa that continue to progress while on AD therapy, as a means to identify those patients with early neuroendocrine transdifferentiation and who are at greater risk for poor outcomes. These patients will be followed with standard of care blood work, imaging, and therapy to determine if there is a difference in clinical outcome between the patients with greater neuroendocrine differentiation as demonstrated with ^{68}Ga-DOTATATE uptake on an initial scan and those without. Results of this pilot study may be used to design larger and more comprehensive studies examining clinical utility.

A. Introduction and Background:

Prostate cancer (PCa) is the most common cancer among men in the United States (*1*). AD (androgen deprivation) therapy is the standard for advanced prostate cancer, with the expectation that most patients will eventually convert to an androgen refractory disease and end up dying from castration resistant prostate cancer (CRPC). Neuroendocrine prostate cancer (NEPC) is an aggressive variant of prostate cancer that most frequently arises in later stages of CRPC. Several recent studies indicate that some of the difficulty in treating patients with CRPC may be due to neuroendocrine differentiation (*2*). The detection of NEPC has clinical implications as androgen receptor (AR) targeted therapies have little effect (*3*).

Diagnosis of NEPC depends on histological confirmation and results in a poor prognosis with limited treatment options. As NEPC diagnosis requires tissue sampling, it is generally only detected in the later stages of the disease when patients continue to progress despite antiandrogen therapy (*4*). Almost all prostate cancers show focal neuroendocrine (NE) differentiation, but most demonstrate only rare or single NE cells in the tissue sample. In 5-10% of patients with PCa, there are zones with a large number of clustered NE cells that are detected by chromogranin A (CgA) immunostaining (*5*). In tumors that can be classified as NEPC, the NE component varies usually between 5% and 30% of the tumor mass (*6, 7*). There is mixed evidence as to whether NE differentiation worsens in typical PCa with androgen deprivation therapy (*4, 8, 9*). Some preclinical and clinical studies support increased NE differentiation in hormonally treated PCa (*10-12*).

The mechanisms by which NE cells influence prostate carcinogenesis are not fully understood. The transdifferentiation process from a typical epithelial-like to a NE-like phenotype may be a consequence of the selective pressure induced by treatments that result in decreased androgen levels, stimulation of NE and neural factors, and loss of tumor suppressors and genomic stability (*13, 14*). NE differentiation is usually determined by immunoreactivity for NE markers, such as CgA and neuron specific enolase. NEPC does not usually express AR and prostate specific-antigen (PSA) (*15*) and does not have a high proliferative activity (*16*). Neuroendocrine differentiation can generally be classified into two categories in PCa: small cell carcinoma of the prostate with neuroendocrine phenotypes (SCCP) which accounts for approximately 1-5% of prostatic malignancies (*17*), and recurrent carcinoma displaying NE features. SCCP is a high grade tumor and may occur de novo or as a recurrent tumor in patients who received ADT (*18*).

Due to the high prevalence of NE differentiation in patients who receive prolonged ADT, the true incidence of NEPC remains controversial. Perez et al. evaluated NE differentiation in 450 patients with PCA and only 3 patients demonstrated NE differentiation (*19*). Conversely, Jimenez et al. evaluated 237 metastases from 187 patients with PCa and 92 metastatic biopsies from 79 patients demonstrated positive NE differentiation (*20*). Seven of these patients initially had negative biopsies that successively became positive.

The diagnosis of NEPC is not straightforward and can be misdiagnosed. CgA is considered a specific NE tumor marker and CgA plasma levels could reflect the NE activity present in different organs, including the prostate (*21*). Serum CgA levels and potentially other markers such as pro-gastrin-releasing peptide (*22*) may be useful in identifying those patients with NE differentiation (*23*). However, there is no standard blood marker that is able to accurately determine NEPC levels. Alternatively, there are reports

that somatostatin specific imaging can identify those patients with NEPC. Somatostatin is a neuropeptide that suppresses prostate growth and neovascularization by inducing cell-cycle arrest and apoptosis. Prostate NE cells produce somatostatin and express high levels of somatostatin receptors with autocrine and paracrine function (*24, 25*).

There are a few preliminary case reports that suggest ^{68}Ga-DOTA labeled somatostatin analogs may have high sensitivity in identifying NEPC (*26-29*). In a recent study involving 12 patients with CRPC, all patients had at least 1 blastic neuroendocrine metastasis with increased radiotracer uptake (*30*). Patients with multiple bone metastases also had significantly higher SUVmax when compared to patients with few metastases. However, none of the available studies have correlated ^{68}Ga-DOTA uptake with histologic confirmation nor disease progression. Additionally, to the best of our knowledge, all studies have focused on patients with late stage, chemotherapy resistant prostate cancer without evaluating early transdifferentiation to NEPC as we propose in this study.

In vivo imaging studies using the ^{111}In-labeled somatostatin analog (DTPA-D-Phe)-octreotide, (OctreoScan) have been used clinically for the localization of primary and metastatic lesions expressing type 2 somatostatin receptors on the cell surface of NE tumors. However, Octreotide has imaging limitations including relatively slow pharmacokinetics, high-energy-emissions, and unfavorable patient dosimetry limiting injectable activity. Clinical studies evaluating OctreoScan as a means to determine NEPC in CRPC found a relatively low positive rate (37%) when compared to bone scintigraphy. Octreotide scintigraphy was also not able to identify clinical responders in patients that underwent Octreotide therapy (*31, 32*). ^{68}Ga-DOTATATE, as compared to OctreoScan, has faster imaging pharmacokinetics and demonstrates higher affinity for somatostatin receptors than Octreotide (*33*). In prostate- and non-prostate neuroendocrine carcinoma patients, ^{68}Ga-DOTATATE demonstrated higher lesion detection rate than Octreotide (*26, 34*) and changed the clinical management in patients with non-prostate neuroendocrine carcinoma that previously had negative Octreotide studies (*35*).

B. Objectives

The goal of our proposal is to determine the feasibility of identifying neuroendocrine transdifferentiation in NEPC patients using noninvasive imaging, and assess whether such an early imaging biomarker can predict eventual progression. Specifically we plan to employ the newly FDA approved PET radiotracer ^{68}Ga-DOTATATE as an off-label probe for somatostatin receptors that have been shown to be upregulated in prostate cancer when compared to somatostatin receptor expression in normal prostate tissue and in benign prostate hypertrophy (*36, 37*). This upregulation of somatostatin receptors in early castration resistance may explain in part the mechanism of neuroendocrine transdifferentiation (*36, 38*). While prostate cancer may be indolent, it can also be rapidly lethal in a subset of patients. Early identification of this progression could potentially be utilized in the future to study adaptive therapy strategies. In addition, NEPC is underdiagnosed as men rarely undergo biopsy of metastatic lesions after spread to soft tissue and bones which is required for histologic confirmation (*2*). Furthermore, standard biopsy is subject to sampling error both within a lesion itself and on a global basis, since all lesions cannot ethically undergo biopsy. Therefore, we will determine if global body interrogation via a noninvasive imaging method to probe for somatostatin receptor upregulation is feasible, and generate preliminary data to investigate the relationship of the degree of PET uptake with treatment outcome with

our ultimate goal to determine if uptake on an initial ^{68}Ga-DOTATATE PET can be used as an early predictive imaging biomarker of outcome.

Primary Objective. Establish the feasibility of using ^{68}Ga-DOTATATE PET as a predictive imaging biomarker for neuroendocrine transdifferentiation in prostate cancer.

Secondary Objective. Correlate progression of disease with degree of uptake on ^{68}Ga-DOTATATE PET examination.

Rationale. As has been outlined in Section A of this proposal, there is no established noninvasive imaging or laboratory technique to identify neuroendocrine transdifferentiation in prostate cancer (NEPC). Our hypothesis is that interrogating the upregulation of the somatostatin receptor which occurs within a subset of prostate cancer patients, or prostate cancer metastatic lesions, is possible by utilizing ^{68}Ga-DOTATATE PET as a visual biomarker, which specifically binds to the somatostatin receptor SSTR2 (the somatostatin receptor most upregulated in NEPC) (*36*). To that end we will perform ^{68}Ga-DOTATATE PET imaging on up to 20 patients to determine the degree of uptake in patients with metastatic prostate cancer (mCRPC) who is about the start first line of treatment (abiraterone acetate or enzalutamide) for castration resistant disease. We believe that this inflection point best balances early detection of potential neuroendocrine transdifferentiation with imaging, as these patients typically have higher ECOG (Eastern Cooperative Oncology Group) performance status than those further along the continuum of their treatment. Patients with mCRPC will continue to receive standard of care therapy with no clinical decisions being made based upon the results of the ^{68}Ga-DOTATATE PET study. The goal of this study is not to compare the diagnostic performance of ^{68}Ga-DOTATATE in neuroendocrine tumors with other imaging modalities, as this has already been externally verified (*39-41*).

Our hypothesis is that patients with higher levels of ^{68}Ga-DOTATATE uptake on an initial PET scan (presumed NEPC) will have a shorter time to progression while on oral agents (abiraterone acetate or enzalutamide) due to inherent resistance to antiandrogen based therapeutics (*42*) when compared to those with lower ^{68}Ga-DOTATATE uptake.

To investigate this secondary objective, we will correlate degree and intensity of uptake of ^{68}Ga-DOTATATE with subsequent progression of disease, being determined by standard of care whole body bone scans (*43*) and CT/MR imaging (*44*), as well as clinical parameters. We will utilize 6 and 12 month progression free survival outcomes within the context of our one year funding mechanism, and believe these parameters are realistic for this patient population. However, as it is likely that some of the patients will not have evidence of progression until after completion of our funding mechanism, patients will be consented to be followed until there is clinical evidence of progression. To the best of our knowledge, there are no studies that have investigated ^{68}Ga-DOTATATE uptake in patients who have recently become castration resistant nor evaluated the correlation between the level of ^{68}Ga-DOTATATE uptake and treatment outcome with oral agents (abiraterone acetate or enzalutamide). This study will use standard of care, well-defined and accepted measures of progression free survival, to correlate with uptake on an initial ^{68}Ga-DOTATATE PET as a surrogate for degree of neuroendocrine transdifferentiation. This study will not be utilizing a follow-up ^{68}Ga-DOTATATE PET for therapy response.

C. Study design and methods

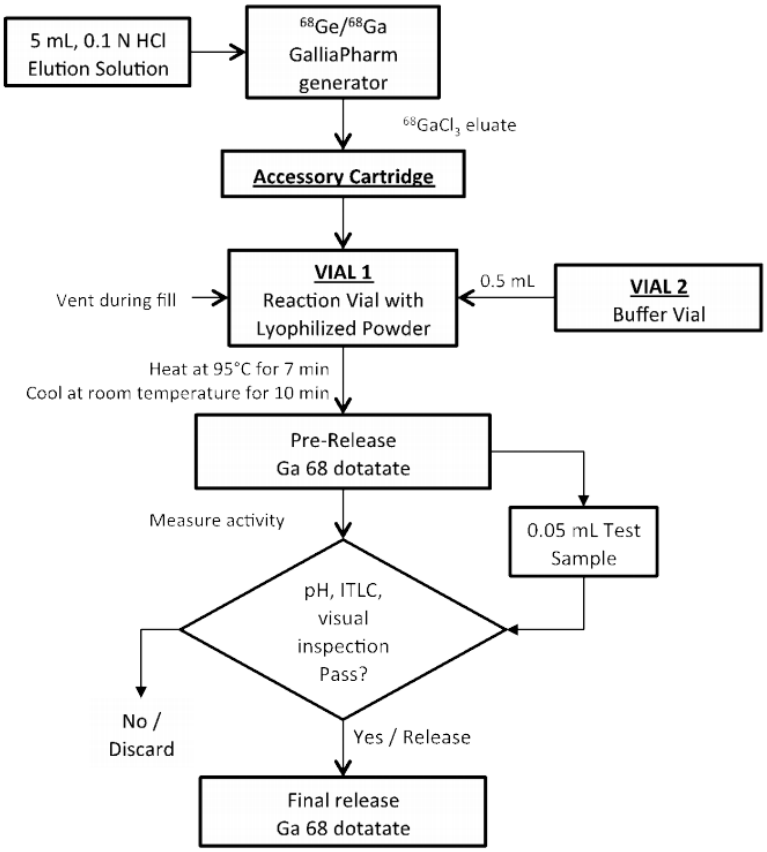
Experimental design. We will undertake a study with 20 patients who have castration resistant metastatic prostate carcinoma with skeletal and/or nodal and/or visceral involvement. The patients will serve as their own control. We will perform a Ga-68 DOTATATE PET-CT of the whole body as per the detailed protocol below (Objective 1). Prior to the Ga-68 DOTATATE PET-CT, all patients will undergo conventional staging including ^{99m}Tc MDP bone scanning and CT or MR within 90 days which are standard of care at our institution. This study will not interfere with standard patient evaluation or delay therapy. Other imaging may also be obtained clinically.

The patients will be also followed up in the context of this study (per clinical routine) for at least one-year post-therapy to determine if the degree of Ga-68 DOTATATE uptake correlates with progression free survival of disease as evidence by imaging progression, PSA progression, clinical progression, which defined by investigator and mortality (Objective 2). It is expected that higher Ga-68 DOTATATE uptake will lead to a shorter time to progression with discrete foci of uptake greater than liver being defined as positive for enhanced receptor expression, and thus indicative of malignancy.

C.1 Ga-68 DOTATATE radiolabeling

Radiochemistry staff will perform syntheses, conduct quality control tests and approve the final preparation following USP standards according to the NETSPOT prescribing information. The NETSPOT kit is supplied as 2 vials and an accessory cartridge which allows for direct preparation of Ga 68 DOTATATE injection with the eluate from an Eckert & Ziegler GalliaPharm Germanium 68/Gallium 68 (Ge 68/Ga 68) generator (Scheme 2). Ge 68 breakthrough and other gamma emitting radionuclides should be ≤ 0.001%. The Ga 68 chloride is sterile as eluted from the GalliaPharm generator. Vial 1 (reaction vial with lyophilized powder contains: 40 mcg dotatate, 5 mcg 1,10 phenanthroline; 6 mcg gentisic acid; 20 mg mannitol) is pierced with a sterile needle connected to a 0.22 micron sterile vented filter to maintain atmospheric pressure within the vial during the reconstitution process. Using a 1 mL sterile syringe, the required volume of the reaction buffer from Vial 2 (buffer vial contains: 60 mg formic acid; 56.5 mg sodium hydroxide and water for injection) is withdrawn. The generator is eluted directly into Vial 1 through the accessory cartridge (accessory cartridge contains: 660 mg porous silica. The accessory cartridge reduces the amount of Ge 68 potentially present in generator eluate) to reconstitute the lyophilized powder with 5 mL of eluate. The syringe and the 0.22 micron sterile air venting filter are removed from vial 1, and Vial 1 is moved to the heating hole of the dry bath, leaving the vial at 203 °F (95 °C, not to exceed 98 °C) for at least 7 minutes (not exceeding 10 minutes heating) without agitation or stirring. After 7 minutes, the vial from the dry bath is placed in an appropriate lead shield and let cool down to room temperature for approximately 10 minutes. After which, the appropriate quality controls are performed according to recommendations. The amount of radioactivity injected into the patient's IV is recorded immediately prior to injection, with residual activity in the syringe recorded immediately after injection. The single IV injection will contain a maximum mass dose of 68Ga-DOTATE of ≤50 μg. The total volume administered is typically between 2 and 20 mL with the recommended amount of radioactivity to be administered for PET imaging is 2 MBq/kg of body weight (0.054 mCi/kg) up to 200 MBq (5.4 mCi).

Scheme 2:



C.2 PET-CT imaging protocol

PET-CT images will be acquired on a GE Discovery 690 (16 Slice) or other PET-CT scanner. All studies will use measured attenuation correction (routinely acquired through the initial CT portion of the scan). Dead time, detector efficiency and scatter corrections will be applied using the routines supplied by the manufacturer. The resulting images will be quantitatively calibrated and have 6 mm isotropic resolution.

Patients are encouraged to drink a sufficient amount of water to ensure adequate hydration prior to administration of Ga-68 DOTATATE. Patients are encouraged to drink and void frequently during the first hours following administration to reduce radiation exposure and should void prior immediately prior to placement on the imaging table. There are no dietary restrictions for or nor activity limitations prior to Ga-68 DOTATATE scans. Within one hour prior to scanning, the patient will drink 450 ml of oral contrast as possible to maximize conspicuity of abdomen and pelvic structures. IV contrast will not be used. An intravenous catheter will be placed into an antecubital vein for a bolus infusion of Ga-68 DOTATATE (5 mCi). The subject will be placed in the tomograph gantry for completion of the PET/CT scan which will include a whole body acquisition from skull to mid-thigh with images acquired 55 to 70 minutes after the intravenous administration of the Ga-68 DOTATATE.

Summary of PET-CT Scanning Procedure

1) The patient will then receive a bolus of Ga-68 DOTATATE injected IV of approximately 5 mCi (185 MBq).
2) The patient will be placed in the tomographic gantry for a CT scan of the skull to proximal thighs (80-120 mA) to be utilized for anatomic imaging and correction of emission data (approximately 1 minute). Patient arms will ideally be positioned overhead to minimize beam hardening and field of view truncation artifacts.
3) Images will be acquired between 55 and 70 minutes after injection. A 3 minutes per bed position PET acquisition will start at the proximal thighs and extend for 7 table position to the skull base or higher.
4) The entire study including injection of radiotracer should take approximately 120 minutes or less.

C.3 Systemic therapy

Patients with metastatic prostate cancer who are failing standard androgen deprivation therapy and diagnosed with castration resistant disease will be the target recruitment demographic for scanning with Ga-68 DOTATATE. Following scanning with Ga-68 DOTATATE, patients will be treated according to standard of care per the clinician`s discretion with oral agents (abiraterone acetate or enzalutamide) or other FDA approved agents. The results of the Ga-68 DOTATATE PET/CT will not influence the clinician's treatment decisions.

C.4 Routine Laboratory and Imaging Biomarkers

As per clinical routine, all patients will undergo routine imaging including CT, MR, FDG/PET/CT or bone scan and PSA evaluation within 90 days prior to the Ga-68 DOTATATE PET-CT study. Subsequent routine imaging and standard laboratory analysis (e.g. PSA level) will be performed according to the clinician's discretion. This is considered a clinical standard and will not be funded from the project budget. These studies will be performed with the standard Emory protocols on file.

C.5 Image Analysis of Ga-68 DOTATATE PET-CT

Methods: The methods of image analysis to be used for the Ga-68 DOTATATE PET-CT are as follows:

1) Images will be reconstructed with iterative technique and hardware fused (PET to CT) on a MimVista or similar workstation which enables SUV (mean, maximum) and total lesion activity as well as standard bi-dimensional size measurements of lesions. Whenever possible we will use 3 dimensional PET-Edge conformational regions of interest (ROI) to encompass the entire structure under question such as a lymph node or prostatectomy bed.
2) Visual inspection of the PET-CT images in separate sessions by a board certified nuclear medicine physician/nuclear radiologist. Up to 5 representative index lesions in each category will be selected as markers of Ga-68 DOTATATE uptake. If 5 lesions each are not definable in each patient, all demonstrable lesions up to 5 will be utilized. Lesions chosen will be independent but may coincide with index lesions on conventional imaging.
3) Ga-68 DOTATATE organ and tumor uptake will be quantified using maximum standardized uptake values (SUVmax) and mean standardized uptake values (SUVmean). SUVmax of pathological findings will be compared with accumulation of the radiotracer in a liver as a reference organ. Definitive criteria defining high, moderate, and mild uptake have not been

established. However, based on literature examples (*30*), a diagnosis of high Ga-68 DOTATATE uptake will be assigned to lesions with a SUVmax ≥ 8, moderate Ga-68 DOTATATE uptake will be assigned to lesions with a SUVmax ≥ 5, and mild Ga-68 DOTATATE uptake will be assigned to lesions with uptake greater than liver and/or SUVmax ≥ 3.

4) In addition, the measurements above will be supplemented by the following from RECIST 1.1 Criteria (*44*).

C.6 Comparison to Ga-68 DOTATATE uptake with standard response criteria

For response criteria to oral agents, patients will serve as their own controls.

1) Ga-68 DOTATATE PET-CT uptake will be correlated with clinical response criteria including time to PSA progression, which is defined as the time from initiation of treatment to the date of earliest objective evidence of PSA progression, which will be assessed at each clinic visit, and is defined as time from initiation of treatment to the date of PSA absolute increase ≥ 2 ng/mL and ≥ 25% above nadir or baseline values confirmed by a second consecutive value obtained at least 3 weeks later or death due to any cause. Repeat imaging during treatment will obtain per clinician discretion such as when any sign of clinical progression or PSA progression. Radiological progression of bone lesions will be determined by using Prostate Cancer Working Group 3 (PCWG3) recommendations for clinical trial conduct in castration resistant disease and radiographic progression of soft tissue lesions will be determine by using modified RECIST 1.1 criteria.

We will utilize 6 and 12 month progression free survival outcomes and patients will be consented to be followed until there is any evidence of progression.

C.7 Follow up

This will be done as part of routine standard of care without special visits required of the patient. Clinical visits will be determined by clinician`s discretion as will be ordering of laboratory tests including CBC, CMP, testosterone and PSA. Within one year after Ga-68 DOTATATE PET-CT imaging (or earlier if progression), imaging response to therapy using standard criteria including repeat CT or MR, bone scan and PSA will be obtained. Accrual goals will be 4 patients every year for a total of 20 patients in 5 years.

D. Patient selection

Patients will be recruited from the Genitourinary Medical Oncology clinic at Winship Cancer Institute per the inclusion and exclusion criteria below. It is estimated that a minimum of 20 patients per month who meet inclusion criteria are seen in the Genitourinary Medical Oncology clinic at Winship Cancer Institute. However, if we do not enroll our target goals, patients with mCRPC from Georgia Cancer Center for Excellence at Grady will be referred to this study as Dr. Bilen also staffs that genitourinary oncology clinic.

Inclusion Criteria:

1) Patients must be 18 years of age or older.
2) Patients with metastatic castration resistant prostate carcinoma with skeletal, visceral and/or nodal involvement.
3) Ability to lie still for PET scanning

4) Patients must be able to provide written informed consent

Written consent will be obtained from the patient prior to the PET scan day and documented. Eligibility checklist will be verified with the patient prior to the scan day once consent is obtained.

Procedures:

PET Scan Day

- Obtain written informed consent if not earlier obtained.
- Inclusion/exclusion criteria review if not earlier done.
- Medical history and medication review if not earlier done.

E. Statistical Analysis

Patient baseline characteristics and digress of 68Ga-DOTATATE uptake will be summarized using descriptive statistics. The inter-rater agreement will be assessed by Kappa statistics or intra-class correlation coefficient. The degree of uptake will be plotted against length of time to progress, and the association will be described by Spearman correlation coefficient with 95% confidence interval (CI). In addition, we will dichotomize degree of update by median and defined it as high vs. low, and apply Wilcoxon rank sum test or Fisher exact test wherever appropriate. The association with progression free survival will be able to describe by Kaplan-Meier method along log-rank p-value (due to the small sample size, this may not be feasible). This is a pilot study with main goal to evaluate the feasibility, and no statistical power is possible.

F. Adverse Events

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug-related.

A significant shift from baseline which can be attributable to the radiotracer injection and not the patient's medical condition will be considered an unexpected AE. **An event greater than 10 hours post scan will not be considered an AE since the radiotracer has effectively decayed by 10 hours.**

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (June 14, 2010) will be used as a guide address potential AEs subject to limitations above and medical and scientific judgment as to plausibility of such criteria in a diagnostic radiotracer study.

Adverse Event Reporting

An SAE is defined as any adverse event occurring at any dose that results in any of the following

outcomes:

• death

• a life-threatening adverse experience

• inpatient hospitalization or prolongation of existing hospitalization

• a persistent or significant disability/incapacity

• a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed. Any serious adverse events (see above) will be communicated by the PI to the Emory IRB using standard adverse event reporting forms. In case of a serious adverse event definitively ascribed to 68Ga-DOTATATE imaging, Drs. Bilen, Parent, and Schuster, will meet formally or communicate via email to investigate the reported adverse event.

The Investigator will report all Serious Adverse Events (as defined above) occurring in a subject on the day of or within 28 days following the Agent administration to Pharsafer® Associates Ltd ("**Pharsafer**") by telephone (+44 1483 212151), FAX (+44 1483 212178) or e mail (drugsafety@pharsafer.com). Events should be reported to Pharsafer within 24 hours of the investigator becoming aware of the events occurrence. The Investigator is responsible for informing the ethics committee of serious events occurring during the study in compliance with local regulations.

Any patient death that may be due to the study procedure (i.e. severe radiotracer reaction), unanticipated problem, would be promptly reported to the Emory IRB office. Additionally any patient death not associated with the study procedure or serious unanticipated event(s) (i.e. radiotracer allergy) will be reported to the Emory IRB and FDA upon continuing review. Protocol deviation/non-compliance will be reported according to IRB Policies & Procedures.

G. Data and Safety Monitoring Plan (DSMP):

Patients will be monitored by the technologists and study nurse before and after whole body Ga-68 DOTATATE PET-CT examination for any adverse events/reactions per clinical routine. They will be given contact phone numbers to call if they experience any problems (i.e. problems with the IV site, any allergic reaction symptoms). They will be followed routinely by their referring oncologist with clinical exams, and the PI will work with the co-investigators and referring physicians to ensure that the patients continue to follow up as scheduled.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will also oversee the conduct of this study (every 6 months or annually – depending on the risk level of the protocol). This committee will review pertinent aspects of study conduct including patient safety, compliance with protocol, data collection and efficacy. The committee will review the charts of 10% of patients enrolled to the study and two of the first 5 patients entered to the study. The Committee reserves the right to conduct additional audits if necessary. The Principal Investigator (PI) or designee is responsible for notifying the DSMC about the accrual of patients when the first 5 have been entered to the study.

It should be kept in mind that this patient cohort typically has a median survival of 18 months and it is of much greater probability that an SAE may occur and be related to the patient's natural disease progression and/or therapy. Only those SAE's related to the radiotracer Ga-68 DOTATATE itself will be reported as part of this trial as the therapy itself is not considered experimental.

H: Pharmaceutical, biologic, and device information

Radiation Dosimetry. The study will be approved by not only the Emory IRB but also the Radiation Safety Committee. The maximum number of PET studies a patient will receive in one year is 1 Ga-68 DOTATATE study.

Depending on the distribution of the radionuclide in the body, the whole body dose may not be the critical factor in single or longitudinal studies. It is also of interest to know which organ receives the highest absorbed dose. This organ is referred to as the critical organ. Often the limit for an individual organ dose is reached before the limit established for the whole-body. The United States Food and Drug Administration in Title 21 CFR Part 361 limits the whole body radiation dose to adult research subjects to less than 3 rem (30 mSv) for a single injection and 5 rem (50 mSv) effective dose equivalent (EDE) annually. A single organ cannot receive more than 5 rem (50mSv) in a single injection and 15 rem (150 mSv) effective dose equivalent annually. These constraints on dose will limit the maximum number of injections for research subjects. The studies proposed in this application fall within these guidelines.

A 5 mCi (185 MBq) injection of Ga-68 DOTATATE results in a whole-body effective dose equivalent of 0.48 rem (4.8 mSv) and critical organ absorbed doses of 2.3 rad (23.1 mGy) to the urinary bladder wall, 1.7 rad (17.0 mGy) to the kidneys, and 5.2 rad (52.2 mGy) to the spleen (*45*).

The level of radiation for the PET scan is the same as received in widely used diagnostic studies such as the currently used 18F-FDG and is equal to or less than 80 percent of the amount allowed a radiation worker in a year (5 rem). The calculated whole body exposure to the individual will be less than 0.5 rem for each PET scan (1.05 total). Radiation exposure for the transmission images on the GE690 PET-CT (with which this study would be conducted) is 0.55 rem (5.5 mSv).

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Required Data Calendar. **(Note that this calendar does not preclude other routine or standard clinical labs.)**

* (or earlier if progression)

	Screening	Ga-68 DOTATATE PET-CT ≤ 90 days Post screen	Continue therapy
Informed consent		**X**	
Standard of care medical history & examination	**X**		
Bone scan	**X**		
CT or MR	**X**		
Standard of care laboratory	**X**		**X**
Ga-68 DOTATATE PET-CT		**X**	
Systemic Therapy			**X**