PROTOCOL TITLE: A Phase 2 Comparison Study of 68Ga-PSMA-HBED-CC Positron Emission Tomography (PET)/CT or PET/MRI Imaging to Magnetic Resonance Imaging (MRI) alone in Men with Prostate Cancer

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IRB Protocol #: 1706018301

ClinicalTrials.gov Identifier: NCT03439033

Current Version April 23, 2020

Prior Version Dates:

Version February 22, 2019
Version September 04, 2018
Version June 04, 2018
Version February 13, 2018

## BACKGROUND

Magnetic resonance imaging (MRI) has proven a valuable tool in the detection, localization, and staging of prostate cancer (PCa). Multiparametric MRI, with diffusion weighted imaging (DWI) and dynamic contrast enhanced (DCE) perfusion imaging, is approximately 80% accurate for the detection of significant PCa in the prostate, and performs similar to computed tomography (CT) and radionuclide bone scan for detection of metastases. However, recent studies have found that conventional MRI has intermediate sensitivity for a patient's status regarding nodal metastases. Positron emission tomography (PET), on the other hand, has the potential to be the most sensitive imaging modality for whole body surveys of metastatic disease, depending on the radiopharmaceutical utilized. Fluorodeoxyglucose (FDG), which measures glucose metabolism and is the most widely utilized PET tracer, is sensitive for most cancers, but not PCa. New, specific PET tracers, which target the extracellular domain of prostate specific membrane antigen (PSMA), have shown similar to superior performance compared with MRI in the detection of metastatic disease and potentially similar performance to MRI for characterization of cancer in the gland. The advent of combination PET-MRI scanners allows for direct comparison of these two techniques, allowing the characterization of the performance of each, and their combination, for the detection and grading of prostate cancer in a number of scenarios, from presumed organ-confined disease for which focal therapy is planned, where accurate measurement of the extent of disease is crucial, to management of advanced disease and biochemical recurrence, where understanding the location and distribution of metastatic lesions could guide radiation therapy. The purpose of this study is to not only compare the sensitivity and specificity of both modalities, but to demonstrate the superiority of 68Ga-PSMA-HBED-CC PET to MRI for sensitivity, and its non-inferiority for specificity.

## STUDY DESIGN

This is a multi-reader methodological study comparing the diagnostic value of 68GaPSMA-HBED-CC PET/CT or 68Ga-PSMAHBED-CC PET/MRI over MRI alone, using histologic confirmation or serial follow-up for up to 3 years as the gold standard for determination of primary prostate cancer or prostatic cancer recurrence/metastasis. Patients at moderate- to high-risk for metastatic disease who are scheduled for (the below outlines the patient cohorts recruited for this study): 1. High risk primary disease with planned surgical extirpation and lymph node dissection (oligometastatic disease) 2. Presumed intermediate or high-risk primary disease with planned targeted prostate biopsy 3. Conventional imaging equivocal or suggestive of metastatic disease, with planned biopsy of presumed metastasis a) PSA less than 0.5 ng/mL b) PSA greater than 0.5 ng/mL 4. Planned focal therapy of intermediate- to high-risk primary lesion. 5. Elevated PSA with no conventional imaging suggestive of metastatic or recurrent disease a) PSA less than 0.5 ng/mL b) PSA greater than 0.5 ng/mL. The purpose of the study is to compare 68Ga-PSMA-HBED-CC PET to conventional MRI. We hypothesize that this will demonstrate the superiority of 68Ga-PSMA-HBED-CC PET to MRI for sensitivity, and the non-inferiority of 68Ga-PSMA-HBED-CC PET to MRI for specificity. This is a paired, case-control design that is appropriate to statistically evaluate the difference in sensitivity and specificity between the two imaging modalities. Therefore, the estimation of Therefore, the estimation of population prevalence is not a study objective, and estimation of clinical utility through calculation of positive and negative predictive

values is not appropriate. Imaging studies and follow up subject scans will be organized so that a panel of independent readers will evaluate the MRI and PET studies to assess the level of suspicion for prostate cancer (see attached statistical methods for more details). The imaging data will be encoded and archived within IDEAL. The non-imaging data collected will be encoded and archived in a RedCap database. Participants will have 1-2 visits. During visit 1 they will receive a single IV dose of 68Ga-PSMA-HBED-CC (study drug) followed by either a PET/MRI scan or, in the event that an MRI cannot be performed concurrently and/or the subject has already undergone an MRI of the abdomen/pelvis or pelvis only, a PET/CT scan 1-3 hours after injection. The PET/MRI will be a combination of standard of care and research (the MRI portion is standard of care but the PET is for research only). The PET/CT scan will be for research purposes only. All subjects will have vital signs assessed before and after study drug injection for safety purposes (not as a research procedure). Histopathological assessment will be performed, as standard of care, on tissue obtained from either RP, with or without EPLND, or biopsy of either the primary lesion or presumed metastases, within two weeks of study drug dosing, where indicated; such standard of care data will be reviewed via chart review. All subjects will be followed via chart review for three years after their visit 1 scan. 68GaPSMA-HBED-CC image data will be evaluated for visible uptake and compared with histopathology. Both 68Ga-PSMAHBED-CC PET and MRI (or CT) image data will be individually assessed for appropriate staging. In the event that subjects undergo focal therapy and are scheduled to receive a post-treatment MRI as standard of care, they will be asked to participate in an optional, second posttreatment visit performed the same way as visit 1 (pre-treatment MRI); a single IV dose of 68Ga-PSMA-HBED-CC (study drug) followed by a PET/MRI scan, 1-3 hours after injection. Please note, in the event that subjects undergoing focal therapy receive a PET/CT instead of a PET/MRI, they will not have the option of participating in a second visit.

INCLUSION AND EXCLUSION CRITERIA

INCLUSION CRITERIA

1. Male aged 21 years or older.

2. Ability to provide signed informed consent and willingness to comply with protocol requirements.

3. Pathologic confirmation of adenocarcinoma of the prostate gland or high clinical suspicion (PSA > 4 ng/mL, or PSA density > 0.15 ng/mL2, or PSA doubling time < 2 years).

4. Meet one of the following 5 Criteria:

a. Planned for surgical extirpation, which may or may not include lymph node dissection (high risk primary disease)

b. Planned for targeted biopsy of primary lesion

c. Conventional imaging equivocal or suggestive of prostate cancer metastasis/es

d. Planned focal therapy (with or without radiation therapy) with serial follow-up

e. Elevated PSA with no conventional imaging suggestive of metastatic or recurrent disease

5. a. If part of PET/MRI cohort, subject will undergo clinically indicated MRI imaging prior to treatment. Or b. If part of PET/CT cohort, subject will have had clinically indicated MRI within 3 months prior to treatment.

6. Participants must agree to use an acceptable form of birth control throughout the study period. Participants must use condoms for a period of seven days after each injection, if engaged in sexual activity."

EXCLUSION CRITERIA

1. Clinical and/or technical factors that would compromise statistical analysis of the PET and/or MRI.

2. If part of PET/MRI cohort and patient cohort 3 or 5, subject does not plan to have a prescribed abdomen2/ MRI

3. If part of PET/MRI cohort and patient cohort 1, 2 or 4, subject does not plan to have a prescribed pelvis MRI

4. If part of PET/CT cohort and patient cohort 3 or 5, subject does not have previous MR imaging of abdomen and pelvis

5. If part of PET/CT cohort and patient cohort 1, 2 or 4, subject does not have previous MR imaging of pelvis

6. If part of PET/CT cohort, investigator review determines that previous MR images do not meet institutional quality standards

7. If part of PET/MRI cohort, contraindications to MRI

8. Contraindications to PSMA IV administration

9. Other unspecified reasons that, in the opinion of investigators, make the subject unsuitable for enrollment

DATA AND SAFETY MONITORING PLAN

Data is recorded both electronically and in paper format Data will be kept in the PIs locked office Data will be kept on a password-protected computer Data will be saved on a secure server.

The study will be stopped if there are any serious adverse events related to any of the study procedures, but this is not anticipated. However, subjects who experience an AE of grade 3 or higher will be reviewed and removed from the study. Vital signs will be obtained before and after the dose administration.

This study will follow standard operating procedures for reporting adverse events and utilize the AE grading from Terminology Criteria for Adverse Events v4.0. AE grading will be defined as the

following categories: Grade 1- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2- Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate Activities of Daily instrumental Living. Grade 3- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living. Grade 4- Life-threatening consequences; urgent intervention indicated. Grade 5- Death related to AE.

The primary endpoint is to assess the sensitivity and specificity on per-subject basis between the diagnosis from MRI and 68Ga-PSMA-HBED-CC. Based on the previous literature, we anticipate a 0.58 sensitivity and a 0.82 specificity that are consistent across all seven scenarios based on MRI. Here, we first assume that an increase in sensitivity of 30%, i.e. 0.75 under 68Ga-PSMA-HBED-CC will provide little benefit over existing MRI approach. Therefore, our statistical test for 68Ga-PSMA-HBED-CC sensitivity will be based on the null hypothesis of a value as 0.58 with the alternative hypothesis of at least 0.75. The sample size calculation is based on a Wald-test statistic under an arcsine transformation of proportion and an effective size 0.36. As a result, a sample of 34 true positive patients will give us 80% power to reject the null hypothesis at a onesided 0.1 significance level. In terms of specificity, we will expect a non-inferior performance from 68Ga-PSMA-HBED-CC compared with MRI. By assuming delta to be the estimated difference in the specificity between MRI and 68Ga-PSMA-HBED-CC, the statistical test for this metric will be constructed under the null hypothesis that the actual difference is larger than delta and the alternative hypothesis of that is smaller or equal to delta. The test statistic will asymptotically follow a normal distribution based on based on a restricted maximum likelihood estimation approach with the sample size obtained by a Wald-test statistic. Assuming delta=0.15, a sample of 12 true negative (TN) patients will allow us 80% power for this a one-sided 0.1 significance level test. In summary, we need a total of 46 patients (34 TP, 12 TN) for each scenario, leading to a total of 322 patients. Since we expect a 20% drop-off rate, we therefore intend to recruit 402 subjects. The sensitivity and specificity for the diagnosis under 68Ga-PSMA-HBED-CC and MRI on a per patient basis will be summarized as descriptive statistics and the two-sided 90% confidence intervals (CIs) will be constructed using the Wilson score method. The superior of 68Ga-PSMA-HBED-CC MRI for detection of metastatic prostate cancer will be determined if two of the three readers show statistically significantly better performance on sensitivity based on the McNemar test of discordant pairs for subjects and a non-inferiority specificity performance based on overlapped confidence intervals. The lesion-level data will be analyzed by McNemar's test adjusted for clustered data (each subject will contribute at least one lesion result, and possibly many lesion results). Published methods will be used for the lesion-level analyses (Durkalski et al, Statist. Med. 2003; 22:2417-2428 "Analysis of clustered matched-pair data"; Statist. Med. 2003; 22:279-290 "Analysis of clustered matchedpair data for a non-inferiority study design"). Reader-specific sensitivities and specificities will be calculated primarily for patient-based results for lymph nodes of any size. Sensitivity and specificity calculations will be performed for each imaging modality with the CIs calculated based on Wilson score method. In addition, we will assess 68Ga-PSMA-HBED-CC PET and MRI image data for cancer staging and compare their performance based on a Wilcoxon signed-rank test. And finally, safety of the 68Ga-PSMA-HBED-CC test will be assessed by tabulation of any procedure-related adverse effects.