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68Ga-PSMA-11 PET/CT for Screening Prior to 177Lu-PSMA-617 Therapy

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Background:

Below is the abstract from the Phase III VISION trial for 177Lu-PSMA-617 therapy for prostate cancer, which Mayo was involved in. This is the seminal trial that led to FDA approval of this new therapy.

Metastatic castration-resistant prostate cancer remains fatal despite recent advances. Prostate-specific membrane antigen (PSMA) is highly expressed in metastatic castration-resistant prostate cancer. Lutetium-177 ((177)Lu)-PSMA-617 is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment.

METHODS: We conducted an international, open-label, phase 3 trial evaluating (177)Lu-PSMA-617 in patients who had metastatic castration-resistant prostate cancer previously treated with at least one androgen-receptor-pathway inhibitor and one or two taxane regimens and who had PSMA-positive gallium-68 ((68)Ga)-labeled PSMA-11 positron-emission tomographic-computed tomographic scans. Patients were randomly assigned in a 2:1 ratio to receive either (177)Lu-PSMA-617 (7.4 GBq every 6 weeks for four to six cycles) plus protocol-permitted standard care or standard care alone. Protocol-permitted standard care excluded chemotherapy, immunotherapy, radium-223 ((223)Ra), and investigational drugs. The alternate primary end points were imaging-based progression-free survival and overall survival, which were powered for hazard ratios of 0.67 and 0.73, respectively. Key secondary end points were objective response, disease control, and time to symptomatic skeletal events. Adverse events during treatment were those occurring no more than 30 days after the last dose and before subsequent anticancer treatment.

RESULTS: From June 2018 to mid-October 2019, a total of 831 of 1179 screened patients underwent randomization. The baseline characteristics of the patients were balanced between the groups. The median follow-up was 20.9 months. (177)Lu-PSMA-617 plus standard care significantly prolonged, as compared with standard care, both imaging-based progression-free survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; P<0.001) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; P<0.001). All the key secondary end points significantly favored (177)Lu-PSMA-617. The incidence of adverse events of grade 3 or above was higher with (177)Lu-PSMA-617 than without (52.7% vs. 38.0%), but quality of life was not adversely affected.

CONCLUSIONS: Radioligand therapy with (177)Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. (Funded by Endocyte, a Novartis company; VISION ClinicalTrials.gov number, NCT03511664.).

Study Rationale

This trial is designed to overcome a clinical access issue that would otherwise block patients from reimbursement of a new cancer therapy, and therefore block or significantly delay their care.

On March 23, 2022, the FDA approved PSMA-targeted radionuclide therapy for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with an androgen receptor pathway inhibitor (ARPI) and taxane-based chemotherapy. PSMA-targeted radionuclide therapy is also known as 177Lu-PSMA-617, Lutetium Lu 177 Vipivotide Tetraxetan, and Pluvicto™.

The FDA approval of PSMA-targeted radionuclide therapy was based on the phase III VISION trial (Sartor, de Bono et al. 2021). In the VISION trial, a specific form of PSMA-targeted PET radiotracer was used to evaluate if patients had PSMA-positive prostate cancer prior to PSMA-targeted radionuclide therapy. The specific form of PSMA-targeted PET radiotracer used in the VISION trial was 68Ga-PSMA-11, also known as Gallium Ga 68 gozetotide. 68Ga-PSMA-11 for the VISION trial was produced with a chemistry kit that was FDA approved on March 23, 2022, now known as Locametz™.

The FDA approval of PSMA-targeted radionuclide therapy specifies to "select patients for treatment using Locametz® or an approved PSMA-11 imaging agent based on PSMA expression in tumors". This FDA language was a surprise, as the medical community expected to be able to use any FDA approved PSMA-targeted PET radiotracer for patient selection for PSMA-targeted radionuclide therapy, and not be restricted to 68Ga-PSMA-11.

Mayo and many other hospitals, imaging centers and clinical practices have an active PSMA-targeted PET imaging practice using 18F-PSMA-DCFPyL PET radiotracer. 18F-PSMA-DCFPyL was FDA approved on May 27, 2021. 18F-PSMA-DCFPyL is also known as, PyL, piflufolastat F 18, and Pylarify™. 18F-PSMA-DCFPyL is more widely available than the more recently FDA-approved 68Ga-PSMA-11. Thus, most medical centers began a PSMA-targeted PET practice with 18F-PSMA-DCFPyL, and few have established access to 68Ga-PSMA-11.

Most patients who have undergone PSMA-targeted PET scans (PET/CT or PET/MR) are likely to have received a 18F-PSMA-DCFPyL PET scan. However, the FDA-approval for PSMA-targeted radionuclide therapy specifies that 68Ga-PSMA-11 PET be used prior to PSMA-targeted radionuclide therapy.

In order to obtain reimbursement for and open access to PSMA-targeted radionuclide therapy for appropriate Mayo patients suffering from prostate cancer this issue has to be resolved. While Mayo and others seek clarification from Medicare on this issue, many Mayo patients would be waiting and suffering.

Therefore, we are establishing a protocol, by which we will allow for a limited number of appropriate patients to obtain a 68Ga-PSMA-11 PET/CT scan. The 68Ga-PSMA-11 PET/CT scan would be available even if the patient had a recent 18F-PSMA-DCFPyL PET scan (PET/CT or PET/MR). The 68Ga-PSMA-11 PET/CT scans will be performed at Mayo Clinic in Rochester at the expense of the Mayo Clinic Rochester Nuclear Medicine Division of the Department of Radiology. The radiotracer, scan, interpretation, study coordinator time and other related costs to run the protocol will be covered without expense to the patient.

The 68Ga-PSMA-11 radiotracer will be produced at Mayo Clinic in Rochester under an active IND (IND 151346). This study has been submitted for FDA review as an extension under the

same IND.

We recognize a patient may, as a result of this protocol, get two PSMA-targeted PET/CT exams within a short period of time. This will result in a small amount of additional radiation. However, without this scan and extra radiation, there could be a significant delay in access to cancer therapy, a therapy which may be life extending. It should be recognized that the PSMA-targeted radionuclide therapy the patient is planning to undergo results in a significantly higher radiation exposure then the additional PSMA-targeted PET/CT scan included in this trial.

We intend to make the 68Ga-PSMA-11 PET/CT imaging and interpretation of that imaging available in the electronic record for patients and their care team, so they can guide clinical care decisions.

We anticipate referrals for 68Ga-PSMA-11 PET/CT under this protocol to come from Urology, Medical Oncology, Radiation Oncology, and Radiology. We anticipate performing up to six 68Ga-PSMA-11 PET/CT scans per day. We anticipate this trial will run for up to 12 months. Therefore, the total population of patients we plan to scan with 68Ga-PSMA-11 PET/CT is not expected to exceed 250.

It is possible we may need to extend this trial and increase the enrollment depending on the timing of the anticipated resolution of the Medicare and Insurance limitations on coverage described above. Alternatively, when our ability to produce an FDA approved version of 68Ga-PSMA-11 allows us to convert our clinical practice away from 18F-PSMA-DCFPyL this protocol will no longer be needed. That practice conversion is currently under active development and is dependent in part on completion of construction of new PET radiochemistry facilities in Charlton North.

Given that production of 68Ga-PSMA-11 is limited at our site, we may need to modulate access to patients in part depending on radiotracer and scanner availability. We also have limitations in terms of access to PET/CT. Thus, we will perform the majority of, or all of these 68Ga-PSMA-11 PET/CT exams within the research facilities of the PET Imaging Resource on Charlton 6.

Primary Endpoint: Safety

Measurement: Monitoring of patients for self-reported unexpected adverse reactions from the time of injection until the time they leave the care of the Division of Nuclear Medicine. If any adverse reactions are reported, the patient will be evaluated by a nurse and/or physician and will receive appropriate care. The PI or those designated by the PI will ascertain the severity of the adverse event and how likely the adverse reaction was associated with the injected 68Ga-PSMA-11.

To date we have seen no adverse reactions to IV administered 68Ga-PSMA-11 at Mayo Clinic in Rochester and we have administered over 400 doses.

68Ga-PSMA-11 Administration

The injected dose will be 185 MBq (5 mCi) (range 111-259 MBq; 3-7 mCi) of 68Ga-PSMA-11. PET imaging will begin 50-100 minutes after injection. A use of existing Central/PICC lines is considered acceptable for 68Ga-PSMA-11 administration.

We may repeat a 68Ga-PSMA-11 injection and PET/CT in either of the following circumstances:

- The patient had an unavoidable delay in care (such as a motor vehicle accident) and there is evidence or clinical concern that the patient's cancer significantly progressed or responded to therapy in a way that could affect management of his cancer.
- The patient still meets the criteria for enrollment in the study and 3 months of time or more has elapsed since the last 68Ga-PSMA-11 injection.

68Ga-PSMA-11 PET/CT protocol

The established 68Ga-PSMA-11 PET/CT imaging protocol will be followed. The scans will be performed on the Siemens VISION 600 PET/CT or GE DMI PET/CT on Charlton 6. The CT will be performed without IV or oral contrast and will follow standard clinical PET/CT protocol parameters. The exams will cover the orbits to thighs, unless otherwise specified by the Radiologist/Nuclear Medicine physician protocoling the specific exam for a given patient.

Patient selection for enrollment

Inclusion Criteria. All the following criteria must be met.

- An adult male patient who…
    - is actively under the care of a Medical Oncology, Radiation Oncology or Urology physician at Mayo Clinic.
    - is deemed eligible (or potentially/likely eligible) for PSMA-targeted radionuclide therapy by a Nuclear Medicine Physician or Radiologist in the Nuclear Medicine therapy practice, or by the Prostate Theranostic Tumor Board (PTuB)
        - eligibility will be documented in the medical record by the clinical practice
        - it is acceptable for the patient to be eligible for PSMA-targeted radionuclide therapy in all regards except for having completed a PSMA-targeted PET scan showing PSMA-positive prostate cancer
        - It is acceptable for a patient to be potentially eligible for therapy, but have a relative contraindication, such as a minor laboratory abnormality, and be on the list for discussion at the PTuB in the future
    - has not received a 68Ga-PSMA-11 PET/CT or PET/MR, or for whom a repeat 68Ga-PSMA-11 PET/CT exam is needed per the clinical practice to ensure eligibility
    - does not otherwise have access to a reimbursable clinical 68Ga-PSMA-11 PET scan
    - An adult above the ages of 18

Exclusion criteria. Any of the following.

- A patient who is:

- unable to consent per Mayo guidelines
- unable to lay still, or otherwise successfully complete the imaging exam

Study procedures

Patients who meet all inclusion and no exclusion criteria will be invited to participate in the study. The study coordinator will set up an appointment with the subject to discuss the study, answer any relevant questions, and obtain informed consent. The study coordinator will schedule the 68Ga-PSMA-11 PET/CT scan. Patient's participation in the study will end once their imaging visit is complete. The 68Ga-PSMA-11 PET/CT scans will be clinically interpreted with the report and imaging available in the patient's medical record.

Radiation Dose Estimate for CT Component of PET/CT

The effective dose for a trunk CT (orbits to mid-thigh) is 6.3 mSv for males. The effective dose for a 7 mCi IV injection of 68Ga-PSMA-11 is 4.4mSv.

Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the IRB and IND sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any suspected adverse reaction that is both serious and unexpected.

Definitions:

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Note: An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Note: For purposes of IND safety reporting, **''reasonable possibility''** means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, defined below.

Unexpected: An adverse event or suspected adverse reaction is considered ''unexpected'' if

- It is not listed in the investigator brochure or.
- Is not listed at the specificity or severity that has been observed; or,
- If an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan (protocol) or elsewhere in the current IND application (as amended).

Serious (previously SAE): An adverse event or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- Inpatient hospitalization or (Prolongation of existing hospitalization), or
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.

Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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.

Life-Threatening: An adverse event or suspected adverse reaction is considered ‘‘life-threatening’’ if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

Note: It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Attribution to agent or procedure:

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE is clearly related to the agent(s)/procedure.
Probable - The AE is likely related to the agent(s)/procedure.
Possible - The AE may be related to the agent(s)/procedure.
Unlikely - The AE is doubtfully related to the agent(s)/procedure.
Unrelated - The AE is clearly NOT related to the agent(s)/procedure.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	**Grade 1 Timeframes**	**Grade 2 Timeframes**	**Grade 3 Timeframes**	**Grade 4 & 5 Timeframes**
Resulting in Hospitalization ≥24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required		7 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] 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. Footnote "1" above applies after this reporting period.

Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

Source Documents

The Source data comprise all information, original records of clinical findings, observations, or other activities in a clinical treatment necessary for the reconstruction and evaluation of the treatment response. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, radiological imaging data, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the study.

Records Retention

The principal-investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. The principal-investigator will retain the specified records and reports as outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717 .

References

1. Sartor, O., et al. (2021). "Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer." N Engl J Med **385**(12): 1091-1103.