CITY OF HOPE NATIONAL MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF Radiation Oncology

TITLE: A Prospective Study of the RefleXion [18F]- DCFPyL PET-CT Subsystem Imaging Performance in Patients with Prostate Cancer

CITY OF HOPE PROTOCOL NUMBER/VERSION: IRB # 22189 **PROTOCOL DATE: 07/08/2022**

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

COH Initial Approval	Protocol Dated 05/03/2022	Packet: 00
Amendment 01	Protocol Dated 07/08/2022	Packet: 01
Amendment 02 at Continuation	Protocol Dated 07/08/2022	Packet 02

SITE:
STAGE (If applicable):
MODALITY:
TYPE:

PRINCIPAL INVESTIGATOR: **Wong, Jeffrey, M.D.**

BIOSTATISTICIAN: Frankel, Paul, Ph.D.

COLLABORATING INVESTIGATOR(S):
Amini, Arya, M.D.
Dandapani, Savita, M.D., Ph.D.
Glaser, Scott, M.D.
Han, Chunhui, Ph.D.
Li, Rose, M.D., Ph.D.
Liu, An, Ph.D.
McGee, Heather, M.D., Ph.D.
Sampath, Sagus, M.D.
Williams, Terence, M.D.
Yamauchi, Dave, M.D.

PARTICIPATING CLINICIANS: **NA**

COMMUNITY PRACTICE SITES: NA

City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010

Clinical Trial Protocol

Protocol Title: A Prospective Study of the RefleXion [18F]- DCFPyL PET-CT Subsystem Imaging Performance in Patients with Prostate Cancer

Version Date:	07/08/2022
Protocol Version:	01
City of Hope IRB #:	22189
Agents:	NA
Sponsor Holder:	City of Hope
Funding Support/Industry Partner:	RefleXion
NCT Number:	Pending
Participating Sites:	City of Hope (Duarte)
Short Title	RefleXion [18F]- DCFPyL PET-CT Subsystem Imaging

Principal Investigator
Jeffrey Y.C. Wong, MD
City of Hope National Medical Center
Dept. of Radiation Oncology
T: 626-218-2247
Email: jwong@coh.org

PROTOCOL TEAM

Co-investigator
Dave Yamauchi, MD
City of Hope
Chief, Division of Nuclear Medcine
Dept. of Dianostic Radiology
T: 626-218-8252
Email: dyamauch@coh.org

Co-Investigator
Savita Dandapani, MD, PhD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: sdandapani@coh.org

Co-investigator
Maria Parayno, MD
City of Hope
Division of Nuclear Medcine
Dept. of Dianostic Radiology
T: 626-218-8252
Email: mparayno@coh.org

Co-Investigator
Rose Li, MD, PhD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: yunroseli@coh.org

Co-Investigator
Scott Glaser, MD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: sglaser@coh.org

Co-Investigator
An Liu, PhD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: aliu@coh.org

Co-Investigator
Chunhui Han, PhD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: chan@coh.org

Biostatisticion
Paul Frankel, PhD
City of Hope
Dept. of Biostatistics
T: 626-XXX_XXXX
Email: pfrankel@coh.org

Co-Investigator
Arya Amini, MD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: aamini@coh.org

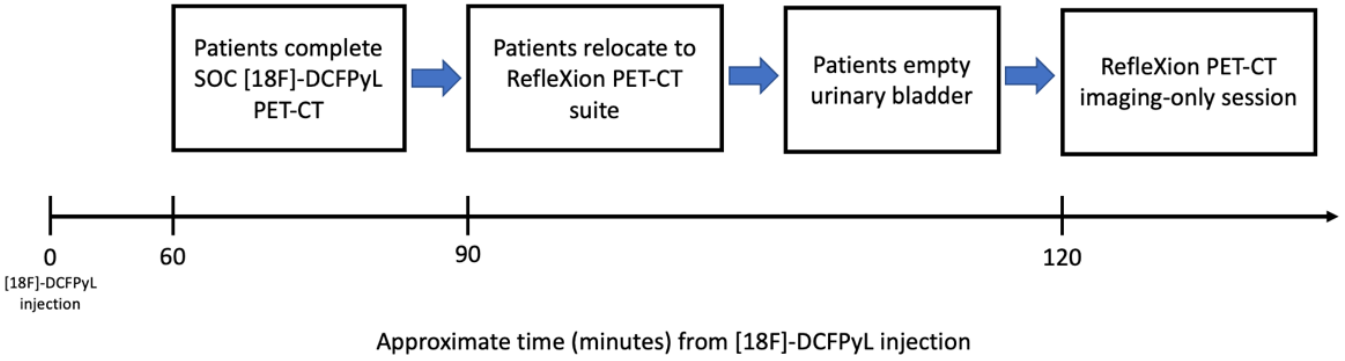
Co-Investigator
Sagus Sampath, MD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: ssampath@coh.org

Co-Investigator
Terence Williams, MD PhD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: twilliams@coh.org

Co-Investigator
Heather McGee, MD, PhD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: hmcgee@coh.org

Co-Invesitagor
Nayana Vora, MD
City of Hope
Dept. of Radiation Oncology
T: 626-218-2247
Email: nvora@coh.org

STUDY SCHEMA



PROTOCOL SYNOPSIS

The RefleXion Medical Radiotherapy System (RMRS) is a hybrid imaging-therapy system that is FDA cleared (K190978) to deliver IMRT/SBRT/SRS external beam radiation therapy. It consists of 6 megavoltage (MV) photon radiotherapy delivery, PET imaging hardware, kilovoltage (kV) X-ray CT imaging, and treatment planning subsystems. The system includes the capability of PET imaging when used in a research mode.

Prostate-specific membrane antigen (PSMA) PET with 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([18F]-DCFPyL) has been approved for imaging PSMA- positive lesions in men with prostate cancer with either (1) suspected metastasis who are candidates for initial definitive therapy or (2) suspected recurrence based on elevated serum prostate-specific antigen (PSA) level. The RefleXion system is designed to facilitate delivery of biology-guided radiotherapy (BgRT). The system uses PET emissions to guide radiotherapy delivery in real-time and has been studied for use with FDG. In the future, BgRT guided by [18F]-DCFPyL as a biological fiducial carries a potential to improve radiotherapy dose distribution for patients with prostate cancer.

As a requirement for such future evaluation of [18F]-DCFPyL as a biological fiducial, an understanding of the performance of the PET imaging subsystem on the RMRS is needed to correctly detect PET signals derived from [18F]-DCFPyL. Therefore, a single-arm, prospective study to better assess and possibly optimize the performance of the PET imaging subsystem for detection of [18F]-DCFPyL PET signals as a foundation to evaluate [18F]-DCFPyL-based BgRT treatment planning and delivery in future studies is being proposed.

On the day of, and upon completing SOC [18F]-DCFPyL PET-CT, patients will undergo an additional “imaging-only session” on the RefleXion PET-CT (Figure 1). Aside from standard of care (SOC) [18F]-DCFPyL, no PET tracer or other molecule will be administered, and no external-beam radiotherapy will be delivered in this study.

Evidence to be gathered in this study is intended to allow assessment of the technical performance of the PET imaging subsystem on RMRS in patients with prostate cancer undergoing SOC imaging with [18F]-DCFPyL for diagnostic purposes. Evidence from this study will supplement and enhance technical understanding of the [18F]-DCFPyL-guided BgRT delivery. As such, the patient population selected for this investigation is meant to optimally represent the spectrum of cases, with respect to motion and radiographic environment that a radiation oncologist may encounter in practice.

Protocol Title	
A Prospective Study of the RefleXion [18F]- DCFPyL PET-CT Subsystem Imaging Performance in Patients with Prostate Cancer	
Study Detail	
Population/Indication(s):	Patients with prostate cancer who will be undergoing ([18F]-DCFPyL) PET-CT scan
Phase:	pilot
Sample Size:	25 evaluable patients
Estimated Accrual Duration:	18 months
Estimated Study Duration	24 months
Participant Duration:	72 hours
Study Agents:	NA

Study Design

Single arm, prospective study

Objectives

Primary Objective(s)

- To determine the imaging performance of 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([18F]-DCFPyL) PET-CT imaging subsystem of the RefleXion Medical Radiotherapy System Device in patients undergoing standard-of-care (SOC) [18F]-DCFPyL PET-CT on the same day.

Endpoints

Primary Endpoint(s):

- To compare imaging performance of the [18F]-DCFPyL PET-CT subsystem on the X1 RMRS to detect lesions (primary and metastatic) in patients with prostate cancer, relative to diagnostic [18F]-DCFPyL PET-CT.

Secondary Endpoint(s):

- Percent of cases where X1 RMRS PET data can be used to generate an acceptable BgRT plan such that dosimetric parameters for the target and the nearby normal anatomy are met based on investigator assessment.

Intervention Description

Baseline Assessments within thirty days prior to the X1 RMRS PET Imaging-only session:

- Demographics & medical history
- SOC diagnostic [18F]-DCFPyL PET-CT
  - Subject weight and height
  - Injected dose and injection time of [18F]-DCFPyL
  - Scan time and image analysis of SOC PET-CT

X1 PET Imaging-only session

- Scan time and image analysis of X1 RMRS imaging-only session

Follow-Up

- Comparison of SOC PET-CT and X1 with respect to image analysis and treatment planning
- Within 72 hours of completion of X1 PET Imaging-only session: Adverse Events assessment by using Common Terminology Criteria for Adverse Events (CTCAE) v5

Main Eligibility Criteria

Main Inclusion Criteria

- Age 21 years or greater
- Able and agree to provide informed consent
- Patients with prostate cancer undergoing SOC [18F]-DCFPyL PET-CT.

Main Exclusion Criteria

- Known psychiatric or substance abuse disorder that would interfere with conduct of the study
- Patient weight exceeding the weight limit (450 pounds) outlined per X1 RMRS specifications sheet.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
CFR	Code of Federal Regulations
COH	City of Hope
CR	Complete Response
CRC	Clinical Research Coordinator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLT	Dose Limiting Toxicity
DSMC	Data & Safety Monitoring Committee
DSMP	Data & Safety Monitoring Plan
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
OCTM	Office of Clinical Trials Monitoring
OIDRA	Office of IND Development and Regulatory Affairs
PD	Progressive Disease
PI	Principal Investigator
PMT	Protocol Management Team
PR	Partial Response
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable disease
UT	Unacceptable Toxicity

1.0 OBJECTIVES

1.1 Primary Objective(s)

- To assess imaging performance of the [18F]-DCFPyL PET-CT subsystem on the X1 RMRS to detect lesions (primary and metastatic) in patients with prostate cancer.

1.2 Secondary Objective(s)

- To determine the feasibility of generating a BgRT plan using X1 RMRS-acquired [18F]-DCFPyL PET data derived from the imaging-only session at the studied dose level.

2.0 BACKGROUND

2.1 Overview and Justification for Study Design

2.1.1 [18-F]-DCFPyL PET-CT

Prostate-specific membrane antigen (PSMA) PET with 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid ([18F]-DCFPyL) has been approved for imaging PSMA positive lesions in men with prostate cancer with either primary high-risk prostate cancer with suspected metastasis who are candidates for initial definitive therapy or suspected recurrence based on elevated serum prostate-specific antigen (PSA) level (1).

This approval was based on findings from the CONDOR (2) and OSPREY (3) studies. The multicenter phase 3 CONDOR study included 208 men with biochemical recurrence, defined as rising PSA ≥0.2 ng/mL after prostatectomy or ≥2 ng/mL above nadir after radiation therapy. A total of 63.9% of patients who had no evidence of disease on conventional imaging had a change in management after [18F]-DCFPyL PET-CT was performed. The disease detection rate was 59% to 66% (at least one lesion detected per patient by [18F]-DCFPyL PET-CT) (2). In the phase 2/3 OSPREY trial, [18F]-DCFPyL PET-CT was assessed in two patient cohorts. Cohort A included men with high-risk prostate cancer undergoing surgery, and the researchers assessed the capacity of [18F]-DCFPyL PET-CT to detect prostate cancer in pelvic lymph nodes. Cohort B included patients with suspected metastatic or recurrent disease, and the researchers examined the performance of [18F]-DCFPyL PET-CT in detecting distant metastases. In cohort A, [18F]-DCFPyL PET-CT detected in the pelvic lymph nodes with a specificity of 97.9%, a sensitivity of 40.3%, and a positive predictive value (PPV) of 86.7%. The sensitivity and PPV rates for detecting metastatic lesions in cohort B were 95.8% and 81.9%, respectively (3). In the OSPREY and CONDOR studies, [18F]-DCFPyL PET-CT was found to be safe and well tolerated (2,3). Another study (4) evaluated 160 patients with high-risk prostate cancer. 56% of the included patients were shown to have metastatic disease based on [18F]-DCFPyL PET-CT, and 17% of patients had a change in management based on the PET-CT findings. Only 1% of patients had to undergo additional imaging because of equivocal findings on the [18F]-DCFPyL PET-CT. Authors concluded that [18F]-DCFPyL PET-CT should be used as first-line imaging modality for therapy selection in patients with primary high-risk prostate cancer.

2.1.2 RefleXion Medical Radiotherapy System and biology-guided radiotherapy

The RefleXion Medical Radiotherapy System (RMRS) is a hybrid imaging-therapy system that is FDA cleared (K190978) to deliver IMRT/SBRT/SRS external beam radiation therapy. It consists of 6 megavoltage (MV) photon radiotherapy delivery, PET imaging hardware, kilovoltage (kV) X-ray CT imaging, and treatment planning subsystems. The system includes the capability of PET imaging when used in a research mode.

It is hypothesized that BgRT guided by [18F]-DCFPyL as a biological fiducial may improve radiotherapy dose distribution for patients with prostate cancer. As a requirement for such evaluation of [18F]-DCFPyL as a biological fiducial, the performance of the PET imaging subsystem on the X1 RMRS to correctly detect PET signals derived from [18F]-DCFPyL, needs to be better understood. Therefore, a single-arm, prospective study to better assess and possibly optimize the performance of the PET imaging subsystem for detection of [18F]-DCFPyL PET signals as a foundation to evaluate [18F]-DCFPyL-based BgRT treatment planning and delivery in subsequent studies, is proposed.

On the day of, and upon completing the standard of care (SOC) [18F]-DCFPyL PET-CT, patients will undergo an addition “imaging-only session” on the X1 RMRS PET-CT (Figure 1). No additional PET tracer or any other molecule will be administered, and no therapeutic radiation will be delivered in this study.

The evidence to be gathered in this study is intended to allow assessment of the technical performance of the PET imaging subsystem on the X1 in a clinically relevant situation, namely in patients with prostate cancer undergoing SOC imaging with [18F]-DCFPyL. Long term, the evidence from this study will supplement and enhance technical understanding of the [18F]-DCFPyL-guided BgRT delivery. As such, the patient population selected for this investigation is meant to optimally represent the spectrum of cases, with respect to motion and radiographic environment, that a radiation oncologist may encounter in practice.

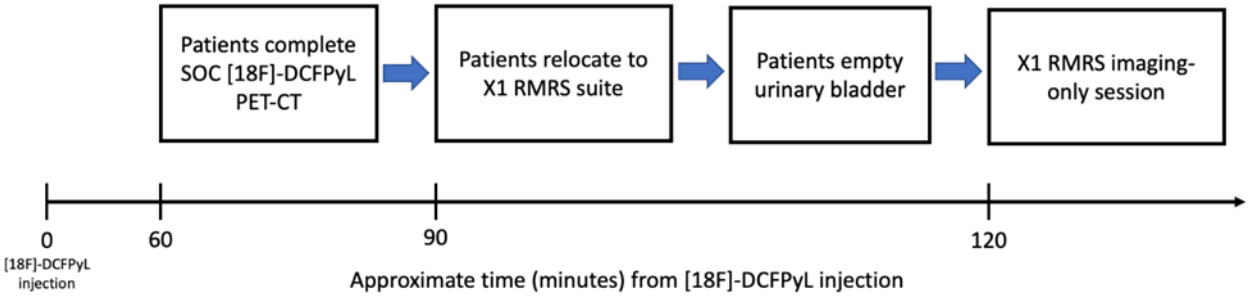


Figure 1: Study Flowchart

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

__1. Documented informed consent of the participant and/or legally authorized representative.
__2. Age: ≥ 21 years
__3. Patients undergoing SOC [18F]-DCFPyL PET-CT
__4. Patients should be scheduled for [18F]-DCFPyL PET-CT prior to study entry

3.2 Exclusion Criteria

__1. Known psychiatric or substance abuse disorder that would interfere with conduct of the study
__2. Patient weight exceeding the weight limit (450 pounds) outlined per X1 RMRS specifications sheet.

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT, ASSIGNMENT

4.1 Pre-Enrollment Informed Consent and Screening Procedures

The informed consent process is to be fully documented (see Section 13.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 7.0 (Study Calendar).

4.2 Participant Enrollment

Registration of participants will be according to the following steps:

- Prospective participants must complete the informed consent process, including a signed informed consent, prior to proceeding to study screening.
- Once all the pre-study requirements have been fulfilled, including a completed eligibility checklist (**Section 3.0**) the study coordinator will register the eligible patient into the OnCore Clinical Trials Management System.
- Patients failing to meet all protocol eligibility criteria, including informed consent, may not be registered for the trial.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Intervention

Notify the study team immediately if the participant screen fails after registration or if the participant does not start intervention.

5.0 STUDY PROGRAM

5.1 Study Plan

SOC [18F]-DCFPyL PET-CT

All SOC [18F]-DCFPyL PET-CT studies should be performed on the Siemens Vision 600 PET-CT machine in the Outpatient Imaging Center (OIC) in the Department of Nuclear Medicine at City of Hope, in accordance with departmental protocol. Patients who demonstrate at least one PET avid site will then have a PET-CT on the RefleXion X1 system. A PET avid site could include the prostate gland or a metastatic site. If no PET avid lesion is seen on the SOC [18F]-DCFPyL PET-CT, then the patient will not have a PET-CT on the RefleXion X1 system.

Imaging-only session on the RefleXion X1 machine

On the day of, and upon completing the standard of care (SOC) [18F]-DCFPyL PET-CT, patients will undergo an addition “imaging-only session” on the RefleXion PET-CT. Site should make every effort to start SOC [18F]-DCFPyL PET-CT scan within 60 minutes of SOC [18F]-DCFPyL injection and subsequently start X1 RMRS scan within 120 minutes post injection (Figure 1). No additional PET tracer or any other molecule will be administered, and no therapeutic radiation will be delivered in this study. See Appendix for additional details of workflow.

Post-image-acquisition transfer of anonymized image data to the Funding Support/Industry Partner will be within one week from the X1 PET scan.

BgRT Planning

Within a week after the X1 RMRS PET scan a BgRT plan will be generated using X1 RMRS-acquired [18F]-DCFPyL PET data derived from the imaging-only session. The percent of cases where X1 RMRS [18F]-DCFPyLPET data can be used to generate an acceptable BgRT plan such that dosimetric parameters for the target and the nearby normal anatomy are met based on investigator assessment will be determined.

5.2 Duration of Study

Enrollment is estimated to occur over twelve to eighteen (12-18) months, and for the total study duration to be approximately eighteen to twenty-four(18-24) months.

5.3 Duration of Study Participation

Study patients can expect to be participants of this study for no longer than 72 hours. Both imaging sessions (SOC [18F]-DCFPyL PET-CT and imaging on X1 RMRS) will take place on the same day, and adverse events assessment will take place within 72 hours after the imaging session.

5.3.1 Withdrawal and Replacement of Subjects

Subjects may withdraw their consent at any time. Subject's withdrawal of consent must be documented. Withdrawn subjects will not undergo any additional follow-up. Patients with imaging results deemed unevaluable will be replaced.

5.4 Sources of Methods of Recruitment

Patients will be recruited from those seen at the Department of Radiation Oncology at City of Hope. After eligibility criteria have been reviewed, eligible patients will be offered the opportunity to participate in the study. A brief description of the study will be given verbally to the patients, followed by written informed consent, and any relevant supplemental material as needed. The patients will be given ample time to review the consent and a time for questions and answers will be provided. No financial incentives will be provided to the patients.

6.0 ANTICIPATED ADVERSE EVENTS

Subjects will undergo localization (positioning) scans with the X1 RMRS integrated fan-beam kVCT imaging prior to the PET image collection session. Effectively, the only extra dose (on top of SOC [18F]-DCFPyL PET-CT scan) will be coming from this kVCT. A significant increase in subjects' risk with this additional imaging session is not expected. For a single additional kVCT scan with the X1 RMRS, the extra effective dose a patient could receive usually ranges between 10-15 mSv, or 1.0-1.5 cGy. Based on the established clinical literature (5,6,7), the degree of risk for populations of this additional low dose is unclear and controversial, but the risk for any one individual is remote. Study subjects will continue to receive standard of care treatments throughout the study, which are not part of these study procedures.

Appropriate clinical assessments will be performed as indicated to identify all AEs. AEs will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5. Signs and symptoms of existing disease progression will not be considered AEs.

7.0 STUDY CALENDAR

Assessments	Baseline*	Day 0	Follow-up^
Informed Consent	X		
Demographics	X		
Medical History	X		
Height/Weight	X		
SOC [18F]-DCFPyL PET-CT		X	
X1 PET Imaging-only session		X	
Toxicity Collection			X

*Within thirty days prior to the X1 PET Imaging-only session:

^Within 72 hours of completion of X1 RMRS PET Imaging-only session: Adverse Events assessment by using Common Terminology Criteria for Adverse Events (CTCAE) v5

8.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

8.1 Primary Endpoint

To compare imaging performance of the [18F]-DCFPyL PET-CT subsystem on the X1 RMRS to detect lesions (primary and metastatic) in patients with prostate cancer with the diagnostic [18F]-DCFPyL PET-CT.

8.2 Secondary Endpoint(s)

Percent of cases where X1 RMRS [18F]-DCFPyLPET data can be used to generate an acceptable BgRT plan such that dosimetric parameters for the target and the nearby normal anatomy are met based on investigator assessment.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Analysis/Statistics

This study will compare the performance of the [18F]-DCFPyL PET-CT subsystem on the RefleXion X1 system to detect selected lesions in patients with prostate cancer with the SOC diagnostic [18F]-DCFPyL PET-CT.

One key metric will be the percent of patients with lesions identified on SOC PET-CT that are not identified on X1 (false negatives if considering SOC the true standard). While patients will not have their SOC scan evaluated prior to X1, we anticipate at least 50% will have positive lesions identified on SOC in our patient population. With 12 patients with SOC detected lesions, there is at least 14% chance of finding a false negative if the true false negative rate is 15%, and 93% of observing a false negative if the true false negative rate is 20%.

For the SOC [18F]-DCFPyL PET-CT, the maximum SUV and the greatest dimension in centimeters will be recorded for each PET avid malignant lesion identified by the nuclear medicine radiologist. The

patient's radiation oncologist will interpret the X1 PET scan for the same metrics. Any discordances will be documented, and the final disposition recorded after a discussion between the radiation oncologist and the nuclear medicine radiologist.

Graphical presentations will be provided to compare SOC positive lesions and X1 positive lesions, and SOC positive lesions and X1 negative lesions with regards to lesion size, lesion location (bone, lymph nodes, soft tissue, visceral organ) and SUV uptake.

The true positive lesions identified on the X1 PET images will be identified and used for BgRT planning. For the secondary endpoint, simulated planning using the RefleXion treatment planning software will be performed, and the radiation dose to organs at risk calculated. Principal investigator will determine whether this plan is acceptable or not. The percent of cases in which RefleXion [18F]-DCFPyLcPET data led to an acceptable plan will be recorded (descriptive statistics).

Because this is an exploratory study, descriptive statistics will be utilized to quantify results. Mean, standard deviation, IQR, and range will be reported for each continuous variable. Frequency and percentage will be reported for categorical variables. Statistical significance will be assessed at the 0.05 level, one-sided.

9.2 Participant Evaluability and Replacement

Patients with imaging results deemed unevaluable will be replaced.

9.3 Sample Size, Accrual Rate and Study Duration

- **Total accrual**: We will accrue a maximum of 25 evaluable participants
- **Accrual rate**: Accrual is expected to be completed in 12 months.
- **Study duration** is expected to be about 18 months.
- **Participant duration** will be about 72 hours

This study is designed to enroll up to 25 evaluable patients, and criteria for patient selection are outlined above. This sample size was determined a priori to represent a sufficient number of patients for a pilot study to evaluate PSMA-positive lesions to describe imaging performance of the [18F]-DCFPyL PET-CT subsystem on the RefleXion X1 system across a spectrum of clinical scenarios.

10.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

10.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

10.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

10.3 Case Report Forms/Data Submission Schedule

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated below.

Data to be collected will include patient's name and medical record number, date of birth, basic disease characteristics, including staging information, location of and extent of involvement, relevant imaging characteristics of the tumor, prior cancer-directed therapies. [18F]-DCFPyL emission data will be collected at time of study acquisition in the Department of Nuclear Medicine. The images sets and [18F]-DCFPyL activity data is stored on a picture archiving and communication system (PACS) per protocol and submitted securely to the appropriate members of the Industry Partner's study team, along with deidentified clinical data. City of Hope approved case report forms (CRFs) for data collection will be used and data entered into a secure electronic data capture (EDC) system. City of Hope will share the raw EDC data with Industry Partner. Every reasonable effort should be made to complete data entry within five business days of data collection. The Principal Investigator or Sub-investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate CRFs.

Baseline Assessments within thirty days prior to the X1 PET Imaging-only session:

- Demographics & medical history
- Subject weight and height
- Injected dose and injection time of [18F]-DCFPyL
- Scan time of SOC [18F]-DCFPyL PET-CT

X1 PET Imaging-only session

- Scan time of X1 RMRS imaging-only session

Follow-Up

- Within 72 hours of completion of X1 RMRS PET Imaging-only session: Adverse Events assessment by using Common Terminology Criteria for Adverse Events (CTCAE) v5

10.4 Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

11.0 ADVERSE EVENTS AND UNANTICIPATED PROBLEMS

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

11.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study procedure, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study procedure, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study procedure, as it follows a reasonable temporal sequence from the time of study procedure, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study procedure, as it follows a reasonable temporal sequence from the time of study procedure and a known response pattern to the study procedure, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Definite –** The event is clearly related to the study procedure, as it follows a reasonable temporal sequence from the time of study procedure and a known response pattern to the study procedure, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

11.2 Reporting of Adverse Events

11.2.1 Routine Recording of Non-Serious Adverse events

Routine recording of the worst grade of all adverse events will occur via data entry into the study eCRF. Collection of adverse events will begin at the beginning of the imaging-only session on the X1 RMRS system and will continue until 72 hours after the end of the scan. Adverse events will be monitored by the Protocol Management Team (PMT). Adverse events that do not meet the criteria of serious OR are not unanticipated problems do not require expedited reporting. AEs reported through expedited processes (i.e. reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

11.2.2 Expedited Reporting Requirements of SAEs and UPs to the COH Regulatory Committees

Adverse events that meet the criteria of serious OR are unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. Reporting of SAEs will begin at the beginning of the imaging-only session on the X1 RMRS machine through 72 hours post completion of the scan, and must be followed until the event is resolved, stabilized, or determined to be irreversible by the investigator. Follow-up SAE reports must be submitted for all events that require expedited reporting when the status of the event changes and until the resolution or stabilization of the event.

11.2.3 Reporting to RefleXion

All serious adverse events and AESIs (initial and follow-up information) will be reported by the study PI to RefleXion per the following guidelines:

Type of Report	Reporting Timeframes to Industry Partner
Pregnancy	**Within 48 hours** of being aware of the event using the protocol case report form.
All expedited SAE reports (includes AESIs)	**Within 24 hours** of being aware of the event via a MedWatch 3500A form.
Aggregate safety reports	Forward to Industry Partner every 6 months (e.g. at time of COH PMT report).

12.0 PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the Clinical Research Protocol Deviation policy. In addition, if contractually obligated, the industry partner/funding source must also approve planned deviations, as necessary.

13.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

13.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

13.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

13.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

13.4 Quality Assurance

Clinical site auditing is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. This trial will be audited by the City of Hope Office for Safety and Data Quality. Details of clinical site auditing are documented in the City of Hope Institutional Data and Safety Monitoring Plan (DSMP).

13.5 Risk Determination

This is a low risk study, as defined in the City of Hope Institutional Data and Safety Monitoring Plan (DSMP). This determination was made because the study is an investigator initiated study and because it involves only an additional scan with no additional infusion of tracer agents nor radiotherapy. This study also satisfies the definition of a Nonsignificant Risk Medical Device Study as defined by the FDA.

13.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

14.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

14.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities (Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, Federal, and State of California regulations must be fulfilled.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

14.4 Informed Consent

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or any relationship they have with

City of Hope. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the investigator and available for inspection by Industry Partner designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

14.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

14.6 Special and Vulnerable Populations

14.6.1 Women and Minorities and Other Underrepresented Populations

The study is open to anyone regardless of race or ethnicity. Efforts will be made to extend the accrual to a representative population impacted by the disease under study and among populations with the City of Hope catchment area. If differences in outcome that correlate to racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

14.6.2 Pediatric Population

Pediatric participants (< 18 years of age) are excluded from this study because the incidence of prostate cancer is rare in the pediatric population.

14.6.3 HIV Positive Individuals

Participants with HIV are included if eligible based on inclusion criteria.

14.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed

consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

14.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the industry partner and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant 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. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

The Investigator/Institution will permit direct access to source data and documents by Industry Partner representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.8 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

14.9 Financial Obligations, Compensation, and Reimbursement of Participants

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible

for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

14.10 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the City of Hope PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with the process determined by mutual written agreement between City of Hope and Industry Partner contained in the Investigator-Initiated Clinical Research Support Agreement between the parties. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov; it is City of Hope policy to register the trial prior to enrollment of the first patient. Results will be reported on ClinicalTrials.gov generally within 12 months after the primary completion date unless criteria to delay submission are met per the final rule.

15.0 REFERENCES

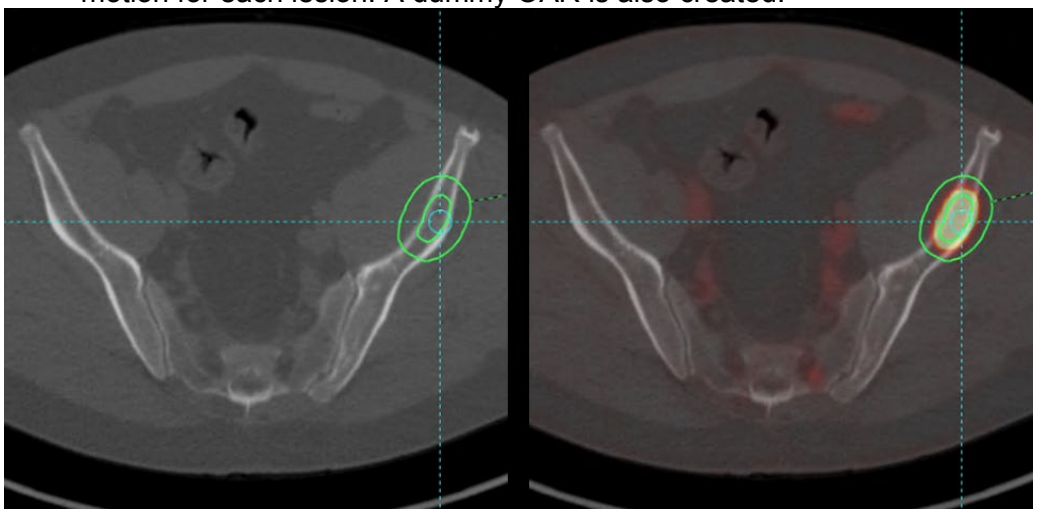
1. Lantheus Receives U.S. FDA Approval of PYLARIFY® (piflufolastat F 18) Injection, the First and Only Commercially Available PSMA PET Imaging Agent for Prostate Cancer. Published online May 27, 2021. Accessed Jan 27, 2022. https://bwnews.pr/3vtMgBh.
2. Morris MJ, Rowe SP, Gorin MA, Saperstein L, Pouliot F, Josephson D, Wong JYC, Pantel AR, Cho SY, Gage KL, Piert M, Iagaru A, Pollard JH, Wong V, Jensen J, Lin T, Stambler N, Carroll PR, Siegel BA; CONDOR Study Group. Diagnostic Performance of ^{18}F-DCFPyL-PET/CT in Men with Biochemically Recurrent Prostate Cancer: Results from the CONDOR Phase III, Multicenter Study. Clin Cancer Res. 2021 Jul 1;27(13):3674-3682. doi: 10.1158/1078-0432.CCR-20-4573. Epub 2021 Feb 23. PMID: 33622706; PMCID: PMC8382991.
3. Pienta KJ, Gorin MA, Rowe SP, Carroll PR, Pouliot F, Probst S, Saperstein L, Preston MA, Alva AS, Patnaik A, Durack JC, Stambler N, Lin T, Jensen J, Wong V, Siegel BA, Morris MJ. A Phase 2/3 Prospective Multicenter Study of the Diagnostic Accuracy of Prostate Specific Membrane Antigen PET/CT with ^{18}F-DCFPyL in Prostate Cancer Patients (OSPREY). J Urol. 2021 Jul;206(1):52-61. doi: 10.1097/JU.0000000000001698. Epub 2021 Feb 26. PMID: 33634707; PMCID: PMC8556578.
4. Wondergem M, van der Zant FM, Broos WAM, Roeleveld TA, Donker R, Ten Oever D, Geenen RWF, Knol RJJ. ^{18}F-DCFPyL PET/CT for primary staging in 160 high-risk prostate cancer patients; metastasis detection rate, influence on clinical management and preliminary results of treatment efficacy. Eur J Nucl Med Mol Imaging. 2021 Feb;48(2):521-531. doi: 10.1007/s00259-020-04782-2. Epub 2020 Jul 27. PMID: 32719916.

5. Hong J, Han K, Jung J, Kim JS. Association of Exposure to Diagnostic Low-Dose Ionizing Radiation With Risk of Cancer Among Youths in South Korea. *JAMA Netw Open.* 2019;2(9):e1910584. doi:10.1001/jamanetworkopen.2019.10584.
6. Vaiserman A, Koliada A, Zabuga O, Socol Y. Health Impacts of Low-Dose Ionizing Radiation: Current Scientific Debates and Regulatory Issues. *Dose Response*. 2018;16(3):1559325818796331. Published 2018 Sep 19. doi:10.1177/1559325818796331
7. Yasser, A. F., Cucinotta, F. A., Ning-Ang, L., Zhou, G. (2020). Cancer Risk of Low Dose Ionizing Radiation. *Frontiers in Physics, 8* 1-9. http://dx.doi.org/10.3389/fphy.2020.00234

APPENDIX

The following describes the general workflow:

- For patients who have SOC imaging within 6 weeks prior to SOC [18F]-DCFPyL PET-CT, suspicious lesion(s) should be identified prior to [18F]-DCFPyL PET-CT.
- Upon completion of SOC [18F]-DCFPyL PET-CT, the images are loaded into the contouring system (e.g., Eclipse, MIM).
- The radiation oncologist identifies the lesion(s) on the SOC [18F]-DCFPyL PET-CT to be imaged on X1 RMRS. Ideally PET-positive lesions should be between 1-5 cm although PET-positive lesions < than 1 cm are acceptable.
- If no lesion is identified, the patient will be informed that he will not need to undergo imaging on X1 RMRS. This patient will be non-evaluable for this study.
- A basic contour of PTV and BTZ is created for each lesion identified. The PTV should be at least 1 cm in diameter. The BTZ should add 10 mm or more depending on the anticipated amount of target motion for each lesion. A dummy OAR is also created.



- Load the CT and contour(s) into X1 RMRS.
- Create an image-only plan with patient reference point (laser confirmation) (to be done by the physicist).
- Safely position the patient onto X1 table, head first, supine: as comfortable and as close to the SOC [18F]-DCFPyL PET-CT position as possible.
- A kVCT localization followed by PET acquisition is then performed on the X1 RMRS.
- Prioritize pelvic lesion(s) first, before bladder accumulates activity, and low SUV lesions first.
- Safely remove the patient from the X1 RMRS.

The estimated time for steps on the X1 RMRS is as follows:

- Loading Patient onto Couch: 5 mins
- Patient Setup: 5 - 10 mins
- Confirming Laser and Move to Scan: 3 mins
- kVCT scan: 3 - 5 mins
- Imaging-only PET scan (depending on scan length): 20 - 35 mins
- Unloading patient from couch: 5 mins
- TOTAL TIME: 40 - 65 mins

Detailed Timeline

Time Point (min)	Nuc Med Tech	CRN	Rad Onc MD	Physicists and technologists
0	Infuse of pylarify	Notify X1, physicist and rad onc MD		
60	Scan starts	Notify X1, physicist and rad onc MD		
90	Scan ends Images moved to PACS (10-20min)	Notify X1, physicist and rad onc MD Transport patient	Scans reviewed and lesion(s) selected Contours added	
105		Patient arrives in Rad Onc		Load the CT and contour(s) into X1 RMRS.X1 system Create an image-only plan with patient reference point (laser confirmation)
120				Put patient onto Couch: 5 mins Patient Setup: 5 - 10 mins Confirm Laser and Move to Scan: 3 mins kVCT scan: 3 - 5 mins Imaging-only PET scan: 20 - 35 mins Remove patient from couch: 5 mins TOTAL TIME: 40 - 65 mins
180				Completed