Stanford Cancer Institute

A Phase 2 Study of ^{18}F-FTC-146 PET/CT in Patients with Newly-Diagnosed Osteosarcoma

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IRB-52746 SARCOMA0041 NCT04365660 IND [redacted]

Version 4, 29 March 2021

(initial) SRC Approval Date: 30 January 2020

PROTOCOL HISTORY TABLE

Version no.	Version Date	Summary or Rationale (brief, following are example changes)
1	16 January 2020	Initial SRC approved protocol on 30 January 2020
2	12 February 2020	1. Minor corrections on doses of ^{18}F-FTC-146
3	27 October 2020	1. Add +/- 20% to dose of ^{18}F-FTC-146. 2. Add information on limited dynamic PET emission scan: A low dose CT will be obtained from vertex to toes; this will use 120 kV and dose modulation based on body habitus, ranging 10 to 105 mA. This will be followed by 30 to 60-minute limited dynamic PET emission scan in a region of interest of known osteosarcoma (a 30-minute scan will be obtained for most patients; this may be extended for up to 60 minutes in 1 to 2 patients). Immediately after the limited dynamic scan, a static whole-body PET emission scan will be acquired (approximately 25 minutes). 3. NCT number added
4	15 March 2021	• Defines that only AEs and SAEs related to PET/CT procedure will be collected and recorded. Related adverse events will be recorded from the time the subject signs informed consent and for 30 days from the time of the last investigational scan. SAEs will be tracked until resolution and 30 days after the last investigational scan. • Inserted Section 4.1 “Treatment / Procedure Plan,” to provide information on screening assessments, enrollment, study procedures, and completion of participation. Subsequent section re-numbered. • Study calendar updated. • Defines that the PROMIS questionnaire may be completed within 2 weeks prior to investigational scans. • Defines that a subject’ participation in the study is complete once the final investigational scan; the PROMIS questionnaire; and pathology report has been collected. • Adds field for unique subject identifier and standard study identifier fields to the Inclusion/Exclusion Criteria Checklist (Appendix A). Also adds 2 additional signature lines for a total of 3 signature lines for eligibility triple check.
5	29 March 2021	• Removes Exclusion Criteria regarding biopsy-proven osteosarcoma that was reviously added in error.

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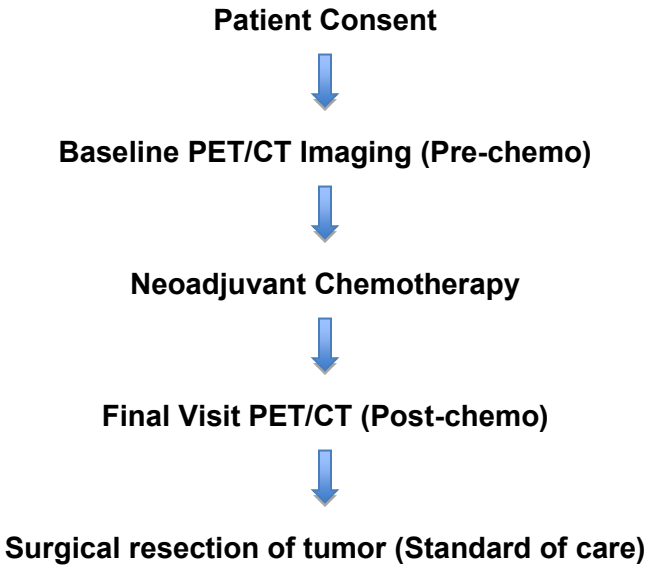
PROTOCOL SYNOPSIS

TITLE	A Phase 2 Study of ^{18}F-FTC-146 PET/CT in Patients with Newly-Diagnosed Osteosarcoma
STUDY PHASE	Phase 2
INDICATION	Tumor imaging
INVESTIGATIONAL PRODUCT	^{18}F-FTC-146
PRIMARY OBJECTIVE(S)	Demonstrate correlation of pre-post reduction in ^{18}F-FTC-146 PET/CT with amount of post-treatment tumor necrosis in newly-diagnosed and treated osteosarcoma patients.
SECONDARY OBJECTIVE(S)	Demonstrate correlation of pre-post reduction in ^{18}F-FTC-146 PET/CT with amount of post-treatment pain reduction in newly-diagnosed and treated osteosarcoma patients.
TREATMENT SUMMARY	Participants will be assessed with ^{18}F-FTC-146 PET/CT imaging at baseline and after neoadjuvant (pre-surgery) chemotherapy but before surgery itself.
SAMPLE SIZE	5
STATISTICAL CONSIDERATIONS	Descriptive statistics and correlations will be calculated. Means, medians, and standard deviations of: 1. Histologically determined percentage of necrosis in post-chemotherapy resected tumor. 2. Pre- and post-treatment SUVmax in tumor ROI, and the pre-post percent change. 3. Pre- and post-treatment pain score, and the pre-post difference. **Primary Analysis** 1. The following will be recorded for each patient (a) the histological percentage of necrosis and (b) the percent reduction in SUVmax. 2. The histological percent necrosis will be plotted against SUVmax percent reduction to calculate rank correlation. **Secondary Analysis** 1. The following will be recorded for each patient (a) the post-treatment reduction in pain score (b) the percent reduction in SUVmax 2. The reduction in pain score will be plotted against SUVmax reduction to calculate rank correlation. **Sample Size** Preliminary approval for this study is for 5 subjects only. An eventual sample size of 20 will provide 90% power at one-sided 5% error to detect a correlation as low as 0.60.

SCHEMA


Patient Consent
Baseline PET/CT Imaging (Pre-chemo)
Neoadjuvant Chemotherapy
Final Visit PET/CT (Post-chemo)
Surgical resection of tumor (Standard of care)

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS (Example)

CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CSM	Conventional Staging Method
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG Performance Status	Easter Cooperative Oncology Group Performance Status
EFS	Event Free Survival
FDG	Fluorodeoxyglucose
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IPI	International Prognostic Index
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
NHL	Non-Hodgkin’s Lymphoma
NPV	Negative Predictive Value
OS	Overall survival
PET/CT	Positron emission tomography – computed tomography
PLT	Platelet
PD	Progressive diseased
PPV	Positive Predictive Value
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RM	Residual Mass

ROC	Receiver-Operative-Characteristic
RR	Response rate
S1R	Sigma-1 receptor
SAE	Serious adverse event
SD	Stable disease
SUV	Standard Uptake Value
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1. OBJECTIVES

1.1. **Primary Objective**

Demonstrate correlation of pre-post reduction in ^{18}F-FTC-146 PET/CT with amount of post-treatment tumor necrosis in newly-diagnosed and treated osteosarcoma patients.

1.2. **Secondary Objective**

Demonstrate correlation of pre-post reduction in ^{18}F-FTC-146 PET/CT with amount of post-treatment pain reduction in newly-diagnosed and treated osteosarcoma patients.

2. BACKGROUND

2.1. **Study Disease**

Osteosarcomas are the most common bone sarcomas in adults. Patients with localized disease are curable with neoadjuvant chemotherapy followed by surgical resection. The single most important prognostic factor is the percent necrosis in the post-chemotherapy resected specimen. Patients with tumors > 90% necrosis have an excellent long-term survivals. However, patients with < 90% necrosis have a poor prognosis with early signs of disease recurrence with metastatic spread.

2.2. **Study Agent/Device/Imaging Procedure**

Fredrick Chin, PhD, has developed a novel sigma-1 receptor (S1R) imaging probe, ^{18}F-FTC-146, that is highly-selective for targeting S1R expressed in brain. S1Rs are widely distributed throughout the brain where they interact with ion channels and neurotransmitters involved in learning, memory, and the development of compulsive behavior. The proposed research is technically innovative because of its use of ^{18}F-FTC-146, the only known tracer that does not suffer from off-target binding and *in vivo* instability, for S1Rs. The S1R targeting specificity of ^{18}F-FTC-146 has already been studied in rodents, monkeys, and more recently in humans. With the departmental support provided by Dr Sanjiv Sam Gambhir (Chair, Department of Radiology), Dr Chin, in collaboration Sanjiv Sam Gambhir, MD, first obtained an Exploratory Investigational New Drug Application (IND 126459) to use ^{18}F-FTC-146 in first-in-human studies, and have previously converted the exploratory IND to a full IND (IND [redacted]) .

Since Dr Chin has shown that ^{18}F-FTC-146 has excellent affinity to S1R (> 100,000-fold higher than any other receptor targets in the brain including S2R) and the lipophilicity of this ligand (logD pbs7.4 = 1.45) falls in an ideal range for the Blood Brain Barrier, these favorable properties allow ^{18}F-FTC-146 to be a promising candidate for selective PET S1R-neuroimaging. He has made ^{18}F-FTC-146 and knows its biodistribution and pharmacokinetics in mice. The radiotracer displays good distribution volume (~2.4) and excellent S1R-specificity and selectivity in WT vs S1R knockout (KO) mice. S1R expression level strongly correlated with ^{18}F-FTC-146 autoradiography signal in brain regions with high S1R expression when compared with immunohistochemical staining. To determine

test-retest variability of brain uptake (%ID/g), 3 healthy mice were injected with ^{18}F-FTC-146 with a 7-day interval between measurements, and results ranged from 10 to 17% in 10 brain regions. In rat biodistribution studies, ^{18}F-FTC-146 demonstrated specific uptake in S1R rich rat organs, including the lungs, pancreas, spleen, and brain. Preliminary monkey PET/MRI studies revealed similar ^{18}F-FTC-146 accumulation in brain (mainly in cortical structures, cerebellum, and vermis) that could be attenuated by pretreatment with S1R agonist haloperidol. In addition, he also performed supporting dosimetry and toxicity studies in rodents for clinical translation. An Exploratory Investigational New Drug (eIND) Application for ^{18}F-FTC-146 was submitted to the Food and Drug Administration (FDA) for first-in-human studies to examine radiotracer biodistribution and pharmacokinetics and first-in-human studies in typically developing volunteers (N = 10) and patients with pain (N = 30) were performed by his group. His initial evaluation of ^{18}F-FTC-146 in humans shows that this radiotracer is safe and the adsorbed radiation doses measured are acceptable to be used for other indications including OCD, HD, and other neurodegenerative diseases. More recently, eIND 126459 was converted to full IND [redacted] (activated 9 May 2018).

2.3. **Clinicaltrials.gov**

This study of ^{18}F-FTC-146 for PET/CT imaging is investigational, and has been submitted to IND [redacted].

This study is registered on ClinicalTrials.gov as NCT04365660.

2.3.1. Clinicaltrials.gov Outcomes

2.3.1.1 Primary Outcome (Outcome 1)

Title: Detection of tumor necrosis post-chemotherapy

Description: Participants will be assessed with ^{18}F-FTC-146 PET/CT imaging at baseline and after neoadjuvant (pre-surgery) chemotherapy but before surgery itself. Chemotherapy will be nominally three 3-week cycles administered over up to 12 weeks. The ability of ^{18}F-FTC-146 PET/CT to evaluate treatment effect will be assessed as the percentage of tumor that is assessed as necrotic after the treatment course. The outcome will be reported as the mean percentage of the resected tumor (removed by surgery) that is assessed by histopathology as necrotic, with standard deviation.

Timeframe: 12 weeks

2.3.1.2 Secondary Outcomes

Outcome 2

Title: Maximum Standardized Uptake Value (SUVmax)

Description: Participants will be assessed with ^{18}F-FTC-146 PET/CT imaging at baseline and after neoadjuvant (pre-surgery) chemotherapy but before surgery itself. Chemotherapy will be nominally three 3-week cycles administered over up to 12 weeks. Based on the PET/CT scans, the maximum standardized uptake value (SUVmax) in the tumor region of interest (ROI) will be calculated at baseline and after treatment. The outcome will be reported as the mean percent change in SUVmax from baseline to post-treatment, with standard deviation.

Timeframe: 12 weeks

Outcome 3

Title: Use of PROMIS (Patient-Reported Outcomes Measurement Information System) to Assess Treatment Effect

Description: Participants will receive neoadjuvant (pre-surgery) chemotherapy, nominally three 3-week cycles administered over up to 12 weeks. The treatment effect of the neoadjuvant chemotherapy will be assessed as the change in scores on the PROMIS (Patient-Reported Outcomes Measurement Information System) questionnaire, from baseline to post-treatment. The result will be reported as the mean difference from baseline to post-treatment, with standard deviation.

Timeframe: 12 weeks

2.4. **Rationale**

Currently, there is no accurate imaging modality evaluating the amount of necrosis in the tumor after neoadjuvant chemotherapy. This study will evaluate the amount of tracer uptake in osteosarcoma tumors prior to chemotherapy and after neoadjuvant chemotherapy. We would also like to see if the uptake correlates with pain. This is a feasibility study, but we will try to correlate the amount of tracer uptake with the amount of necrosis in this small patient population. If there is correlation, we will proceed with a larger study to confirm the results.

2.5. **Preliminary results**

The pre-clinical information below is from a personal communication with Brian K Flesner, DVM, MS, DACVIM (Oncology); Assistant Professor of Oncology, College of Veterinary Medicine at the University of Missouri.

Current evidence for pain/gait outcomes in canine osteosarcoma is described by relatively few studies. Subjective owner questionnaires, force plate analysis, and serum biomarkers

have been utilized to assess response. His group hypothesized that intervention would cause objective evidence of pain control when evaluating S1R activity in canine tumors. Evaluations of 3 dogs with primary bone cancer included ^{18}F-FTC-146 PET/CT scans, gait and kinematic motion analysis, validated owner questionnaires (CBPI), and serum N-telopeptide (NTx) concentration. Dogs received baseline staging; ^{18}F-FTC-146 PET prior to treatment and on Day 28; and Day 0; 7; 14; and 28 CBPI; serum banking for NTx; orthopedic exam; and gait analysis. Each dog received a different treatment: Dog 1 received radiation and zoledronate; Dog 2 received single agent zoledronate; and Dog 3 had an amputation. Dog 1 had a 50% decrease in S1R activity on its day 28 PET scan. Dog 2 had a 25% decrease in activity. Dog 3 will have its second scan in the next few weeks. Both dogs finishing their treatment have had improvement in subjective pain assessment. Data analysis of their CBPI, NTx, and force plate stance are underway.

2.6. **Study Design**

This is an open-label, single-arm phase 2 study to evaluate ^{18}F-FTC-146 PET/CT in newly-diagnosed osteosarcoma patients.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

3.1. **Inclusion Criteria**

3.1.1 Patients with biopsy-proven osteosarcoma requiring local surgical intervention

3.1.2 Age ≥ 18 years

3.1.3 ECOG ≤ 2

3.1.4 Ability to understand and the willingness to sign a written informed consent document

3.2. **Exclusion Criteria**

3.2.1 Chemotherapy in the past 2 months

3.2.2 Prior history of allergic reaction to ^{18}F-FTC-146

3.2.3 Pregnant or nursing

3.3. **Informed Consent Process**

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4. **Study Timeline**

3.4.1. Primary Completion:

Primary completion is the date that the final datum is obtained/expected to be obtained for the primary outcome. The timeframe for primary completion for an individual subject

is approximately 3 to 4 months from time of consent. This datum is expected to be obtained approximately 12 months from the time the study opens to accrual.

3.4.2. **Study Completion**:

The study is expected to reach overall completion (last datum from last subject) approximately 18 months from the time the study opens to accrual.

4. IMAGING AGENT/DEVICE/PROCEDURE INFORMATION

4.1. **Treatment / Procedure Plan**

This is a phase 2 study of ^{18}F-FTC-146 PET/CT in patients with newly-diagnosed osteosarcoma. The study will be conducted at Stanford University.

This study will be conducted over the period in which subjects receive 3 cycles of neoadjuvant chemotherapy, which is standard of care. This time period may vary from subject to subject. Each participant will be individually told how long their chemotherapy will take.

It is anticipated that this study will require approximately 3 days of active participation from each study subject and will involve:

- Screening assessments,
- Two ^{18}F-FTC-146 PET/CT scans
- Two PROMIS Questionnaires surveys, ie, Quality of Life (QoL) surveys (Appendix B)

Participants must sign the IRB-approved consent form prior to participation in any study-specific procedure.

Screening: Screening assessments must occur within 28 days prior to start of treatment. Screening tests, examinations, or procedures include:

- Demographics: Date of birth, sex, ethnicity.
- Medical history: Review of medical history, including surgery and cancer history, other cancer treatments subject has received, current and past medicines subject is taking or has taken, and reproductive status.
- Performance status: Subject will be asked about their ability to perform everyday tasks.
- β-HCG (pregnancy test): β-HCG must be done within 7 days of first scan. Subjects who are currently pregnant or breast-feeding may not participate in this study. It is not known whether ^{18}F-FTC-146 is safe for the fetus (unborn child) or a breast-fed baby.

Enrollment:

Subjects may be enrolled into the study if they meet all eligibility requirements.

Study Procedures:

- **2 PET/CT Scans**
- **2 PROMIS QoL surveys**

The ^{18}F-FTC-146 PET/CT scans and QoL surveys will occur before subjects start chemotherapy and the final study visit will occur after subjects have completed chemotherapy. It is anticipated that the entire research study will take approximately 1 year.

PET/CT: All subjects in this study will receive 2 PET/CT scans using the experimental investigational radiotracer ^{18}F-FTC-146. After receiving an ^{18}F-FTC-146 PET/CT scan at baseline, subjects will receive 3 cycles of neoadjuvant chemotherapy as determined by their oncologist. This treatment is part of subject's regular medical care. At the final study visit, after completing the 3 cycles of neoadjuvant chemotherapy, subjects will have a 2nd PET-CT scan.

PROMIS Questionnaires: At the baseline Study Visit (before first scan) and Final Study Visit (before second scan), subjects will be asked to complete questionnaires about pain intensity and pain interference with their life.

Completion of participation:

Patient's participation in the study is complete 30 days after the final investigational scan, once the PROMIS questionnaire and pathology report have been collected.

4.2. **PET/CT Scan**

- **Radionuclide or imaging agent and chemical form:** ^{18}F-FTC-146
- **Number of radioisotope / imaging agent administrations; route of administration; and administered activity in mCi)**: For PET scans, each subject will receive a manual, injection of 10 mCi +/- 20% ^{18}F-FTC-146 intravenously; this is usually through a peripheral IV line in the extremities, and may also be through a peripherally inserted central catheter (PICC line), a Port-A-Cath, or Hickman catheter. These participants will be administered twice with ^{18}F-FTC-146, once at baseline (pre-chemotherapy) and once at final study visit (post chemotherapy).
- **Dosimetry information:**

  We estimate that the amount of radiation exposure is about 19.2 mSv, which is approximately equal to 38% of the limit that radiation workers (for example, a hospital x-ray technician) are allowed to receive in one year. (Hjørnevik, *et al*, 2017)

  An Exploratory Investigational New Drug (eIND) Application for ^{18}F-FTC-146 (IND [redacted]) was approved by the Food and Drug Administration (FDA) for first-in-human studies to examine radiotracer biodistribution and pharmacokinetics and first-in-human studies in typically developing volunteers (N = 10) and patients with pain (N = 15) [see reference below] were performed by our group. (Cipriano, *et al*, 2018; Shen B, *et al*, 2017; Hjørnevik, *et al*, 2017)

  Our initial evaluation of ^{18}F-FTC-146 in humans provided evidence that this radiotracer is safe and the adsorbed radiation doses measured are acceptable to be used for other indications including OCD, HD, and other neurodegenerative diseases. (Cipriano, *et al*, 2018; Shen B, *et al*, 2017; Hjørnevik, *et al*, 2017) In May 2018, eIND 126459 was successfully converted to the full IND 136678.

- **Source of the study agent:** ^{18}F-FTC-146 will be prepared under aseptic conditions and its quality assessed in the MIPS Cyclotron and Radiochemistry Facility within the Division of Nuclear Medicine and Molecular Imaging at Stanford Hospital and Clinics.
- **Agent ordering:** The agent will be requested by a member of the study team, and prior to radiopharmaceutical administration, use of ^{18}F-FTC-146 will be approved and prescribed by a study investigator or sub-investigator.
- **Radionuclide / imaging agent management, control, and security :** A member of the research team trained in radiation safety will securely transport the dose of ^{18}F-FTC-146 to the PET/CT suite in the Stanford Nuclear Medicine for imaging. The nuclear medicine technologist will follow radiation safety procedures when checking in the package.
- **Scan description (for well-established imaging procedures):** A low-dose CT will be obtained from vertex to toes; this will use 120 kV and dose modulation based on body habitus, ranging 10 to 105 mA. This will be followed by 30 to 60-minute limited dynamic PET emission scan in a region of interest of known osteosarcoma (a 30-minute scan will be obtained for most patients; this may be extended for up to 60 minutes in 1 to 2 patients). Immediately after the limited dynamic scan, a static whole-body PET emission scan will be acquired (approximately 25 minutes).
- **Number of scans to be performed on a single research subject:** Each subject will receive 2 PET/CT scans.
- **For each imaging procedure provide the setup and technique sufficient to permit research subject radiation dose modeling:** The chief technologist can usually provide this information. Set up will be according to standard institutional practice for whole body PET/CT scans.

5. STUDY PROCEDURES

5.1. Criteria for Removal from Study

Subjects will be removed from the study if there is withdrawal of consent, non-compliance, or if the subject is female and has become pregnant.

5.2 Alternatives

The alternative is to not be on this study and receive standard of care treatment.

6. STUDY CALENDAR

	Screening [b]	Baseline (Pre-chemo)	Final Visit [e]
Investigational Scan [a]		X	X
Informed consent	X		
Demographics	X		
Medical history	X		
Height		X	
Weight		X	
Performance status	X		
β-HCG	X		
PROMIS Questionnaires		X [c]	X [c]
Adverse event evaluation [d]		X	X
Pathology report			X [e]

a Patients will receive neoadjuvant chemotherapy, which is standard of care. It is not part of this protocol. Neoadjuvant chemotherapy will start after baseline investigational scan. The second investigational scan will occur after neoadjuvant chemotherapy.

b Screening: Screening period is 28 days. β-HCG must be done within 7 days of first scan.

c Patients will complete PROMIS questionnaires at Baseline (before 1st scan) and at Week 9 (before 2nd scan). Questionnaire may be completed within 2 weeks prior to each investigational scan.

d Adverse events: Adverse events will be recorded from the time of the first investigational scan and for 30 days from the time of the final investigational scan. Only AEs related to PET/CT procedure will be collected and recorded.

e Patient's participation in the study is complete 30 days after the final investigational scan, once the PROMIS questionnaire and pathology report have been collected.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1. Potential Adverse Events

The patients will be injected with ^{18}F-FTC-146, which is an investigational drug. An IND application has previously been filed with FDA (IND [redacted] IND-holder Guido Davidzon, MD). Toxicity studies performed by unbiased party have shown no treatment related toxicity at 3 and 15 days after treatment with a single dose (250-fold the expected clinical dose) in a single rodent species. There are no known pharmacological risks of the drug. However, there is risk of radiation dose as described below.

This research study involves exposure to radiation from two 10 mCi +/- 20% doses of ^{18}F-FTC-146. The radiation exposure from two 10 mCi +/- 20% doses of ^{18}F-FTC-146 is

maximally 19.2 mSv, which is approximately equal to 38% of the limit that radiation workers (for example, a hospital X-ray technician) are allowed to receive in 1 year. This amount of radiation involves minimal risk and is necessary to obtain the research information desired.

7.2. **Adverse Event Reporting**

Adverse events will be graded according to CTCAE v5.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study-specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochures, and related to the investigation. Only adverse events related to PET/CT procedure will be captured. All Serious Adverse Events (SAEs) will be tracked until resolution and 30 days after the last investigational scan.

8. REGULATORY CONSIDERATIONS

8.1. **Institutional Review of Protocol**

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants, questionnaires) will be reviewed and approved by the Stanford IRB and Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB and SRC prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

8.2. **Data Management Plan**

The research coordinator will be responsible for database records of subject data. The data will be kept in an OnCore online database, under password protection with access limited to specific areas of the database. A chart with all of the relevant research subject information will be maintained for each subject by the research coordinator. Subject charts will be reviewed by Stanford PI and Study Coordinator for yearly audits.

8.3. **Data and Safety Monitoring Plan**

The Protocol Director will oversee the conduct of the trial.

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will audit study related activities at least annually in accordance with the DSMC SOP to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of regulatory binders, case report forms, medical notes, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of DSMC audits will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

9. MEASUREMENTS

9.1. Primary and Secondary Endpoints

1. Histologically-determined percentage of necrosis in post-chemotherapy resected tumor.
2. Pre- and post-treatment SUVmax in tumor ROI, and the pre-post percent change.
3. Pre- and post-treatment pain score, and the pre-post difference.

9.2. Measurement Methods

1. Assessment of necrosis in osteosarcoma specimens is performed by subspecialized bone-soft tissue pathologists and pediatric pathologists. The resection specimen is sequentially sliced at 0.5 cm intervals to yield a series of macrosections. A full single macrosection, including tumor, is entirely submitted for microscopic evaluation with the coordinates of histologic sections mapped to a photograph of the macrosection. Histologic assessment of the proportion of viable tumor is performed on H&E-stained sections.
2. PET SUVmax will be measured in an ROI drawn over the lesion (based on CT).
3. Patients will rate pain level using PROMIS (Patient-Reported Outcome Measurement Information System) Questionnaires.

9.3. Measurement Time Points

1. Imaging and pain measurements will be made just before and after treatment (3 cycles of chemotherapy).
2. Tumor histology will be measured on the post-chemotherapy resected tumor, after the second PET/CT scan.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical Design

This is an one-arm, non-randomized prospective cohort study.

10.2. Descriptive Statistics and Exploratory Data Analysis

Descriptive statistics and correlations will be calculatedconsisting of the means, medians, and standard deviations of:

1. Histologically determined percentage of necrosis in post-chemotherapy resected tumor.
2. Pre- and post-treatment SUVmax in tumor region of interest (ROI), and the pre-post percent change.
3. Pre- and post-treatment pain score, and the pre-post difference.

10.3. **Primary Analysis**

10.3.1. Analysis Population

All enrolled subjects.

10.3.2. Analysis Plan

1. The following will be recorded for each patient

   (a) the histological percentage of necrosis and

   (b) the percent reduction in SUVmax.

2. The histological percent necrosis will be plotted against SUVmax percent reduction to calculate rank correlation.

10.4. **Secondary Analysis**

10.4.1. Analysis Population

All enrolled subjects.

10.4.2. Analysis Plan

1. The following will be recorded for each patient

   (a) the post-treatment reduction in pain score.

   (b) the percent reduction in SUVmax.

2. The reduction in pain score will be plotted against SUVmax reduction to calculate rank correlation.

10.5. **Sample Size**

Preliminary approval for this study is for 5 subjects only. An eventual sample size of 20 will provide 90% power at one-sided 5% error to detect a correlation as low as 0.60.

10.6. **Accrual estimates**

Stanford treats roughly 8 to 10 adult osteosarcoma patients per year. We expect to be able to recruit at least half of them.

10.7. **Criteria for future studies**

This study will be judged to be successful if both:

(a) the correlation between necrosis and PET signal reduction is ≥ 0.60.

(b) the correlation between pain reduction and PET signal reduction is ≥ 0.60.

11. REFERENCES

Cipriano PW, Lee SW, Yoon D, *et al*. "Successful treatment of chronic knee pain following localization by a sigma-1 receptor radioligand and PET/MRI: a case report." *Journal of Pain Research*. 2018;11:2353.

Shen B, Park JH, Hjørnevik T, *et al*. "Radiosynthesis and First-In-Human PET/MRI Evaluation with Clinical-Grade 18F-FTC-146." *Molecular Imaging and Biology*. 2017;19(5):779-786.

Hjørnevik T, Cipriano PW, Shen B, *et al*, Gambhir SS. "Biodistribution and radiation dosimetry of 18F-FTC-146 in humans." *Journal of Nuclear Medicine*. 2017;58(12):2004-2009.

Appendix A: Inclusion/Exclusion Criteria Checklist

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

Protocol Information

Protocol Title:	A Phase 2 Study of ^{18}F-FTC-146 PET/CT in Patients with Newly-Diagnosed Osteosarcoma
eProtocol number: OnCore number:	IRB-52746 SARCOMA0041
Principal Investigator:	Kristen Ganjoo, MD

Subject Unique ID: SAR41-____ ____			
Inclusion Criteria (From IRB-approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Patients with biopsy-proven osteosarcoma requiring local surgical intervention.	☐	☐	
2. Age ≥ 18 years	☐	☐	
3. ECOG ≤ 2	☐	☐	
4. Ability to understand and the willingness to sign a written informed consent document.	☐	☐	
Exclusion Criteria (From IRB-approved protocol)			
1. Chemotherapy in the past 2 months.	☐	☐	
2. Prior history of reaction to ^{18}F-FTC-146.	☐	☐	
3. Pregnancy or nursing patients	☐	☐	

IV. Statement of Eligibility

This subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study.

Study Coordinator printed name:	Date:
Signature:	

Investigator printed name:	Date:
Signature:	

Triple-check reviewer printed name:	Date:
Signature:	

Appendix B: PROMIS (Patient-Reported Outcomes Measurement Information System) Questionnaires

Pain Intensity – Scale

Please respond to each item by marking one box per row.

	In the past 7 days…	Had no pain	Mild	Moderate	Severe	Very severe
PAINQU6	How intense was your pain at its worst?....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINQU8	How intense was your average pain?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		No pain	**Mild**	**Moderate**	**Severe**	**Very severe**
PAINQU21	What is your level of pain right now?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Intensidad del dolor – Cuestionario abreviado 3a

Responda a cada pregunta marcando una casilla por línea.

	En los últimos 7 días …	No tuve dolor	Muy poco	Moderado	Intenso	Muy intenso
PAINQU6	¿Qué intensidad tuvo el dolor en su peor momento?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINQU8	¿Qué intensidad tuvo el dolor que sintió en su punto medio?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
		Ningún dolor	**Muy poco**	**Moderado**	**Intenso**	**Muy intenso**
PAINQU21	¿Cuál es su nivel de dolor en este momento?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Spanish (Universal)
06 September 2012

Pain Interference – Short Form 4a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
PAININ9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ34	How much did pain interfere with your household chores?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Efectos del dolor – Cuestionario abreviado 4a

Responda a cada pregunta o enunciado marcando una casilla por línea.

	En los últimos 7 días ...	**Nada**	**Un poco**	**Algo**	**Mucho**	**Muchísimo**
PAININ91	¿En qué medida el dolor interfirió en sus actividades diarias?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ222	¿En qué medida el dolor interfirió en el trabajo en el hogar?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ313	¿En qué medida el dolor interfirió en su capacidad para participar en actividades sociales?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ344	¿En qué medida el dolor interfirió en sus tareas domésticas?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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