A PILOT STUDY OF [^{18}F]F-ARAG PHARMACOKINETICS IN TUMORS AND NON-MALIGNANT TISSUE USING DYNAMIC TOTAL BODY PET IMAGING IN HEALTHY SUBJECTS AND IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (NSCLC)

Study Number:	CST-FARAG-203
Indication:	Non-Small Cell Lung Cancer (NSCLC)
Phase:	Pilot
Funding Source(s):	Cellsight
Agent / Modality:	**[^{18}F]F-ARAG/TOTAL BODY PET IMAGING**
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PROTOCOL SIGNATURE PAGE

Protocol Number: CST-FARAG-203

Protocol Title: A Pilot Study of [^{18}F]F-ARAG Pharmacokinetics in Tumors and Non-Malignant Tissue using Dynamic Total Body PET Imaging in Healthy Subjects and in Patients with Non-Small Cell Lung Cancer (NSCLC)

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

Simon R. Cherry, PhD
Investigator Name (print)

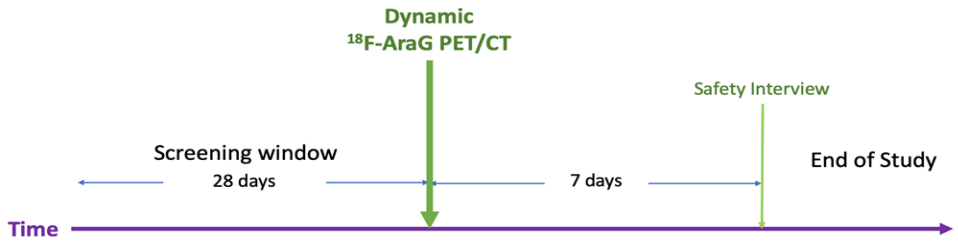
_____
Investigator Signature

_____
Date

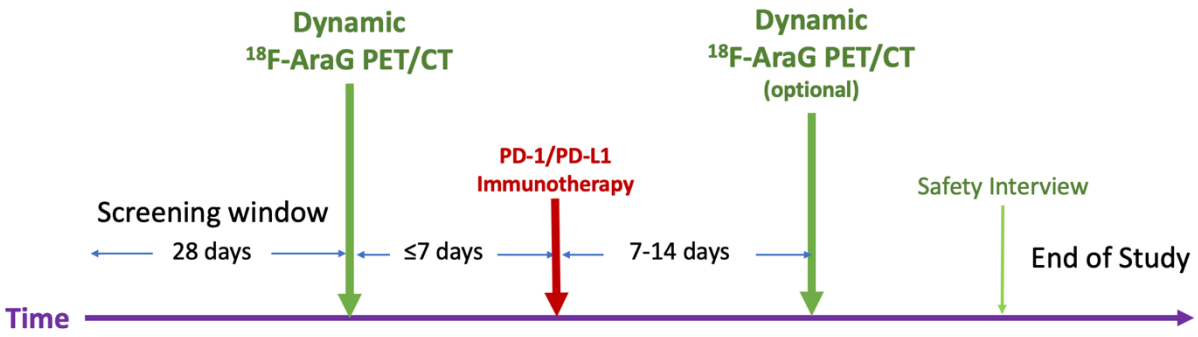
SCHEMA

Name of Sponsor/Company: CellSight Technologies	
Name of Study Product: [^{18}F]F-AraG	
Protocol Number: CST-FARAG-203	**Indication:** • Healthy subjects • non-small cell lung cancer (NSCLC) patients
Title of Study: A pilot study of [^{18}F]F-AraG pharmacokinetics in tumors and non-malignant tissue using dynamic total body PET imaging in healthy subjects and in patients with non-small cell lung cancer (NSCLC).	
Study Center: UC Davis Comprehensive Cancer Center	
Planned Number of Subjects: 2-4 healthy subjects 2-4 NSCLC subjects	**Study Development Phase:** Phase I/II
Study Outcome Measures: • Quantitative assessment of [^{18}F]F-AraG biodistribution in healthy tissues as a function of time. • Quantitative assessment of [^{18}F]F-AraG biodistribution in tumor lesions relative to non-malignant tissues in NSCLC subjects as a function of time. • Recommended post-infusion time window to acquire a static [^{18}F]F-AraG PET/CT scan. • Quantitative assessment of change in PET signal pre- and post- first dose of PD-1/PD-L1 immunotherapy.	

Study Flow Diagram (Healthy Subjects)



Study Flow Diagram (NSCLC Subjects)



NOTES:

1. IMMUNOTHERAPY IS NOT A PART OF THIS STUDY BUT IS A PART OF SOC TREATMENT OF THESE PATIENTS
2. THE POST-TREATMENT [^{18}F]F-ARAG PET/CT SCAN IS OPTIONAL FOR PATIENTS

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LIST OF ABBREVIATIONS

%	Percent
AE	Adverse Event
ANCOVA	Analysis of Covariance
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CRF	Case Report Form
CFR	Code of Federal Regulations
CRO	Contract Research Organization
CT	Computed Tomography
CTL	Cytotoxic T-Lymphocytes
CTCAE	Common Terminology criteria for Adverse events
CV	Curriculum vitae
DLT	Dose Limiting Toxicity
DP	Drug Product
DSMC	Data Safety and Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorine-18-flurodeoxyglucose
g/dL	grams/deciliter
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practices
HPB	Human Peripheral Blood
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart Rate
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
IEC	Independent Ethics Committee
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IUD	Intra Uterine Device
IV	Intravenous
Kg	Kilograms
Mg	Milligram
mCi	MilliCurie
MRI	Magnetic resonance imaging
MedDRA	Medical Dictionary for Regulatory Activities
mg/dL	Milligram/deciliter
mmol/L	Millimole/Liter

msec	Milliseconds
NSCLC	Non-Small Cell Lung Cancer
PBMC	Peripheral Blood Monocyte Cells
PD1	Programmed cell death protein
PDL1	Programmed cell death protein ligand
PET	Positron emission tomography
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
RBC	Red Blood Cells
RECIST	Response evaluation criteria in solid tumors
RR	Respiration Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	Standard of Care
SOP	Standard Operating Procedures
SUV	Standardized uptake value
TBD	To be determined
TEAE	Treatment Emergent Adverse Event
TV	Treatment Visit
Tx	Treatment, Cancer Treatment
U/L	Units/Liter
USA	United States of America
USP	United States Pharmacopeia
WBC	White Blood Cells
WBS	Whole Body Scan
WHO	World Health Organization
µL	Microliter

1. BACKGROUND

1.1 Therapy Approaches for NSCLC

Lung cancer is the leading cause of cancer-related deaths in both men and women in the US. (https://seer.cancer.gov/statfacts/html/lungb.html). The majority of NSCLC patients present with advanced or metastatic disease, which is not amenable to surgical resection.

Immunotherapy has attracted much attention in recent years, since (i) identification of molecularly-defined tumor antigens (TA) [1, 20] has provided well defined moieties to be used as immunogens and as markers to monitor the immune response; (ii) characterization of the molecular steps leading to an immune response [5, 6] has facilitated the development of effective immunization strategies; and (iii) availability of cytokines has provided reagents to modulate the immune response. Because of the general belief that T cells play a major role in the control of tumor growth [15, 16], the application of T cell-based immunotherapy has been emphasized.

1.2 Immune-Checkpoint Blockade Immunotherapy Approaches

Immunotherapies have changed the treatment strategy of some types of tumor including melanoma and, more recently, non-small-cell lung cancer (NSCLC). Immune checkpoints are crucial for the maintenance of self-tolerance and it is known that some tumors use checkpoint systems to evade antitumor immune response. The treatment of advanced NSCLC by immunotherapy, such as immune-checkpoint blockade targeting the programmed cell death protein-1 (PD1/PDL1), has led to significant clinical benefit either as monotherapy or in combination therapy [4].

1.3 Need for Tumor Response Assessment

The landscape of novel cancer therapies is undergoing fundamental changes, with great promise in the immunotherapy trials as illustrated by the United States Food and Drug Administration (FDA) approval of multiple checkpoint inhibitors for various cancer indications, a monoclonal antibody (mAb), ipilimumab, for treatment of metastatic melanoma [12] and a vaccine for prostate cancers as the first vaccine against non-viral cancers [13]. There is a pressing need for accurate, timely assessment of immunotherapy treatment response in cancer patients to improve clinical management and facilitate drug development. A standard for response assessment is measuring tumor size with CT or MR and then classifying tumor size reduction according to RECIST [8]. RECIST and other standard response measures are ill suited to monitor response to immunotherapy, largely due to “pseudoprogression” caused by immune mediated increase in contrast enhancement. However, molecular imaging can measure important biologic responses that precede tumor size reduction, such as cellular metabolism, proliferation, and vascularity.

1.4 A Specific T-Cell Activation Imaging Agent for Tumor Response Assessment

Early preclinical and clinical studies have shown promise for immunotherapy treatments for several malignancies [22]. Immunotherapy is expected to grow in importance; however, it presents

difficult challenges for response assessment. For instance, successfully treated tumors may actually increase in size after therapy due to inflammation and only later shrink [25]. RECIST criteria [8] designed to detect early effects of cytotoxic agents by size reduction, or the more recently proposed immune-related response criteria (irRC) [19] do not allow an early assessment of immunotherapeutic response since both depend on tumor size change. Furthermore, FDG PET is confounded by inflammatory effects causing hypermetabolism [2, 11]. Thus, it is imperative to develop new imaging and analysis protocols to evaluate immune-checkpoint blockade approaches. A method that evaluates T cell activation would permit an assessment of a basic first step in the process of assessing immunotherapy efficacy.

1.5 Investigational Agent: [^{18}F]F-AraG

CellSight Technologies (CST), Inc. is a company that is developing a suite of PET tracers targeted at visualizing immune response early in a patient's immunotherapy regimen. Their lead PET imaging tracer targeted at imaging activated T-cells is a fluorine-18-labeled analog of an FDA-approved drug Nelarabine [^{18}F]F-AraG, trade name VisAcT. VisAcT is independent of the type of immunotherapy regimen being administered - adoptive cell therapy, checkpoint inhibitors, cancer vaccines or a combination of immunotherapy and conventional medicines. VisAcT is relatively specific to activated T-cells that are critical to any immune modulated therapy. In vivo, real time imaging of activated T-cells in solid tumors before and at a timepoint during and after checkpoint inhibitor therapy (CkIT therapy) can help understand the effects of check point blockade therapy. Additionally, in vivo whole-body imaging of activated T-cells can provide critical information about the effect of immunomodulation in autoimmune diseases, as well as help their prediction as adverse events.

1.5.1 Preclinical Characterization

Molecular imaging of immune activation by positron emission tomography (PET) is a potential noninvasive strategy to monitor immune activation after treatment with immunotherapy. Increased activity of nucleoside salvage pathways has been associated with the proliferation of adaptive and innate immune cells [10, 24]. In preclinical models of cancer and autoimmunity, the PET probe [^{18}F]–2-fluoro-d-(arabino-furanosyl)cytosine ([^{18}F]-FAC), which targets the deoxycytidine salvage pathway, was shown to localize to sites of immune activation [21] and is predominantly accumulated in proliferative CD8+ T-cells [17].

Recently, a radiofluorinated AraG imaging agent, [^{18}F]F-AraG(2′-deoxy-2′-fluoro-9-β-D-arabino-furanosylguanine; trade name VisAcT) was synthesized [18] with a goal of development for human use. F-AraG is a fluorinated purine derivative with selective T-cell toxicity. A water-soluble AraG prodrug, Nelarabine, is FDA approved for the treatment of relapsed T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphomas [7]. [^{18}F]F-AraG preferentially accumulates in murine and human activated T-cells than in naive T-cells (Figure 1).

[18F]F-AraG was evaluated in three different preclinical models: rheumatoid arthritis [9], GvHD [23], colon cancer [14].

Figure 1: [18F]F AraG accumulation in activated T cells.

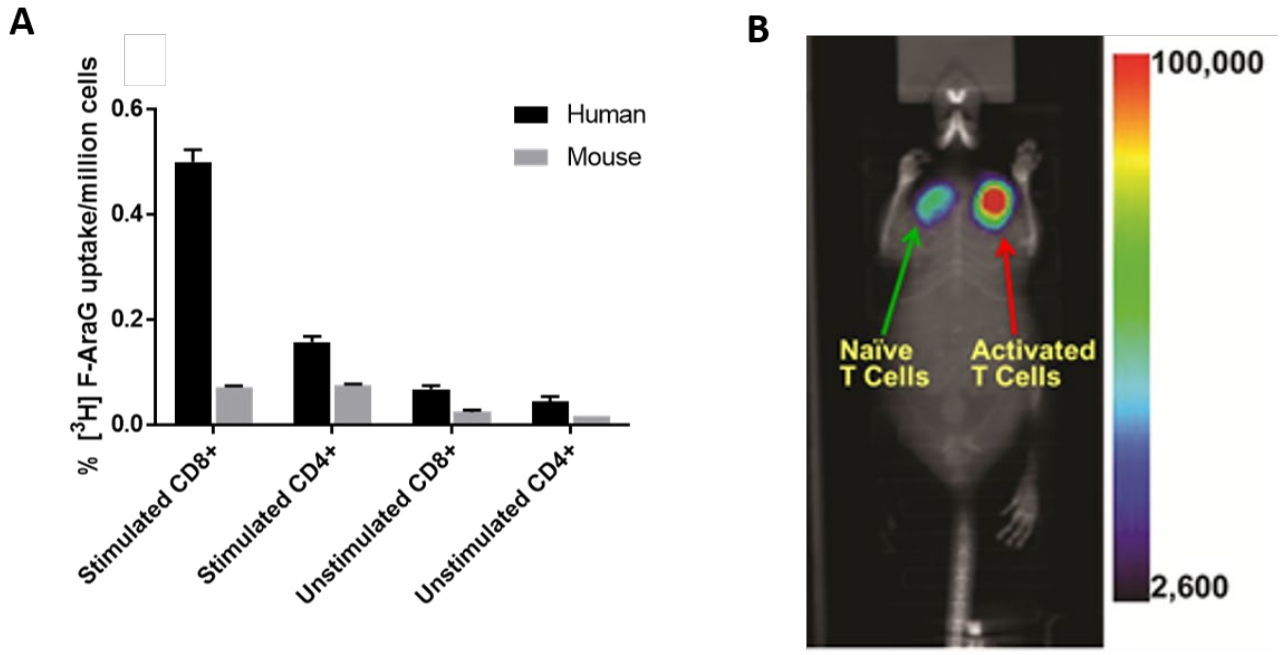

Figure 1: [18F]F-AraG preferentially accumulates in activated T-cells than in naive T-cells. **A**) Uptake of [18F]F-AraG in human and mouse primary T-cells post-stimulation. **B**) Pan T-cells were isolated from spleen and lymph nodes of mice. Untreated cells as well as CD3/CD28 activated T-cells (48 hours) were incubated with [18F]F-AraG before subcutaneous implantation into the shoulders before PET/CT imaging.

The accumulation of [18F]F-AraG in human activated T-cells is also significantly higher than other immune cells, including B cells, macrophages, and dendritic cells [14]. Furthermore, endogenously induced anti-tumor immune response in a viral induced rhabdomyosarcoma (MSV) mouse model was correlated with enhanced [18F]F-AraG uptake within the tumors (Figure 2A). Analysis of isolated tumors showed that tracer preferentially accumulated in activated CD8+ T-cells (Figure 2B).

Figure 2: Visualization of endogenously induced anti-tumor immune response

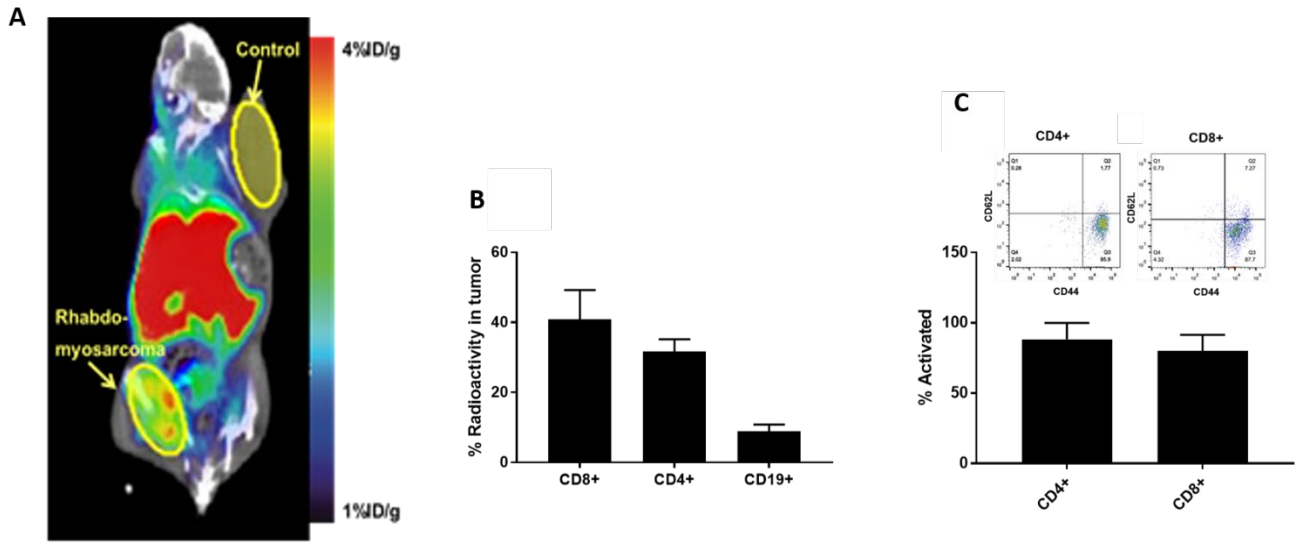

Figure 2: Visualization of endogenously induced anti-tumor immune response in a viral induced rhabdomyosarcoma (MSV) mouse model with [18F]F-AraG PET. **A**) Viral induced rhabdomyosarcoma was implanted in the left hindleg, and P815 mastocytoma (control) was implanted in the right shoulder. PET/CT was performed on Day 14 during the peak anti-tumor immune response in the rhabdomyosarcoma model. **B**) CD8+, CD4+ and C19+ cells were isolated from rhabdomyosarcoma tumor one hour after probe injection for radioactivity assay. Lymphocytes take up more than 80% of tumor associated [18F]F-AraG, with CD8+ and CD4+ cells acquiring the largest portion of the tracer (72%). The low uptake in B cells (CD19) is only observed in mice. Human B cells do not accumulate the tracer. **C)** FACS analyses of the isolated lymphocytes showed an activated phenotype (CD44+ CD62L-) in majority of CD8+ (79.9±11.5) and CD4+ cells (88.3±11.7). Error bars represent standard deviation.

1.5.2 Clinical experience

The first-in-human study of [18F]F-AraG was performed at UCSF in 2015 (abstract of meeting presentation available here: http://www.wmis.org/meetings/archives-of-past-meetings/wmic-2015-first-in-human-study-3/).

[18F]F-AraG was administered at a subpharmacologic, tracer microdose consistent with imaging practices in six healthy volunteers (3 males and 3 females). The distribution of the tracer was evaluated over the first 4 hours after injection. A representative whole body PET/MR image in a healthy volunteer is shown in Figure 3 ([23]; [18F]F-AraG Investigator's Brochure). The tracer was well tolerated by all patients and there were no > Grade 1 adverse events (AE). The only AE that occurred in more than 1 volunteer was positive white blood cell (WBC) esterase in the urinalysis without urinary symptoms. Normal uptake was seen in the clearance organs: liver, kidneys and bladder. There appeared to be uptake in the thyroid and parotid glands, as well as

limited accumulation in the cardiac muscle. In these first-in human studies, no additional drugs were administered to subjects as the biodistribution was determined for radiation dose estimates. [23].

Figure 3: Whole body [^{18}F]F AraG PET image in a healthy volunteer.

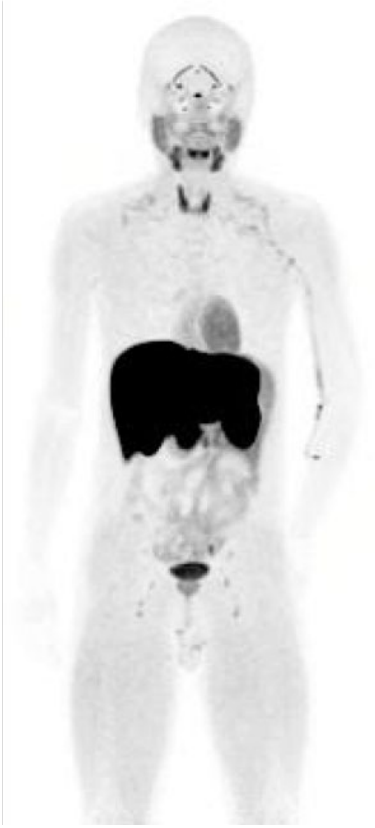

Figure 3: Maximum intensity projection (MIP) of a whole body [^{18}F]F-AraG PET image of a healthy volunteer acquired 90 minutes post infusion.

[^{18}F]F-AraG is currently being tested in several Phase I/II clinical trials. The clinical trials aim to evaluate the use of [^{18}F]F-AraG in cancer patients undergoing immunotherapy. Cancer types include solid tumors of all types including, among others, lung cancer, melanoma, breast cancer and head & neck cancer. Non-oncology focused trials include an HIV trial at UCSF to help see differences in repositories of T cells in HIV patients and a trial at Stanford is determining if [^{18}F]F-AraG will be useful as an early predictor of Graft vs Host Disease.

Investigators from Stanford have reported early clinical evidence that [^{18}F]F-AraG PET scans demonstrate imaging of activated T-cells in vivo. In a study that aims to evaluate immunological response to Anti-PD-1 treatment in squamous cell carcinoma of the head and neck (SCCHN),

investigators reported a correlation in the change in total SUV and change in the CD8+T-cells post PD-1 antibody infusion (Figure 4).

Figure 4: [18F]F-AraG PET/CT images pre and post Anti PD 1 Ab therapy.

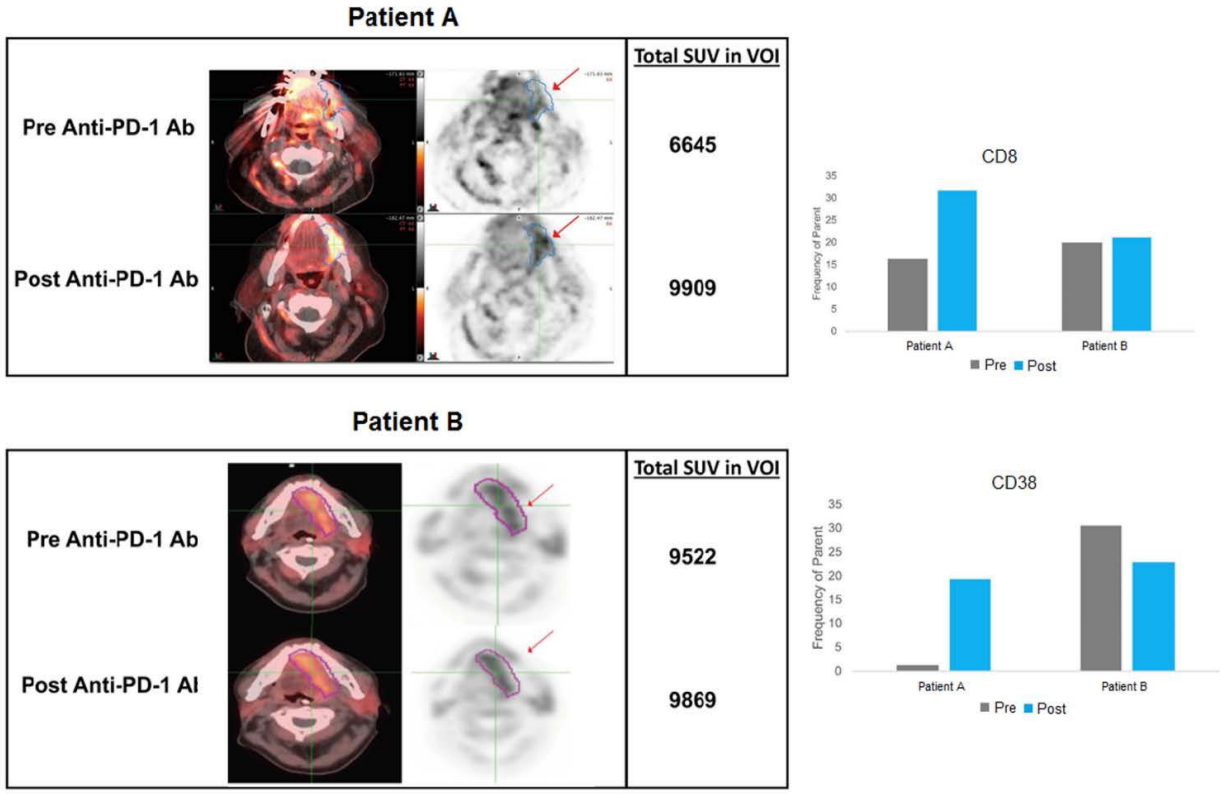

Figure 4: [18F]F-AraG PET/CT images of 2 SCCHN patients pre and post Anti-PD-1 Ab therapy. [18F]F-AraG signal increased dramatically after only one injection of PD-1 Ab in Patient A. FACS analysis revealed a higher proportion of both CD8+ cells and higher expression of CD38 activation marker after one treatment. In Patient B, there was not a significant increase in total SUV in VOI and correspondingly there was not an increase in the CD8+ cells as analyzed by FACS. Bar graphs show proportion of cells expressing CD8 and CD38 markers in tissue samples pre and post Ab therapy in patient A and B.

2. STUDY RATIONALE

Given that immunotherapeutic strategies, in particular immune checkpoint antibodies, focus on the generation of T-cell-based antitumor immunity, uptake of [18F]F-AraG within the tumor is hypothesized to correlate with T-cell mediated immune response seen in the biopsy samples of cancer patients treated with immune checkpoint blockade. Correlation of pre- and post-treatment intratumoral immune infiltration by means of PET imaging will guide the development of future

clinical trials investigating the role of [^{18}F]F-AraG in the monitoring of anti-tumor immune responses. Therefore, proper quantification of [^{18}F]F-AraG uptake in tumor lesions, and understanding its relation with physiologic uptake in background tissues is important. *Note: checkpoint therapy in this study is standard-of-care and is not under investigation.*

The distribution of radiotracer activity depends on post-injection imaging time for both anatomical structures and pathologic processes. Anatomic structures with physiologic uptake and pathologic abnormalities are likely to be characterized by distinct time-activity curves [3]. Therefore, the pharmacokinetic relationship between tumor activity and a variety of tissue background activity is important, which is best understood from dynamic images. Dynamic imaging of cancer subjects pre- and post-treatment is expected to provide data to establish this relationship between tumor and background, as well as the effect of treatment on the relationship.

While understanding tumor vs background activity in cancer patients is important, such subjects are likely to have prior or ongoing treatment, which may affect accurate baselining. Therefore, understanding normal tissue activity in healthy volunteers in whom radiotracer distribution is likely unencumbered by any effect of prior or ongoing treatment can be important to establish baseline dynamic data. In addition, healthy volunteers are likely to tolerate the long dynamic scan better than cancer subjects, improving the chances of obtaining standard baseline data.

Available PET/CT scanners can obtain dynamic images only on a portion of the body as large as their axial field of view, generally anywhere between 15-30 cm. The 194 cm long uEXPLORER total-body PET scanner is the world's first device to offer the ability to tomographically image all parts of the body simultaneously. Thus, the uEXPLORER PET/CT (now commercially available and with FDA 510(k) clearance) is the only scanner in the world capable of acquiring total-body dynamic images.

In this pilot study, 2-4 healthy volunteers will undergo [^{18}F]F-AraG dynamic imaging on the uEXPLORER total body PET/CT scanner to obtain preliminary data regarding pharmacokinetics and early biodistribution images. In addition, 2-4 patients with NSCLC and planned for standard-of-care PD-1/PD-L1 immunotherapy will undergo [^{18}F]F-AraG dynamic imaging similarly on the uEXPLORER total body PET/CT scanner to obtain data regarding pharmacokinetics of the tracer in tumor lesions in the context of normal tissue uptake. An optional second similar scan will be performed 7-14 days after the first dose of immunotherapy to explore and document any treatment related changes in [^{18}F]F-AraG uptake and kinetics.

The study and data collected will be important to recommend an ideal time to acquire a whole body static scan using conventional and widely available PET/CT scanners for adequate tumor to background contrast and quantification, which in turn, will be essential for further clinical development of [^{18}F]F-AraG to aid the monitoring of anti-tumor immune responses.

3. OBJECTIVES

The study is exploratory in nature with the following objectives:

3.1 Primary Objectives

- To obtain preliminary data on the baseline whole-body pharmacokinetics of [^{18}F]F-AraG physiologic uptake in various healthy tissues using the uEXPLORER PET/CT scanner.

- To obtain preliminary data on the pharmacokinetics of [^{18}F]F-AraG pathologic uptake in tumor lesions relative to uptake in background tissues in NSCLC subjects using the uEXPLORER PET/CT scanner.

- To recommend an ideal time window post [^{18}F]F-AraG infusion to acquire static whole-body scans using standard PET scanners used in clinical care.

3.2 Secondary Objectives

- To assess [^{18}F]-AraG uptake in NSCLC before and after the first dose of PD-1/PD-L1 immunotherapy.

4. STUDY POPULATION

4.1 Inclusion Criteria

Subjects are eligible if they meet ALL of the following criteria:

<u>For all subjects</u>:

1. Age ≥ 18 years.
2. Ability to understand the purposes and risks of the trial and has signed an IRB-approved informed consent form.
3. Willingness and ability to comply with all protocol required procedures.
4. For men and women of child-producing potential, willingness to use of effective double barrier contraceptive methods during the study, up to 1 day after the last administration of the investigational product.

<u>For NSCLC subjects only:</u>

5. Patients with histologically confirmed advanced, locally advanced, or localized NSCLC.
6. Planned to undergo treatment with a PD-1 or PD-L1 inhibitor either as 1) monotherapy or as combination therapy with concurrent chemotherapy as treatment for advanced/metastatic disease 2) As consolidation therapy following chemoradiation for locally advanced disease or 3) As induction therapy either as monotherapy or combination therapy with chemotherapy prior to planned surgical resection

7. At least 1 tumor lesion > 1 cm (cannot be only in liver) documented on CT or MRI or FDG-PET/CT (RECIST criteria 1.1; >1.5 cm for nodal lesions) within 45 days prior to scan date.
8. Per investigator's assessment and in consultation with oncologists, at least one eligible lesion must be sufficiently separated from tissues with known high [^{18}F]F-AraG uptake, such as salivary glands, bladder, liver and kidneys so that quantification will be feasible.
9. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
10. Meeting all clinical safety lab values per institution's standard of care, or Investigator's discretion, for patients receiving cancer treatment.

4.2 Exclusion Criteria

Subjects are not eligible if they meet ANY of the following criteria:

1. Serious comorbidities (nonmalignant disease or other conditions) that in the opinion of the investigator could compromise protocol objectives.
2. History of recent COVID-19 infection within the last 2 months OR history of COVID requiring hospitalization with lung injury at Investigator's discretion
3. Subjects with a diagnosis of immunodeficiency or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the scan
4. Subjects receiving therapy with nucleoside analogs including but not limited to: acyclovir, valaclovir, penciclovir, famciclovir, ganciclovir, ribavirin, valganciclovir, glanciclovir
5. Pregnant women or nursing mothers
6. Body weight more than 240 kg (529 pounds)

<u>For NSCLC subjects only:</u>

7. Prior Treatment with anti-PD-1/PD-L1 immunotherapy.

<u>For Healthy subjects</u>

8. No primary care physician

4.3 Subject recruitment

4.3.1 NSCLC Subjects:

Patients will be recruited by Dr. Daly and other physicians within the UC Davis Cancer Center from their clinics. Dr. Daly regularly sees lung cancer patients as part of her clinical practice. The physicians will not be separately screening charts, but will recruit from among their patients.

4.3.2 Healthy Subjects:

Up to 4 normal subjects will be recruited by means of a flyer posted in specific areas: the Division of Nuclear Medicine (Davis Tower, Ambulatory Care Center (ACC)), the UC Davis Explorer Molecular Imaging Center located at 3195 Folsom Blvd, Sacramento, CA, the Radiology Academic office (ACC, Suite 3100), and the research laboratories of Dr. Simon Cherry and Dr. Jinyi Qi (Main campus, GBSF). Flyers will be posted in other academic offices at ACC including cardiology, ophthalmology, orthopedics, etc. Additionally, the study will be announced on the EXPLORER website: https://explorer.ucdavis.edu/ and on the UC Davis Clinical Study Pages site: https://studypages.com/ucdavis/

5. STUDY DESIGN

Protocol CST-FARAG-203 is a pilot study using the uEXPLORER total-body PET/CT system to acquire dynamic [^{18}F]F-AraG scan data in healthy individuals and patients with NSCLC.

Screening will consist of eligibility confirmation, the patient signing the consent form, and any assessments outlined in the study calendars below. This will also include a query about status and date of COVID-19 vaccination.

Eligible healthy subjects will undergo a single dynamic [^{18}F]F-AraG PET/CT scan (of duration up to 90-minutes) on the uEXPLORER PET/CT scanner within 28 days of screening or on the day of screening if possible and convenient to the subject. There will be a follow-up visit or call 7 days after the scan to assess any AEs that could be attributed to either the scan or the administration of [^{18}F]F-AraG.

Eligible subjects with NSCLC who are planned to receive PD-1/PD-L1 immunotherapy will undergo a pre-therapy dynamic [^{18}F]F-AraG PET/CT scan, and an optional post-therapy (first dose only) dynamic [^{18}F]F-AraG PET/CT scan on the uEXPLORER total-body scanner.

For each enrolled patient, [^{18}F]F-AraG will be administered by a licensed Nuclear Medicine technologist under the supervision of a board-certified Nuclear Medicine physician (ABNM or ABR certified) on an outpatient basis. It will be administered as a single bolus injection of 5 mCi +/-20% IV into a vein. Vital signs will be assessed just prior to and after completion of dynamic [^{18}F]F-AraG PET scan.

For each scan, the subject will be prepared according to the site's standard procedures and asked to void the bladder immediately prior to imaging. For the scan, an intravenous (IV) line will be placed in a vein and the subject will be positioned supine on the scanner table. The PET/CT imaging will begin with a low-dose CT scan on the uEXPLORER PET/CT scanner. This CT scan will provide information for anatomic localization and attenuation correction purposes.

[18F]F-AraG will then be infused as above and a 90-minute dynamic PET scan will be performed on the uEXPLORER. The IV line will be removed after dynamic acquisition. For subjects who may not be able to undergo a 90-minute dynamic scan, a 60-minute dynamic PET scan will be performed, followed by a 10-minute static scan starting at 80 minutes post [18F]F-AraG infusion. The separate static scan at 80 minutes will be obtained along with an ultra-low-dose CT which is needed for attenuation correction of this separate scan.

The study will be an open label, non-randomized, single arm trial. Patients and care providers will not be blinded to any part of the study.

5.1 Study Calendar

Table 1: Study Schedule of Events (Healthy Volunteers)

Protocol Assessments	Visit 1[1] Screening (Day -28 to Day 0)	Visit 2[1] PET/CT scan (Day 0)	Safety Interview (Day 7)
Informed consent	X		
Medical History and Physical Examination[2]	X		
Eligibility Assessment	X	X	
Urine Pregnancy Test[3]	X	X	
Concomitant medications	X	X	
[18F]F-AraG PET/CT imaging		X	
Adverse events collection[4]		X	X[5]

1. Visits 1 & 2 can be merged into a single visit done on the same day.
2. Includes vital signs, height, weight, BMI
3. In women of 18-60 years old unless documented hysterectomy or bilateral ovarian removal is available.
4. AE collection: Up to 2 hours of [18F]F-AraG infusion on Day 0; AEs that occur prior to this will be considered baseline.
5. The follow up safety interview can be performed telephonically and does not require a separate in-person visit.

Table 2: Study Schedule of Events (NSCLC subjects)

	Visit 1	Visit 2	Visit 3	Visit 4Ψ	
Protocol Assessments	**Screening (Day -28 to Day 0)**	**PET/CT scan (Day 0)**	**(Day 0-7)**	**PET/CT (7-14 Days after V3)**	**Safety Interview (7 days after last PET/CT scan)**
Informed consent	X				
Medical history and Physical Examination[2]	X				
Eligibility Assessment (including eligible lesions assessment)	X	X			
ECOG Performance Status Assessment	X				
SOC CT/MRI and/or FDG-PET/CT collection	X[1]				
Urine Pregnancy Test[3]	X	X		X	
[18F]F-AraG PET/CT imaging		X		X	
Administration of PD-1/PD-L1 Treatment			X		
Adverse events collection[4]		X		X	X[5]
Concomitant medications	X	X		X	

1. CT or MRI or FDG-PET/CT performed up to 45 days prior to Visit 2 is acceptable.
2. Includes vital signs, height, weight, BMI
3. In women 18-60 years old unless documented hysterectomy or bilateral ovarian removal is available
4. AE collection: Up to 2 hours of [18F]F-AraG infusion on Visits 2 and 4; AEs that occur prior to this will be considered baseline.
5. The follow up safety interview can be performed telephonically and does not require a separate in-person visit.

Ψ Optional visit

5.2 Participant Duration

Healthy volunteer subjects will have up to 3 visits over a period of one to four weeks. NSCLC patients will have up to 4 visits over a period of one to four weeks, prior to and after cancer treatment.

We anticipate enrollment will be completed within 12 months after the start of enrollment and that the study will be completed in 2 years.

5.3 Participant Compensation

Participants will be compensated $100 per PET/CT scan in the form of gift cards. The maximum total will be $200 for NSCLC patients and $100 for healthy volunteers.

6. MATERIALS AND METHODS

6.1 Study DRUG: [^{18}F]F-AraG

6.1.1 Manufacture

[^{18}F]fluoride (n.c.a.) in [^{18}O]water is passed through a PS-HCO_3 cartridge, eluted with 1 mL of a phase transfer catalyst solution containing Kryptofix222 (15 mg) and K_2CO_3 3.5 mg) in 10:1 acetonitrile/water. The K222/K[^{18}F]F complex is heated and dried under Helium at 65 °C for 3 minutes, followed by heating at 95 ºC for 1 minute. After cooling to ~50 ºC, a solution containing [^{18}F]F-AraG trifylate precursor (6 mg in 1 mL DMSO) is added to the reactor and the solution heated to 115 °C for 45 minutes. After cooling down to ~40 °C, to the reaction mixture was added sodium methoxide, and heated at 100 ºC for 10 minutes. Reaction is cooled to 40 ºC and after addition of 0.5 mL of 1 N HCl stirred at 95 ºC for 10 minutes. The reaction mixture is then cooled to 30 ºC and diluted with a solution of 0.5 mL of 1N $NaHCO_3$ in 9.5 mL of water (SV3). The solution in the reactor is transferred through 4 × C-18 cartridges via a V31 valve and collected in a waste container. The cartridges are backwashed to the reactor with 2 mL of methanol in the pre-HPLC tube. Methanol is removed under vacuum with the flow of helium at 90 ºC for 13 minutes. After cooling the reactor to 30 ºC water is added and the solution transferred through a 0.45 µm filter into a pre-HPLC container.

Crude [^{18}F]F-AraG is injected on to a HPLC Luna C18 semi-preparative reversed-phase column (5 µm, 10 × 250 mm). The desired product fraction (Rt ~ 16 minutes) is collected into the round bottom flask pre-filled with 30 mL of water. The diluted fraction is passed through the C18 plus cartridges and rinsed with water (10 mL), then the trapped product is eluted by ethanol (1 mL) into a collection vial for subsequent dilution with saline (9 mL). [^{18}F]F-AraG for Injection is prepared by then passing through a 0.22 µm Millex GV sterile filter to a pre-assembled septum-sealed sterile collection vial (30 mL) for filtration and sterilization. The final sterile empty vial, product needle, vent needle, 4 mm GV filter for vent and sterile GV filter (33 mm) are assembled in a sterile LFH (laminar flow hood). The final product is released compliant to release specifications as submitted to the FDA. No further testing is required at the research site prior to injection.

[^{18}F]F-AraG will be supplied by Cellsight at no cost to study patients.

6.1.2 Availability

The [^{18}F]F-AraG will be synthesized, on a per scan basis, under cGMP at one of CellSight's identified qualified production sites. All qualified production sites are FDA-approved clinical manufacturers of the tracer. Cellsight carries the IND. Cellsight submitted all the manufacturing CMCs to the FDA for all approved sites. As needed, the facility staff will be trained by Cellsight in synthesizing this radiopharmaceutical. Please refer to CellSight Pharmacy Manual.

6.1.3 Agent Ordering

The [^{18}F]F-AraG will be individually requested per subject by Nuclear Medicine research coordinators or technologists, under the supervision of the Nuclear Medicine investigators, for synthesis under cGMP at the identified production site. Please refer to CellSight Pharmacy Manual.

6.1.4 Study Treatment Accountability

The Investigator or designee will verify the contents of each shipment against the shipping documents. A study treatment accountability log will be kept by the Investigator to maintain current and accurate inventory records (batch, expiry, and quantity) covering the receipt, dispensing and the destruction of all the study treatments.

At the conclusion of the study, or other situations as applicable (ex. site closure, IP expiry, etc.) the Investigator must agree to return or destroy all study materials as instructed by the Sponsor.

Please refer to CellSight Pharmacy Manual.

6.1.5 Dispensing [^{18}F]F-AraG

The [^{18}F]F-AraG will be ordered and synthesized under cGMP at qualified sites by radiochemistry staff in the Nuclear Medicine department.

Each dose will be manufactured on a per patient, per scan basis, according to the investigator physician's prescription order. Upon receipt, qualified personnel will ensure that the study drug is delivered in good condition, inventoried, stored properly, labeled and dispensed in compliance with the pharmacy manual, all regulatory agencies and per the investigator physician's prescription order.

The [^{18}F]F-AraG dose will be measured by the qualified personnel in a dose calibrator prior to dispensing. Then the syringe will be placed in a shielded carrier for administration via venous infusion. After the dose administration, the qualified personnel will return the syringe for residual measurement by the nuclear medicine technologists at the site. Measured radioactivity values and times of measurement will be documented, as well as the total injected volume.

Regulatory agencies require accounting for the disposition of all investigational drugs received by each clinical site. Information on drug disposition required by law consists of the date received, date dispensed, quantity dispensed, and the patient identification number to whom the drug was dispensed. The Investigator is responsible for accounting for all unused study drug and destroying all used study drug containers in compliance with the pharmacy manual.

6.2 uEXPLORER PET/CT Scan

For the purpose of this study, [^{18}F]F-AraG PET/CT scan images must only be acquired on the uEXPLORER scanner and that scanner must undergo regular Quality Control (QC) checks. Documentation of such QC activities must be available upon request or audit. Image acquisition will be obtained in list mode and the raw data saved to allow for virtual radioactive dose reconstruction at a later date.

7. RISKS TO SUBJECTS

7.1.1 Risks from [^{18}F]F-AraG PET/CT scan

In this study, 2-4 healthy subjects and 2-4 NSCLC patients will undergo research PET/CT imaging with [^{18}F]F-AraG as specified in the experimental imaging section. [^{18}F]F-AraG PET imaging has been performed on 6 healthy volunteers in a separate study with no drug-related side effects. In addition, [^{18}F]F-AraG has been administered to 13 cancer patients with 7 of those patients getting two doses for pre and post immunotherapy scans, also without any drug-related side effects.

Given the prior clinical safety experience thus far, we expect few, if any, adverse effects from [^{18}F]F-AraG administration in this study. Presently there are no standard surrogate biomarkers or imaging modalities that can substitute for these procedures. The alternative will be for the patient to withdraw from the imaging study.

The safety monitoring practices employed by this protocol are adequate to protect the subjects' safety and should detect all Treatment Emergent Adverse Events (TEAEs). An indirect health benefit to the subjects enrolled in this trial is the free medical tests received at screening and during the study.

Due to the (up to) 90-minute long scan time through which the participants are expected to remain still, the patients may feel discomfort and/or fatigue from laying on the scanner table. In addition, they may experience claustrophobia from being inside the scanner bore, which is a partially enclosed space.

Another risk is possible bruising and/or infection at the IV site.

Reproductive Risks are associated with PET: (PET) radiotracers studies on the fetus (unborn child) have not been done. To avoid risk to the fetus, it is important that female participants not become pregnant while they are participating in this research study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if they choose to be sexually active, they should use an appropriate "double barrier" method of birth control (such as female use of a diaphragm, intrauterine device (IUD), or contraceptive sponge, in addition to male use of a condom) or the female should be using prescribed "birth control" pills, injections, or implants. Such birth control methods should be used for as specified by their doctor prior to beginning their participation in the research study and continues for as long as specified by their doctor after their final study visit. If they choose to be sexually active during this study, even with the use of these birth control measures pregnancy could still result. The risks of participation in the research PET studies while pregnant include potential loss of pregnancy or possible birth defects. If participant is a woman18-60 years old, they will undergo a urine pregnancy test within 24 hours prior to each PET session unless documented hysterectomy or bilateral ovarian removal is available. If participant becomes aware that they are pregnant during the course of their participation in this study, they should contact immediately the study doctor.

It is possible that uEXPLORER PET/CT scans may detect false positive findings that may require further follow-up (clinical, imaging or surgical) with all the risks associated with these follow-up procedures. The PET/CT images created for this study are for research and are not meant to evaluate subject health, as they would be if they were part of a clinical (non-research) visit to the doctor or hospital. The images will not receive any routine clinical review by radiologists who interpret PET/CT scans. This means that some findings may be overlooked or misinterpreted. However, if the PET/CT technologists do notice findings that cause concern, they will notify the Study Radiologist. Additionally, if a member of the research team notices any findings that cause concern while conducting image review for study purposes, they will notify the Study Radiologist. The Study Radiologist will conduct a brief review of part of the study images for quality purposes. If the Study Radiologist thinks a clinical problem is present, one of the IRB-approved study physicians will discuss these possible problems with the subject within 8 weeks or immediately upon recognition of any critical finding that requires immediate and/or urgent intervention as described in the Department of Radiology Critical Findings policy (full dataset of images are sometimes not available for review in less than 3 days). Upon written request, we will provide the subject with a copy of a subset of their CT images to take to the physician of their choosing. A subset of PET images may also be shared with the subject unless the images from the study are clinically uninterpretable. In addition, the sponsor may restrict sharing of PET images due to the nature of the research protocol or to protect intellectual property (e.g. proprietary radiotracers). We will send a standard letter to the designated licensed medical provider identified by the subject, unless one of the study physicians is part of the subject's care. The standard letter will state that (i) the subject's images were acquired exclusively for a research study and incidental findings that may be related to a medical condition were observed by a UC Davis radiologist; (ii) the images did not receive any dedicated

routine clinical review and findings may have been overlooked or misinterpreted; (iii) the subject's physician can contact the study doctor at any time if there are any concerns regarding the study or the subject's findings.

7.1.2 Radiation Risk

Each patient will receive up to two 5 mCi +/-20% doses of [^{18}F]F-AraG. Dosimetry assessment estimated an effective dose of 0.58 and 0.62 mSv/mCi for males and females, respectively. Risks from the PET/CT itself include additional radiation exposure from the CT attenuation correction scan (estimated to be 10 mSv for each low dose CT scan and 1 mSv for each ultra low dose CT scan). The table below shows the estimated effective radiation dose received by the subjects in this protocol:

	Healthy Subjects	**NSCLC Patients**	**NSCLC Patients who cannot undergo 90 minutes continuous scanning**
Low dose CT scan	10 mSv	10 mSv	10 mSv
Ultra low dose CT scan	N/A	N/A	1 mSv
[^{18}F]-AraG PET scan	2.9 +/- 0.29 mSv(male) 3.1 +/- 0.31 mSv(female)	2.9 +/- 0.29 mSv(male) 3.1 +/- 0.31 mSv(female)	2.9 +/- 0.29 mSv(male) 3.1 +/- 0.31 mSv(female)
Total estimated dose	12.9 +/- 0.29 mSv(male) 13.1 +/- 0.31 mSv(female)	12.9 +/- 0.29 mSv(male) 13.1 +/- 0.31 mSv(female)	13.9 +/- 0.29 mSv(male) 14.1 +/- 0.31 mSv(female)
Number of scans	1	2	2
Maximum estimated dose	13.2 mSv (male) 13.4 mSv (female)	26.4 mSv (male) 26.8 mSv (female)	27.4 mSv (male) 27.8 mSv (female)

The total estimated dose from the combined PET/CT examination will be 13.4 mSv or less for normal subjects and 27.8 mSv or less for patients with NSCLC. The use of radiation involves minimal risk and is required to obtain the desired research information.

8. POTENTIAL BENEFITS TO SUBJECTS

There will be no direct benefit to the subjects. The therapy for NSCLC Subjects will not be changed based on the [^{18}F]F-AraG PET findings.

9. CONCOMITANT MEDICATIONS

Subjects must be questioned at each study visit concerning any new medications or changes in current medications including over-the-counter and topical medications. All medications and therapies administered or taken by the subject beginning 30 days prior to signing the ICF and throughout the study will be recorded in the source documents and on the appropriate page of the CRF. Intravenous fluid documentation will NOT include IV fluids used to administer medications, only the medications administered through the IV fluid will be documented. Intravenous fluids used to keep the vein open or used for flushing will also not be documented in the concomitant medication CRF.

For each medication and non-study treatment, the following will be documented:

- Medication/treatment name (generic name may be used if trade name is unknown)
- Dose, unit, and frequency of dosing (individual dosages, not total daily dose). Note: Each new dose of medication should be recorded as a separate entry, with the exception of medications that are given on a sliding scale. For these, it is acceptable to enter the range of the dosage, including the start and stop dates for which the specified dosage range was used.
- Route of dosing
- Indication for use (Indication should include exact medical terminology)
- The start date
- The stop date (if medication/therapy is not ongoing)

10. OUTCOME MEASURES AND ANALYSIS

10.1 Physiological Time-Activity Curves of [^{18}F]F-AraG Uptake within Healthy Tissues

One of the primary objectives of the study is to obtain baseline pharmacokinetic information in the form of [^{18}F]F-AraG uptake in healthy tissues as a function of time. To achieve this outcome, data on [^{18}F]F-AraG uptake in several tissue types will be collected from healthy subjects. This data will be presented in the form of time-activity curves (TAC) generated for each tissue type.

10.2 Time-Activity Curves of [^{18}F]F-AraG Uptake within Tumors and Background Tissues

Another objective of the study is to obtain pharmacokinetic information in cancer subjects in the form of relative [^{18}F]F-AraG uptake in tumor lesions and background tissues as a function of time. To achieve this outcome, data on [^{18}F]F-AraG uptake in tumor lesions and background activity in

the same tissues as in Section 10.1 will be collected. This data will be similarly presented in the form of time-activity curves (TAC) generated for each tissue type as in Section 10.1, as well as for tumor lesions against their background tissues.

10.3 Recommended time post [^{18}F]F-AraG infusion to acquire a single static PET/CT scan

The TAC analysis of [^{18}F]F-AraG uptake will provide insight into the earliest time to achieve adequate tumor versus non-malignant background tissue activity, as well as time to reach and remain in steady state up to 90 minutes. Such information can guide a recommendation for the ideal time window for a static [^{18}F]F-AraG PET scan for future trials and potential clinical use.

10.4 Change in PET signal pre- and post- first dose of PD-1/PD-L1 immunotherapy

For NSCLC subjects who undergo two [^{18}F]F-AraG PET/CT scans, the signal at a static time point post [^{18}F]F-AraG infusion (obtained from the result of one of the outcome measures; Section 10.3) from both scans will be observed for trends.

10.5 Safety Outcome Measures

- Incidence of Treatment-Emergent Adverse Events (AEs).
- Incidence of withdrawals due to AEs.
- Serious Adverse Events (SAEs)

Analyses of safety outcomes will be conducted using the safety population. Adverse events will be coded using MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the first treatment. TEAEs will be summarized by treatment group and by stage of the study, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- TEAEs by severity grade
- TEAEs by relationship to study treatment.

In addition, separate summaries of serious adverse events, and adverse events resulting in discontinuation of study treatment will be presented.

10.6 Efficacy Outcome Analysis

Descriptive statistics will be used to summarize the characteristics of study participants, including their age, gender, primary tumor sites and clinical stages, concomitant medications, etc. Frequency tables will be used to summarize categorical variables. Median and inter-quartile ranges will be used to describe no-normally distributed continuous variables. Mean and standard deviation will be used to summarize normally distributed continuous variables.

Feasibility will be assessed per patient basis. The percentage of patients who can be successfully evaluated by [^{18}F]F-AraG PET imaging will be computed and summarized.

11. STATISTICAL METHODS AND DATA ANALYSIS

11.1 Number of Subjects

The primary goal of this pilot study is to acquire preliminary dynamic [^{18}F]F-AraG scan data in healthy individuals and patients with NSCLC. Given the preliminary nature of this study, a power calculation was not performed. 2-4 subjects are likely sufficient for a general understanding of healthy tissue uptake as a function of time. Similarly, 2-4 NSCLC subjects are considered adequate to provide at least one lesion with positive and sufficient tumor uptake of [^{18}F]F-AraG to provide a general understanding of tumor tracer kinetics.

11.2 Scan Data

Data from uEXPLORER scanner will be acquired in listmode. Data will be reconstructed using manufacturer's recommendations. Image quality, quantitative comparisons and preliminary biodistribution data collection will be performed by means of volumes of interest (VOIs) drawn in different organs, tissue types and tumor lesions (in NSCLC subjects). These will be used to generate standard uptake values, normalized to body weight (SUV-bw) for the purpose of quantitative analysis of spatial as well as temporal tracer distribution.

11.3 General Statistical Considerations

All collected study data will be presented in subject data listings. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables.

11.4 Analysis populations

The details of the analysis population to be used for the study are described below:

11.4.1 Efficacy population

The efficacy population is defined as all subjects who have received at least one (up to) 90-minute dynamic [^{18}F]F-AraG PET scan.

11.4.2 Per-protocol (PP) Population

The Per Protocol (PP) population is defined as the set of subjects who meet the efficacy population requirements and were not associated with a major protocol violation.

11.4.3 Safety Population

The Safety population is defined as all subjects receiving at least one dose of [^{18}F]F-AraG.

11.5 Statistical Methods

11.5.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, enrolled, completed, and discontinued during the study, as well as the reasons for all post-

enrollment discontinuations will be summarized for healthy and NSCLC subjects respectively. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

11.5.2 Demographics and baseline characteristics analysis

Demographics and baseline characteristics will be summarized for healthy and NSCLC subjects respectively using appropriate descriptive statistics.

11.5.3 Concomitant Medications/Therapies

Concomitant medications/therapies will be summarized separately for the Safety population. All prior and concomitant medications recorded in the case report form will be coded to all matching Anatomic Therapeutic Classification codes using the most recent version of WHO Drug. Descriptive summaries, by study group and stage of the study, will be prepared using the coded term. All concomitant medications/therapies recorded in the case report form will be listed.

11.5.4 Medical history

The medical history will be summarized and/or listed descriptively.

11.5.5 Study Treatment Compliance

The study treatment compliance data will be summarized and/or listed descriptively.

12. SAFETY REPORTING OF ADVERSE EVENTS

12.1 Assessment of Safety

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs as detailed in this Section of the protocol.

12.2 Adverse Events

An adverse event (AE) is defined as any unfavorable or unintended sign, symptom, or disease that occurs or is reported by the patient to have occurred, or a worsening of a pre-existing condition. An adverse event may or may not be related to the study treatment.

AEs will be elicited through direct questioning and subject reports. Any abnormality in physical examination findings or laboratory results that the investigator believes is clinically significant to the research subject and that occurred after initiation of the first study treatment will be reported as AEs. Abnormal findings that are NOT clinically significant should not be recorded as an AE.

12.3 Reporting of Adverse Events

Report initiation for all AEs and serious adverse events (SAEs) will begin immediately after the first infusion of [^{18}F]F-AraG (Visit 2) and continue until the Day 7 follow up. The Day 7 adverse event assessment may be telephonic and does not require an office visit. All events will be followed to resolution or until they are considered to be not clinically significant according to the investigator's judgment.

All AEs must be recorded in the subject's medical records and on the CRF. AEs will be reported using customary medical terminology along with the following information: the onset and end dates, whether the event is at the site of [^{18}F]F-AraG administration, whether the event is considered to be a SAE, the impact the event had on study treatment, the CTCAE grade (intensity) of the event, the causality of the event, whether treatment was given as a result of the event, and the outcome of the event.

Serious Adverse Events

An AE should be classified as an SAE if any of the following criteria are met:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational treatment.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

12.4 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA in accordance with CFR 312.32 (IND Safety Reports).

12.5 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and

end dates), regulatory seriousness criteria if applicable, suspected relationship to the investigational treatment (see following guidance), and actions taken.

The guidelines outlined in CTCAE v5.0 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Table 3: CTCAE v5.0 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.‡

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

‡Unlike the AE outcome assessment (see Section **Error! Reference source not found.**), a subject may have more than one Grade 5 event.

-Common Terminology Criteria for Adverse Events (CTCAE), v5.0: November 27, 2017

12.6 Causality

Adverse events will be assigned a relationship (causality) to the study treatment. The Investigator will be responsible for determining the relationship between an AE and the study treatment. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment. Relationship of AEs to study treatment will be classified as follows:

- Not Related: No relationship exists between the AE and the treatment. The event is attributed to a pre-existing medical condition or an intercurrent event unrelated to the study product.
- Possibly Related: Follows the treatment but may have developed as a result of an underlying clinical condition or treatments/interventions unrelated to the study product.
- Probably Related: Follows the treatment but is unlikely to have developed as a result

of the subject's underlying clinical condition or other treatment or other interventions.

- Definitely Related: Follows the treatment and physical evidence shows a convincing relationship to the treatment.

12.7 Reporting Requirements for SAEs

The Investigator is required to report all SAEs. Once the Investigator becomes aware of an SAE, he/she must report the SAE to CellSight within 24 hours at:

Phone: 650-799-1589
Email: adverse.events@cellsighttech.com

The CellSight Medical Monitor may request additional supporting documentation as it becomes available, such as lab reports, ECG reports, discharge summary, hospital notes, etc.

The Investigator is also responsible for reporting all SAEs to the appropriate Institutional Review Board (IRB) in accordance with local laws and regulations. The Investigator is responsible for maintaining documentation in the study file that indicates the IRB has been properly notified. Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in an IND safety report (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible, but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting. Participating investigators include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1)).

13. QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring Requirements

In an effort to fulfill the obligations outlined in 21 CFR Part 312 and ICH guidelines which require the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent telephone and written communication. The Investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

The Investigator will permit representatives of the Sponsor and/or designated CRO to inspect all CRFs and corresponding study subject original medical records (source documents) at regular intervals throughout the study. Subject original medical records and other relevant data must be available to support all data recorded in the CRF. In addition to the original medical records, these data may include but are not limited to, study, laboratory and diagnostic reports, wound images and tracings, etc.

Site inspections serve to verify strict adherence to the protocol and the accuracy of the data being entered on the CRFs, in accordance with federal regulations. A Monitoring Log will be maintained at each study site that the monitor will sign, date, and state the type of visit.

The Investigator should be aware that the study site and subject records may be inspected by the Sponsor and or representatives of the designated CRO, FDA, or other regional regulatory authority.

13.2 Acceptability of Case Report Forms

All CRFs will be completed as soon as possible after the subject's visit. Corrections to data on the CRFs will be made according to standard data correction procedures. The Investigator will review CRFs to indicate that, to his/her knowledge, they are complete and accurate. CRFs may be reviewed by the Sponsor's or designated CRO's monitor, who will make a decision as to their acceptability.

13.3 Modification of Protocol

The Investigator will not modify or alter this protocol without first obtaining the concurrence of the Sponsor. Approval by the Investigator's IRB must also be obtained prior to implementation of the change, with two exceptions:

1. When necessary to eliminate apparent immediate hazard to the subject; or
2. When the modification does not involve the subject's participation in the trial.

An amendment may also require modification of the ICF. The Investigator will provide an approval letter for the amendment and revised ICF, if applicable, to the Sponsor. An amendment must be in writing and dated by both the Sponsor and the Investigator. If necessary, the Sponsor will submit protocol amendments to FDA and other appropriate regulatory authorities.

13.4 Reporting Protocol Deviations

The Investigator is obligated to follow the protocol without departure from the requirements written in the protocol. If the Investigator deems a deviation from the protocol requirements is necessary for a particular subject, the Sponsor will be notified and consulted prior to the subject's continuation in the study. The Sponsor also has the right to discontinue the subject for protocol violations. The IRB may also have to be contacted if safety to the subject or if the scientific soundness of the study is involved. All protocol deviations must be documented in the CRFs.

13.5 Subject Premature Withdrawal from Study

A subject who is enrolled into the study but does not complete the study will be considered prematurely discontinued.

All subjects have the right to withdraw at any point during the study without prejudice. It will be documented whether or not each subject completed the clinical study. If, for any subject, study treatment or observations were discontinued, the reason(s) will be recorded and the Sponsor should be notified promptly. All efforts must be made to collect data and report records and test results as completely as possible. Reasons for subject withdrawal/discontinuation may constitute one of the following:

- Subject withdrew consent
- Subject chooses to withdraw from study
- Subject is withdrawn due to an AE
- Pregnancy
- Lost to follow-up
- The Investigator determines that it is in the subject's best interest
- Excessive protocol deviations, as determined by the Investigator
- Discontinuation of study by the Sponsor

Important Notes:

1. Subjects may drop out or be withdrawn at their own request. Although subjects do not need to give a reason for requesting withdrawal from the trial, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

2. Any subjects reporting Serious Adverse Events (SAEs) that have not resolved by their last study visit will be followed to resolution or until 30 days after the subject completes the study.

3. Every attempt should be made to collect follow-up information. The reason for withdrawal from the study (if known) will be recorded in the source documents and on the appropriate page of the CRF.

4. Before a subject is identified as lost-to-follow-up, the site should make all reasonable efforts to contact the subject. These attempts must be documented and should include at a minimum one phone call and one follow-up certified letter.

14. DATA AND SAFETY MONITORING COMMITTEE

In addition to the requirements for adverse event reporting as outlined in Section 11.0, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional

and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data and Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

According to the UCDCC Data and Safety Monitoring Plan, any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC SRC determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the Data and Safety Monitoring Committee will appoint a DSMB. The DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

Results of the DSMC audit will be communicated to CellSight, IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

15. ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

15.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.2 IND Holder Information

CellSight Technologies is the holder of the IND (IND# 123591). The company is sponsoring this clinical trial and is responsible for the imaging costs incurred in the trial. The radiotracer will be manufactured under the direction of CellSight Technologies at a qualified production site.

15.3 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board Committee (IRB). A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Cellsight before study initiation. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

15.4 Informed Consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s). In accordance with UCD policy an original signed and dated participant Informed Consent document will reside in a secured location within the department of radiology. Copies of the signed and dated Informed Consent document will be provided to the study participant and UCD Health System Information Management for inclusion in the participant's UCD Health System Medical Record.

The informed consent form is considered to be part of the protocol and must be submitted by the investigator with it for IRB/IEC/REB approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the

study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

15.5 Sharing of Results with Subjects

The results of this research will not be shared with subjects. However, results may be shared as described in Section 7.1.1.

15.6 Disclosure and Confidentiality

☒ I understand that if this study involves the use of the UC Davis Health Electronic Health Record (EMR/EPIC) it also contains the clinical data for Marshall Medical Center (MMC). I understand that MMC patient data cannot be accessed for research purposes and that I must take the necessary steps to ensure that MMC data is not accessed, used, or disclosed for UC Davis Health research purposes.

In order to maintain patient privacy, all study reports and communications will identify the patient by initials and the assigned patient number. Data capture records and drug accountability records will be stored in secure cabinets in the department of radiology. Medical records of patients will be maintained in strict confidence according to legal requirements. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored according to IRB approved specifications, and will be transmitted to the Sponsor. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Sponsor research

staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived as per IRB approved specifications.

15.7 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

15.8 Compensation for Research-Related Injury

If a subject is injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by the University or the study sponsor or may be billed to the subject's insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

15.9 Economic Burden to Subjects

All study-related procedures will be paid by the study and not charged to the subject.

16. REFERENCES

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17. APPENDICES

Appendix 1: ECOG and Karnofsky Performance Status Scores[1,2]

ECOG PERFORMANCE STATUS	KARNOFSKY PERFORMANCE STATUS
0—Fully active, able to carry on all pre-disease performance without restriction	100—Normal, no complaints; no evidence of disease 90—Able to carry on normal activity; minor signs or symptoms of disease
1—Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	80—Normal activity with effort, some signs or symptoms of disease 70—Cares for self but unable to carry on normal activity or to do active work
2—Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours	60—Requires occasional assistance but is able to care for most of personal needs 50—Requires considerable assistance and frequent medical care
3—Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours	40—Disabled; requires special care and assistance 30—Severely disabled; hospitalization is indicated although death not imminent
4—Completely disabled; cannot carry on any selfcare; totally confined to bed or chair	20—Very ill; hospitalization and active supportive care necessary 10—Moribund
5—Dead	0—Dead

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Appendix 2: Study Registration and Participant visits

A. The subject will sign and date the Informed Consent Form (ICF), and Health Insurance Portability and Accountability Act (HIPAA) authorization (according to site's practices) prior to any study-related procedures with the exception of the standard-of-care (SOC) diagnostic/tumor staging CT or MRI that would be accepted for imaging review to assess eligibility of NSCLC subjects, if done within 45 days prior to Visit 2.
B. Once signed, informed consent has been obtained; patients will be entered on study. To register a patient, the study coordinator must complete the Eligibility Checklist. The study coordinator will register the patient onto the study and assign a unique an Enrollment ID before initiation of the study drug administration.
C. Pre-study laboratory tests must be completed prior to registration within the time frame specified in the protocol.
D. A subject failing to meet all protocol requirements may not be registered. If you have any questions regarding eligibility, please contact the coordinating site PI or Study Coordinator
E. Unscheduled visits may be required in addition to the scheduled visits per the Investigator's discretion. The details of these unscheduled visits with subjects will be recorded in the medical records and on the Case Report Form (CRF).
F. If a subject misses a visit, the site is to make every effort to have the subject return as soon as possible to make up the visit. Once the subject is seen, he/she is to return to his/her original visit schedule.
G. A subject who has signed the consent form but does not receive any [^{18}F]F-AraG infusion is classified as a screen failure. Subject number, demographic information, and reason for screen failure will be collected.
H. A subject who is classified as a screen failure will be replaced. A subject who does not receive at least one infusion of [^{18}F]F-AraG and the associated PET/CT scans will also be replaced.