UCSF Helen Diller Family Comprehensive Cancer Center

NCT# 03007719

Functional imaging of T-cell activation with [^{18}F]F-AraG in urothelial carcinoma patients receiving neoadjuvant therapy or patients with cancer receiving standard of care anti-PD-1/L1

Protocol Number: CC # 16709

Study Drug: 2′-deoxy-2′-[18F]fluoro-9-β-Darabinofuranosylguanine ([^{18}F]F-AraG)

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Protocol Signature Page

Protocol No.: 16709 **Version Date:** 02-20-2018

1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

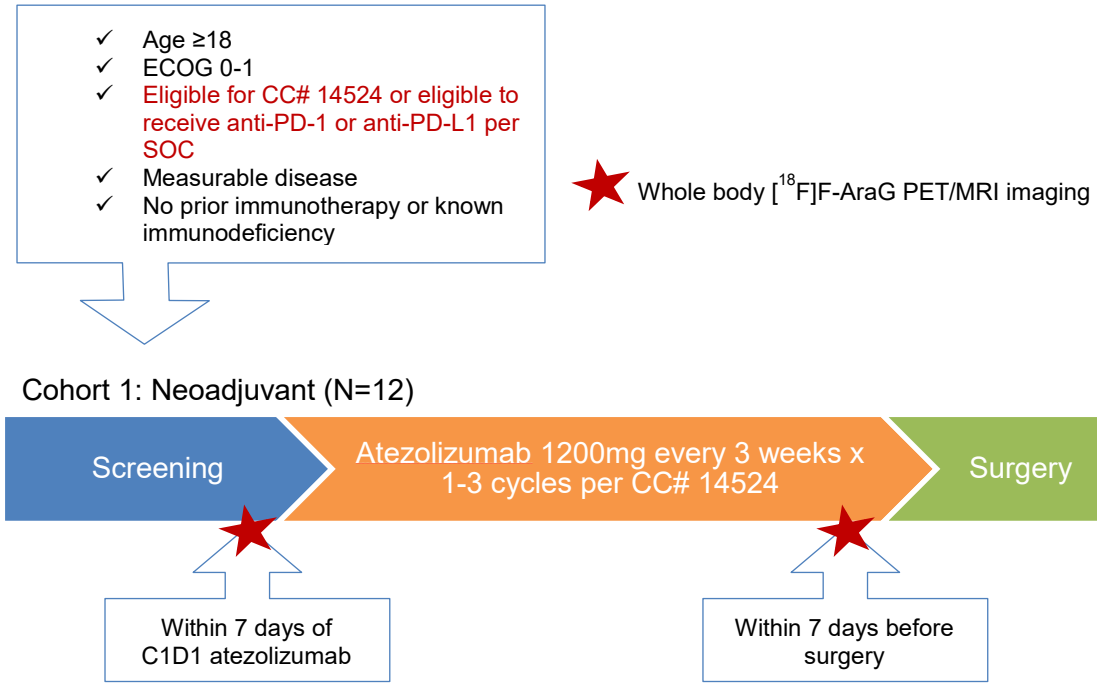
Abstract

Title	Functional imaging of T-cell activation with [^{18}F]F-AraG in urothelial carcinoma patients receiving neoadjuvant or patients with cancer receiving standard of care anti-PD-1 or anti-PD-L1
Patient population	1. Patients with localized bladder cancer who are eligible for the UCSF phase 2 clinical trial of neoadjuvant anti-PD-1 or anti-PD-L1 before definitive surgery (NCT02451423) (Cohort 1), and 2. Patients with any cancer type who are planned to initiate standard of care (SOC) anti-PD-1 or anti-PD-L1 (Cohort 2).
Rationale for Study	[^{18}F]F-AraG is a novel PET imaging agent that has demonstrated selectivity for activated T-cells in preclinical models and T-cell leukemia cell lines. [^{18}F]F-AraG has the potential to serve as a noninvasive functional biomarker in the monitoring of T-cell mediated anti-tumor immune response following administration of an immunotherapeutic agent. [^{18}F]F-AraG had been administered in six healthy volunteers with no > Grade 1 adverse events, and the biodistribution of [^{18}F]F-AraG has been determined in these volunteers on which radiation dosimetry estimated have been based. In this study, [^{18}F]F-AraG uptake in the tumor before and after treatment with the anti-PD-1 or anti-PD-L1 antibody will be measured in localized bladder cancer patients receiving neoadjuvant anti-PD-1 or anti-PD-L1 in the context a clinical trial, as well as in patients with any cancer type (locally advanced or metastatic) receiving SOC anti-PD-1 or anti-PD-L1. Clinical response as well as T cell infiltration within the tumor of a pre-treatment biopsy or resection specimen will be correlated with changes in [^{18}F]F-AraG uptake. In the neoadjuvant cohort, pathologic response as well as T cell infiltration within the tumor of the surgical specimen will also be correlated with changes in [^{18}F]F-AraG uptake. Results from this pilot study will help to guide future clinical trials of [^{18}F]F-AraG in the monitoring of anti-tumor immune responses.
Primary Objective	To assess the change in [^{18}F]F-AraG uptake in primary and/or metastatic tumor(s) on whole-body [^{18}F]F-AraG PET/MR imaging associated with neoadjuvant and SOC anti-PD-1 or anti-PD-L1 treatment.

Secondary Objectives	1. To correlate change in [^{18}F]F-AraG uptake within the primary tumor with clinical and pathologic response in patients treated with neoadjuvant anti-PD-1 or anti-PD-L1 (Cohort 1). 2. To assess [^{18}F]F-AraG uptake in lymphoid organs before and after anti-PD-1 or anti-PD-L1 (Cohort 1 and 2).
Exploratory Objectives	1. To correlate change in [^{18}F]F-AraG uptake within the primary tumor with quantification of tumor-infiltrating T cells in cystectomy specimen (Cohort 1). 2. To correlate change in [^{18}F]F-AraG uptake within the primary tumor and/or metastatic tumor(s) with quantification of tumor-infiltrating T cells in a pre-treatment biopsy or resection specimen (Cohort 1 and 2).
Study Design	This is a single-center cross-sectional imaging study in patients with localized bladder cancer undergoing neoadjuvant atezolizumab as part of the companion clinical trial CC# 14524 (NCT02451423; Phase 2 study of atezolizumab in non-metastatic bladder transitional cell carcinoma), and patients with any cancer type (locally advanced or metastatic) receiving standard of care (SOC) anti-PD-1 or anti-PD-L1. For the neoadjuvant cohort, study participants will undergo whole body PET/MR imaging with [^{18}F]F-AraG within 7 days of initiating atezolizumab and within 7 days before surgery. For the SOC cohort, study participants will undergo whole body PET/MR imaging with [^{18}F]F-AraG within 7 days of initiating Cycle 1 anti-PD-1 or anti-PD-L1, and between Cycle 1 Day 15 (C1D15) and Cycle 2 Day 7 (C2D7) anti-PD-1 or anti-PD-L1 (see Study Schema). A Simon's two-stage design will be utilized.
Number of patients	A total of 31 patients will be enrolled over an accrual period of approximately 20 months. 12 patients will be enrolled in the neoadjuvant atezolizumab cohort, and approximately 19 patients will be enrolled in the SOC anti-PD-1 or anti-PD-L1 cohort.
Duration of Therapy	Each patient will undergo two PET/MR imaging scans. The first imaging will be performed within 7 days of starting anti-PD-1 or anti-PD-L1 (baseline). The second imaging will be performed within 7 days before surgery in the neoadjuvant cohort, and between C1D15 and C2D7 anti-PD-1 or anti-PD-L1 in the SOC cohort. A bolus injection of [^{18}F]F-AraG will be administered at each imaging time point. Each injection will be followed by up to two whole-body PET/MR scans. Each probe injection plus PET/MR imaging session is estimated to last up to three hours.
Duration of Follow up	All patients will be followed for 7 days after each [^{18}F]F-AraG PET/MR imaging time point for safety assessment.

Duration of study	The study is anticipated to reach completion 20 months from the time the study opens to accrual.
Study Drugs	2′-deoxy-2′-[18F]fluoro-9-β-Darabinofuranosylguanine ([^{18}F]F-AraG) is a radiopharmaceutical imaging agent that will be produced under CGMP (Current Good Manufacturing Practice) regulations under the direction of Dr. Jim Slater in the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility at UCSF. A one-time nominal injection dose of ≤5.7mCi for male subjects and ≤4.4mCi for female subjects will be administered at each imaging time point. A simultaneous whole body MRI will be used for attenuation correction and anatomic localization of [^{18}F]F-AraG uptake and SUV calculation.
Safety Assessments	Patients will be evaluated one day and one week via telephone visit after each radiopharmaceutical injection for safety follow-up. All adverse events will be recorded. Due to the noninvasive and non-therapeutic nature of the study, potential risks of the study are anticipated to be low.
Unique Aspects of this Study	To our knowledge, this is the first study to investigate changes in activated T cell localization in the setting of immunotherapy for cancer utilizing functional PET imaging.

Study Schema:



List of Abbreviations

AE	adverse event
BMP	basic metabolic panel
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CGMP	Current Good Manufacturing Practice
CR	complete response
CRC	Clinical Research Coordinator
CRF	case report form
CT	computerized tomography
CTCEA	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
dCK	deoxycytidine kinase
dGK	doexyguanosine kinase
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FAC	2-fluoro-d-(arabinofuranosyl)cytosine
F-AraG	2′-deoxy-2′-fluoro-9-β-D-arabinofuranosylguanine
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
F/U	follow-up
GCP	Good Clinical Practice
HDFCCC	Helen Diller Family Comprehensive Cancer Center
HIPAA	Health Insurance Portability and Accountability Act (HIPAA)
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IND	investigational new drug application
IRB	Institutional Review Board
IHC	Immunohistochemistry
IV	Intravenous
MR	magnetic resonance
MRI	magnetic resonance imaging
NCI	National Cancer Institute

List of Abbreviations

PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PK	Pharmacokinetics
PR	partial response
PRC	Protocol Review Committee
RECIST	Response Evaluation Criteria in Solid Tumors
SOC	standard of care
SUV	standardized uptake values
TURBT	transurethral resection of bladder tumor
UA	urinalysis
WBC	white blood cell

Table of Contents

1 Background and Study Rationale

In recent years, advances in immunotherapy have resulted in remarkable and durable clinical responses in a subset of patients with advanced cancers. However, even among the tumor types that respond – including advanced melanoma and renal cell carcinoma – only 20%-30% of patients benefit from treatment, suggesting intrinsic immune resistance or an insufficient immune response (Restifo N et al., 2016). Furthermore, because immunotherapeutic agents act by inducing cancer-specific immune responses, clinical responses are typically delayed in comparison to conventional cytotoxic agents (Wolchok JD et al., 2009). A significant unmet need in the field is therefore the development of biomarkers to predict which patients are most likely to benefit from immunotherapy.

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 (Fox CJ et al., 2005, Soler C., 2001). In preclinical models of cancer and autoimmunity, the PET probe [^{18}F]–2-fluoro-d-(arabinofuranosyl)cytosine ([^{18}F]-FAC), which targets the deoxycytidine salvage pathway, was shown to localize to sites of immune activation (Radu CG et al., 2008) and is predominantly accumulated in proliferative CD8+ T cells (Nair-Gill E et al., 2010).

Recently, a radiofluorinated AraG imaging agent, [^{18}F]F-AraG (2′-deoxy-2′-fluoro-9-β-D-arabinofuranosylguanine; trade name VisAcT) was synthesized (Namavari M et al., 2010) 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 (DeAngelo DJ, 2009). [^{18}F]F-AraG preferentially accumulates in murine and human activated T cells than in naive T cells **(Figure 1)**. The accumulation of [^{18}F]F-AraG in human activated T cells is also significantly higher than other immune cells, including B cells, macrophages, and dendritic cells (unpublished data). Furthermore, endogenously induced anti-tumor immune response in a viral induced rhabdomyosarcoma (MSV) mouse model was correlated with enhanced [^{18}F]F-AraG uptake within the tumors **(Figure 2a)**. Analysis of isolated tumors showed that tracer preferentially accumulated in activated CD8+ T cells **(Figure 2b).**

[^{18}F]F-AraG is a high affinity substrate for doexyguanosine kinase (dGK) and a low affinity substrate for deoxycytidine kinase (dCK). Both dGK and dCK are over-expressed in activated T cells. Blocking the expression of either dGK or dCK causes reduction in [^{18}F]F-AraG accumulation, while over-expression of either dGK or dCK leads to increased accumulation of [^{18}F]F-AraG.

The first-in-human study of [^{18}F]F-AraG was performed at UCSF in 2015 (Yaghoubi S et al., 2015). [^{18}F]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**. The tracer was well tolerated by all patients and there were no > Grade 1 adverse events. The only AE that occurred in more than one volunteer was positive 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. However, in the present study, oral fluid intake and a diuretic (furosemide) will be administered for subjects to allow rapid clearance of the excreted radiotracer from the renal collecting systems and to provide diluted radiotracer within the background of the bladder, and to enable clear evaluation of distribution of the radiopharmaceutical in the walls of the ureters, bladder, and surrounding structures.

Given that immunotherapeutic strategies, in particular immune checkpoint antibodies, focus on the generation of T-cell-based antitumor immunity, we hypothesize that uptake of [^{18}F]F-AraG within the tumor will correlate with T-cell mediated immune response in cancer patients treated with immune checkpoint blockade. In May 2016, atezolizumab (Tecentriq), an anti-PD-L1 developed by Genentech Inc. was granted FDA approval for the treatment of previously treated locally advanced or metastatic urothelial carcinoma that had progressed during or following platinum-containing chemotherapy or that had progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This approval was based on results of a single-arm phase 2 study of atezolizumab in 310 patients with locally advanced or metastatic urothelial carcinoma, demonstrating an objective response rate (ORR) of 14.8% overall, and an ORR of 26% in patients classified as PD-L1 positive by immunohistochemistry (Rosenberg JE, 2009). Since then, in April 2017, atezolizumab was also approved in the front-line setting in patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-based chemotherapy (Balar AV et al., 2017).

Currently, PD-L1 inhibitors are approved for bladder cancer, non-small cell lung cancer, and Merkel cell skin cancer (Merkel cell carcinoma), and PD-1 inhibitors are approved for melanoma of the skin, non-small cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin lymphoma. FDA-approved anti-PD-1/L1 medications include:

- Pembrolizumab
- Avelumab
- Atezolizumab
- Nivolumab
- Durvalumab

In this study, patients with localized bladder cancer eligible for a companion neoadjuvant trial of atezolizumab in non-metastatic bladder transitional cell carcinoma (CC# 14524; NCT02451423), as well as patients with any cancer type (locally advanced or metastatic) planned to receive anti-PD-1 or anti-PD-L1 per SOC will undergo two whole body PET/MR imaging to assess for changes in tracer uptake with PD-L1 blockade. The neoadjuvant cohort in this study provides a unique opportunity to evaluate the correlation of post-treatment intratumoral immune filtration as well as pathologic clinical response with tracer uptake. Results from this study will guide the development of future clinical trials investigating the role of [^{18}F]F-AraG in the monitoring of anti-tumor immune responses.

Figure 1: [^{18}F]F-AraG preferentially accumulates in activated T cells than in naive T cells. (A) Uptake of [^{18}F]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 [^{18}F]F-AraG before subcutaneous implantation into the shoulders before PET/CT imaging.

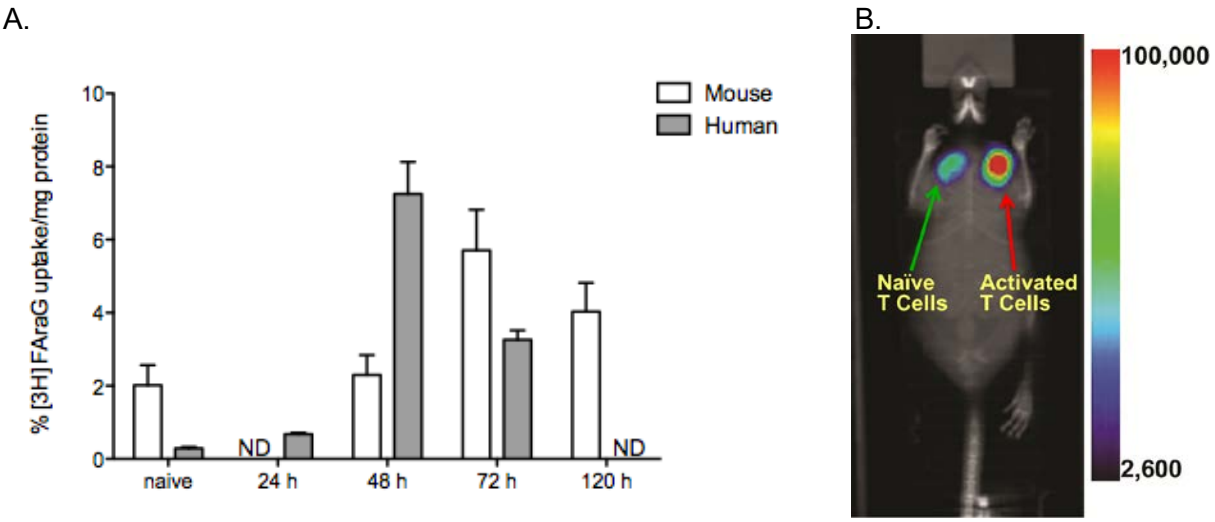


Figure 2: Visualization of endogenously induced anti-tumor immune response in a viral induced rhabdomyosarcoma (MSV) mouse model with [^{18}F]F-AraG PET. (A) Viral induced rhabdomyosarcoma was implanted in the left hindleg, and P815 mastocytoma (control) was implanted in the right shoulder. PET/CT was 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.

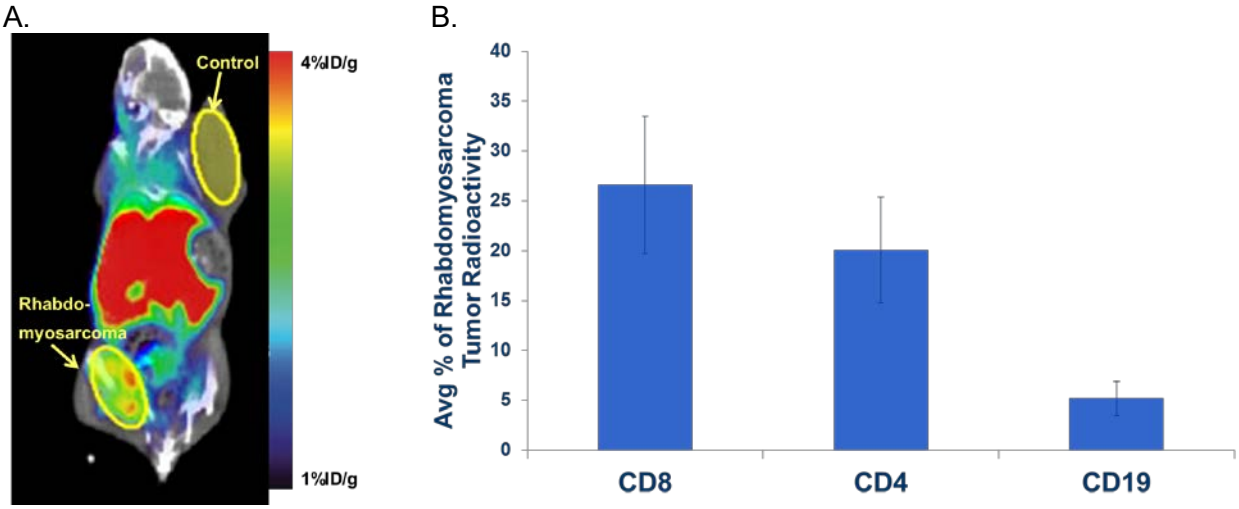
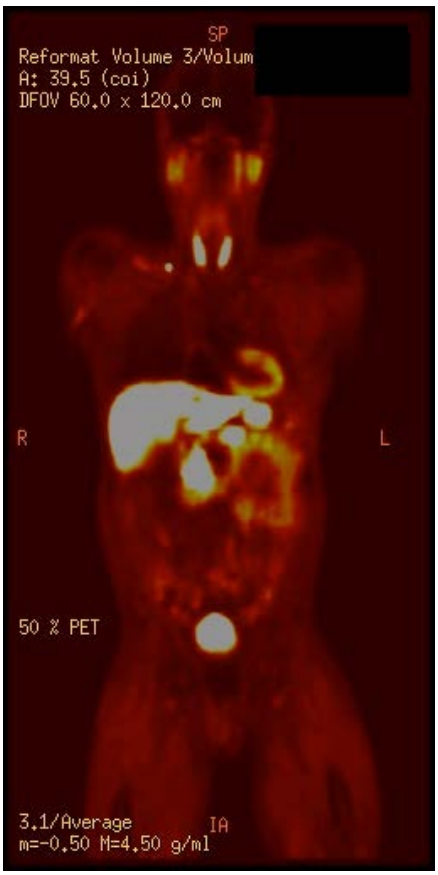


Figure 3: Whole body [^{18}F]F-AraG PET/MR image in a healthy volunteer.



2 Objectives and Endpoints of the Study

2.1 Objectives

2.1.1 Primary Objective

To assess the change in [^{18}F]F-AraG uptake in primary and/or metastatic tumor(s) on whole-body [^{18}F]F-AraG PET/MR imaging associated with neoadjuvant and SOC anti-PD-1 or anti-PD-L1 treatment.

2.1.2 Secondary Objectives

1. To correlate change in [^{18}F]F-AraG uptake within the primary tumor with clinical and pathologic response in patients treated with neoadjuvant atezolizumab (Cohort 1).

2. To assess [^{18}F]F-AraG uptake in lymphoid organs before and after anti-PD-1 or anti-PD-L1 (Cohort 1 and 2).

2.1.3 Exploratory Objectives

1. To correlate change in [^{18}F]F-AraG uptake within the primary tumor with quantification of tumor-infiltrating T cells in cystectomy specimen (Cohort 1).

2. To correlate change in [^{18}F]F-AraG uptake within the primary tumor and/or metastatic tumor(s) with quantification of tumor-infiltrating T cells in a pre-treatment biopsy or resection specimen (Cohort 1 and 2).

2.2 Endpoints

2.2.1 Primary Endpoint

To describe the change between pre-treatment and post-treatment maximum standardized uptake values (SUV_{max}) in the primary and/or metastatic tumor(s) on whole-body [^{18}F]F-AraG PET/MR imaging by study cohort.

2.2.2 Secondary Endpoints

1. To compare change in SUV_{max} of the primary tumor in patients who achieve pathologic down-staging (e.g. complete pathologic response) or clinical response (measured by RECIST v1.1), and those without pathologic or clinical response at time of surgery in patients receiving neoadjuvant atezolizumab (Cohort 1).

2. To describe the change between pre-treatment and post-treatment SUV_{max} in lymphoid organs (e.g. lymph nodes) on whole-body [^{18}F]F-AraG PET/MR imaging (Cohort 1 and 2).

2.2.3 Exploratory Endpoints

1. To correlate change in SUV_{max} of the primary tumor with the number of tumor-infiltrating CD3+ and CD3+CD8+ T cells in the surgical specimen quantified by immunohistochemistry (IHC) and image analysis in patients receiving neoadjuvant atezolizumab (Cohort 1).

2. To correlate change in SUV_{max} of the primary and/or metastatic tumor(s) with the number of tumor-infiltrating CD3+ and CD3+CD8+ T cells in the pre-treatment biopsy or resection specimen quantified by immunohistochemistry (IHC) and image analysis in patients receiving SOC anti-PD-1 or anti-PD-L1 (Cohort 1 and 2).

3 Study Design

3.1 Characteristics

This is a single-center cross-sectional imaging study in patients with localized bladder cancer undergoing neoadjuvant atezolizumab as part of the companion clinical trial CC# 14524 (NCT02451423; Phase 2 study of atezolizumab in non-metastatic bladder transitional cell

carcinoma), and patients with any cancer type (locally advanced or metastatic) receiving SOC anti-PD-1 or anti-PD-L1. Only anti-PD-1/L1 FDA approved for a given cancer will be used for Cohort 2. For the neoadjuvant cohort, study participants will undergo whole body PET/MR imaging with [^{18}F]F-AraG within 7 days of initiating atezolizumab and within 7 days before surgery. For the SOC cohort, study participants will undergo whole body PET/MR imaging with [^{18}F]F-AraG within 7 days of initiating Cycle 1 anti-PD-1 or anti-PD-L1 and between Cycle 1 Day 15 and Cycle 2 Day 7 anti-PD-1 or anti-PD-L1.

3.2 Number of Subjects

A total of 31 patients will be enrolled over an accrual period of approximately 20 months. Twelve (12) patients will be enrolled in the neoadjuvant atezolizumab cohort, and 19 patients will be enrolled in the SOC anti-PD-1 or anti-PD-L1cohort.

3.3 Eligibility Criteria

Patients must have baseline evaluations performed prior to the first injection of [^{18}F]F-AraG and must meet all inclusion and exclusion criteria. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

3.3.1 Inclusion Criteria

1. Age $\geq$18 years
2. Histologically or cytologically documented cancer to which anti-PD1 or anti-PDL1 are approved therapies
3. Eligible for with plan to undergo neoadjuvant treatment with atezolizumab followed by surgery as part CC# 14524, or planned to undergo treatment with anti-PD-1 or anti-PD-L1 per standard of care
4. Must have measurable disease by RECIST v1.1 regardless of disease stage (e.g. localized, locally advanced, or metastatic)
5. In female patients, negative pregnancy test with no plans to become pregnant during the duration of the study
6. Able to provide informed consent and follow the study guidelines
7. Archival tumor tissue from biopsy or resection will be required for all patients. Archival tissue should be of good quality based on total and viable tumor contents. Fine-needle aspiration, brushing, and cytologic cell pellets are not acceptable.

3.3.2 Exclusion Criteria

1. History of prior treatment with immune checkpoint antibodies (e.g. anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody) or co-stimulatory agonist antibodies (e.g. anti-41BB, anti-OX40)

   a. Prior intravesical treatment with BCG is allowed. However, the last dose must be at least 6 weeks from time of enrollment and patients must have documented progressive disease at least 6 weeks from completion of last BCG.

2. Diagnosis of immunodeficiency including history of Human Immunodeficiency Virus (HIV)

3. Receiving systemic steroid therapy or any form of immunosuppressive therapy within 7 days prior to first injection of [^{18}F]F-AraG.
   a. Topical and inhaled corticosteroids are allowed.

4. Prior allogeneic stem cell or solid organ transplant

5. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study

6. Biopsy or resection of the primary tumor within 14 days the first injection of [^{18}F]F-AraG

7. Contraindication to MRI imaging, as determined through review of the UCSF MRI screening form by study investigator (Appendix 4)
   a. UCSF screening form available online: https://radiology.ucsf.edu/sites/radiology.ucsf.edu/files/wysiwyg/research/brainchange/MRI%20Screening%20Form-BrainChange.pdf

8. Evidence of active infection within 14 days of study enrollment

9. Female patients who are pregnant or breastfeeding

10. Inability to receive furosemide (Lasix), in the opinion of the treating investigator

11. Patients that plan to receive off-label use of anti-PD1 or anti-PDL1

3.4 Duration of Follow Up

Patients will be followed for 7 days after each [^{18}F]F-AraG PET/MR imaging time point for safety assessment. Specifically, patients will be evaluated by telephone one day and one week after each radiopharmaceutical injection for safety follow-up. All adverse events will be recorded and graded according to CTCAE v4.0.

3.5 Subject Replacement

All patients who receive any dose [^{18}F]F-AraG of will be analyzed for safety. Subjects who discontinue from study participation prior to completing a second PET/MR scan will be replaced. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related AEs to Grade 0-1.

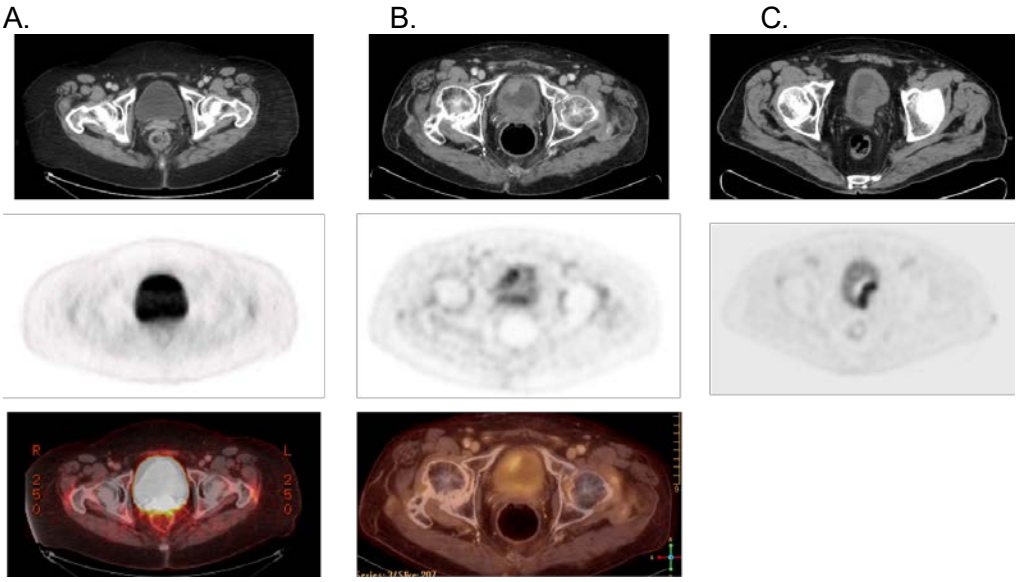
4 Imaging Agent

[^{18}F]F-AraG is a radiopharmaceutical that will be produced under cGMP under the direction of Jim Slater, PhD., in the Department of Radiology and Biomedical Imaging Radiopharmaceutical Facility. The radiopharmaceutical will be prepared in the same facility in which the injection and imaging will take place, the China Basin Imaging Center. In a prior study of 6 healthy volunteers imaged with [^{18}F]F-AraG, there were no Grade >1 adverse events related to tracer injection, and organ-specific dosimetry was within acceptable range.

[^{18}F]F-AraG will be administered by a licensed nuclear medicine technologist under the supervision of a physician boarded in nuclear medicine on an outpatient basis. It will be administered at a single time point intravenously prior to PET imaging, at a subpharmacologic, tracer microdose consistent with imaging practices. The one-time nominal injected dose will be less than or equal to 5.7 mCi for male patients and less than or equal to 4.4 mCi for female patients. A simultaneous whole body MRI (PET/MR) will be used for attenuation correction and anatomic localization of [^{18}F]F-AraG uptake and SUV calculation. Each [^{18}F]F-AraG injection will be followed by a whole body PET/MR acquisition, immediately followed by a limited PET/MR acquisition that includes only the pelvic region. The patient will not need to be repositioned between the acquisitions. The limited PET/MR dedicated pelvic region acquisition will not add any additional radiation exposure, and will require only 5-10 additional minutes. Each probe injection plus PET/MR imaging session (on and off the scanner) is estimated to last approximately 60 to 90 minutes.

Patients will be asked to drink 16 ounces of water approximately 30 minutes prior to furosemide (Lasix) administration. 20 mg Lasix will be administered intravenously 10-30 minutes prior to injection of radiopharmaceutical. The patient will void 30 to 45 minutes after Lasix administration. PET/MR imaging will then be performed from the bottom up so that the surrounding tissues is optimally visualized. After completion of the whole body imaging, a repeat 3-minute tumor image will be acquired at the end of imaging.

Figure 4: Bladder tumor visualization with [^{18}F]FDG. (A) No Lasix administration. (B) Patient with exophytic bladder mass with Lasix administration at time of tracer injection. (C) Patient with bladder thickening with Lasix administration at time of tracer injection.



5 Study Procedures and Observations

A written, signed, informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A copy of the signed ICF will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

5.1 Study Assessments

The Screening procedures and assessments must be completed within 28 days of the day 1 Visit unless otherwise noted (i.e., baseline staging scans).

- Vital signs
- Height and weight
- Physical examination and medical history
- Performance status
- Baseline staging scans with CT chest, head, and/or neck + CT or MRI of the abdomen/pelvis ± bone scan within 42 days of study enrollment
    - Patients may receive staging scans and [^{18}F]F-Ara PET/MR imaging on the same day if the patient meets eligibility criteria for the study as assessed by Principal Investigator prior to the completion of the scan.
- MRI screening form (Appendix 4)
- Tissue collection
    - Archival tumor tissue from biopsy or resection will be collected for all patients.
- Baseline labs performed during screening window of Day -28 to Day +1
    - CBC with differential*
    - BMP*
    - Urinalysis*
    - Pregnancy test for women of childbearing potential*

*If already performed in the screening window (e.g. during screening for corresponding neoadjuvant atezolizumab study protocol), will not need to be repeated.

5.2 Study Procedures

[^{18}F]F-Ara experimental PET radiopharmaceutical (hereafter referred to as "radiopharmaceutical")

- Vital signs and EKG will be recorded before and after completion of imaging.
- Administration of Furosemide (Lasix)
    - Patients who are not eligible to receive Lasix are excluded from this study (Section 3.3.2).

- Because [^{18}F]F-AraG is renally excreted with uptake in the urine, patients will be encouraged to drink 16 ounces of water approximately 30 minutes before furosemide (Lasix) administration, and will receive 20 mg of Lasix intravenously within 10-30 minutes prior to injection of the radiopharmaceutical.
- Patients will void 30 to 45 minutes after Lasix administration. PET/MR imaging will then be performed from the bottom up so that the surrounding tissue is optimally visualized.
- A Foley catheter may be placed if Lasix diuresis and voiding fails to provide adequate image quality.

- [^{18}F]F-AraG PET/MR imaging
  - Patient shall begin imaging between 1 to 180 minutes after the injection of the radiopharmaceutical. Coverage for the scan will extend from the top of the patient's head through the toes.
  - Each [^{18}F]F-AraG injection will be followed by a whole body PET/MR acquisition, immediately followed by a limited PET/MR acquisition that includes only the targeted tumor region. The patient will not need to be repositioned between the acquisitions. The limited PET/MR dedicated target region acquisition will not add any additional radiation exposure, and will require only 5-10 additional minutes.
  - Simultaneous whole body MRI (PET/MR) will be performed for attenuation correction.
  - Each probe injection plus PET/MR imaging session (on and off the scanner) is estimated to last approximately 60 to 90 minutes.
  - No formal report of the findings from imaging studies will be created. Each study will be reviewed by a board certified nuclear medicine physician and radiologist within one week after completion of the study. An expert molecular imaging investigator will analyze all data.
    - Exception: If an acute and new finding is found on MRI, this finding will be reported and documented, and the investigator will be notified.

5.3 Follow Up Procedures

Patients will be evaluated one day and one week by telephone after the radiopharmaceutical injection for safety follow-up. All adverse events will be recorded.

- Cohort 1 (neoadjuvant cohort):Following completion of neoadjuvant atezolizumab cycles per corresponding study protocol, the patient will return for repeat imaging within 7 days of undergoing surgery.
- Cohort 2 (SOC cohort): Between Cycle 1 Day 15 and Cycle 2 Day 7 anti-PD-1 or anti-PD-L1, the patient will return for repeat imaging.

5.4 Prohibited Medications

Patients should receive no systemic therapy for their cancer other than anti-PD-1 or anti-PD-L1 prior to completion of the two planned [^{18}F]F-AraG PET scans.

5.5 Safety

Patients will be evaluated via telephone on the day after and at one week after each radiopharmaceutical injection for safety follow-up. All adverse events will be recorded. For patients in the neoadjuvant cohort (Cohort 1), the principle investigator and study personnel (e.g. clinical research coordinator) of the corresponding neoadjuvant atezolizumab study will also be informed of the [^{18}F]F-AraG PET/MR imaging dates for each patient, and will follow up with any adverse events related to imaging during subsequent study clinic visits (e.g. Cycle 1 Day 1 visit after baseline imaging).

Potential risks of the study are anticipated to be low. Should a patient experience a Grade 1 or Grade 2 adverse event at the time of baseline scan which subsequently resolves, he/she may proceed with undergoing the second (pre-surgery) PET/MR imaging.

In the situation that a patient experiences a Grade 3 or higher adverse event at the time of baseline scan, the study should be permanently discontinued for that patient. The study will be halted after one serious adverse reaction attributable to [^{18}F]F-AraG is seen or if over 20% of patients experience Grade 3 or higher toxicities for re-evaluation of tracer dose (Section 8.4).

6 Study Calendar

		First (baseline) imaging			Second imaging		
	Screening (Day -28 to 1)	Day 1 (Image)	Safety Follow Up		Day 1 (Image)	Safety Follow-Up	
			Day 2 (Tele)	Day 8 (Tele)		Day 2 (Tele)	Day 8 (Tele)
Informed consent	X						
Medical history	X						
Physical exam	X						
Performance status	X						
Baseline staging scans[1]	X						
Height	X						
Weight	X						
Vitals[2]	X	X			X		
Pregnancy test[3]	X						
CBC, BMP and UA[4]	X						
MRI screening form[5]	X						
Tissue collection[6]	X						
Furosemide (Lasix)[7]		X			X		
[^{18}F]F-AraG PET/MR imaging[8]		X			X		
Electrocardiogram[9]		X			X		
AE Assessment[9]		X	X	X	X	X	X

[1] Patients may receive staging scans and [^{18}F]F-Ara PET/MR imaging on the same day if the patient meets eligibility criteria for the study as assessed by Principal Investigator prior to the completion of the scan.
[2] Vitals consist of heart rate, blood pressure, blood oxygen %, temperature, and respiratory rate. On imaging days, vitals are collected before and after imaging.
[3] Pregnancy tests are performed for women of childbearing potential.
[4] Screening labs, including CBC with differential, BMP and urinalysis are required if not already performed by the corresponding neoadjuvant atezolizumab study protocol or SOC.
[5] The study investigator will review the UCSF MRI screening form to confirm no contraindication to MRI imaging.
[6] Archival tissue from tumor resection or biopsy should be of good quality based on total and viable tumor contents. Fine-needle aspiration, brushing, and cytologic cell pellets are not acceptable.

[7] Patients will be encouraged to drink 16 ounces of water approximately 30 minutes before furosemide (Lasix) administration, and will receive 20 mg of Lasix intravenously within 10-30 minutes prior to injection of the radiopharmaceutical. Patients will void 30 to 45 minutes after Lasix administration before PET/MR imaging.
[8] PET/MR imaging will be performed from the bottom up so that the surrounding tissues is optimally visualized.
[9] Electrocardiograms are assessed before and after imaging. Adverse events are assessed by a physician on the research team after imaging.

7 Reporting and Documentation of Results

7.1 Evaluation of efficacy (or Activity)

7.1.1 Definitions

Evaluable for toxicity

All patients will be evaluable for toxicity from the time of [^{18}F]F-AraG administration.

7.2 Evaluation of Safety

Analyses will be performed for all patients receiving the radiotracer. The study will use the CTCAE v4.0 for reporting of adverse events.

7.3 Definition of Adverse Events

7.3.1 Adverse Event

An adverse event (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an adverse event (can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

7.3.2 Adverse Reaction

An adverse reaction is defined as any adverse event caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event.

7.3.2.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.3.2.2 Unexpected

An adverse event or suspected adverse reaction is considered *unexpected* if it is not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed, or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

7.3.2.3 Serious

An adverse event or suspected adverse reaction is considered *serious* if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Congenital anomaly/birth defect

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.3.2.4 Life-threatening

An adverse event or suspected adverse reaction is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

7.4 Recording of an Adverse Event

All grade 3 and above adverse events will be recorded using the NCI CTCAE v4.0. The Investigator will assign attribution of the possible association of the event with use of the investigational drug.

Relationship	Attribution	Description
Unrelated to investigational drug/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely	The AE *is doubtfully related* to the intervention
Related to investigational drug/intervention	Possible	The AE *may be related* to the intervention
	Probable	The AE *is likely related* to the intervention
	Definite	The AE *is clearly related* to the intervention

Signs or symptoms reported as adverse events will be graded and recorded by the Investigator according to the CTCAE. When specific adverse events are not listed in the CTCAE they will be graded by the Investigator as *none*, *mild*, *moderate* or *severe* according to the following grades and definitions:

Grade 0	No AE (or within normal limits)
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local, or noninvasive intervention (e.g., packing, cautery) 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

7.5 Follow-up of Adverse Events

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

7.6 Expedited Reporting

Reporting to the Data and Safety Monitoring Committee

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair (or qualified alternate) within 1 business day of knowledge of the event. The contact may be by phone or e-mail.

Reporting to UCSF Institutional Review Board

The Principal Investigator must report events meeting the UCSF IRB definition of “Unanticipated Problem” (UP) within 10 business days of his/her awareness of the event.

Expedited Reporting to the Food and Drug Administration

If the study is being conducted under an IND, the Sponsor-Investigator is responsible for determining whether or not the suspected adverse reaction meets the criteria for expedited reporting in accordance with Federal Regulations (21 CFR §312.32).

The Investigator must report in an IND safety report any suspected adverse reaction that is both serious and unexpected. The Sponsor-Investigator needs to ensure that the event meets all three definitions:

- Suspected adverse reaction (as defined in 7.3.2.1)
- Unexpected (as defined in 7.3.2.2)
- Serious (as defined in 7.3.2.3)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

The timeline for submitting an IND safety report to FDA is no later than **15 calendar days** after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)).

Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than **7 calendar days** after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

8 Statistical Considerations and Image Analysis

8.1 Image Processing and Analysis

Trained nuclear medicine physicians and molecular imaging scientists will evaluate the reconstructed PET, PET/MR images using a PET volume computer-assisted reading software package. Volumetric regions of interest will be chosen around tumors based on anatomic (MR) images and activity within the tumor will be expressed in a standardized uptake value (SUV) format where SUV will be defined as [concentration of tracer in tumor]/(injected dose/body weight). Tumor SUV at baseline (before anti-PD-1 or anti-PD-L1 treatment) will be compared with the post–therapy values to determine the change in SUV associated with the therapy. Whole body images will be analyzed to determine differences in tracer distribution relative to pre/post therapy and versus the normal subject pool already studied.

8.2 Sample Size Determination

The sample size determination is based on the primary endpoint of the study, the change between pre-treatment and post-treatment SUV_{max} in the primary and/or metastatic tumor(s) and on [^{18}F]F-AraG PET/MR imaging. The null hypothesis is that post-treatment SUV_{max} increases by at least 2-fold compared to baseline SUV_{max} in 1% patients. The alternative hypothesis is that post-treatment SUV_{max} increases by at least 2-fold compared to baseline SUV_{max} in 20% patients. For the SOC cohort (Cohort 2), a Simon's two-stage design will be used. Eight patients will be accrued

initially, if no patient is observed to have a post-treatment SUV_{max} that increases by at least 2-fold compared to baseline SUV_{max}, the study will be halted; otherwise, an additional 11 patients will be accrued. The null hypothesis will be rejected if 2 or more of the 19 patients are observed to have at least a 2-fold increase in post-treatment SUV_{max} compared to baseline SUV_{max}. This design yields a type I error rate of 0.05 and power of 80%. For the neoadjuvant cohort (Cohort 1), one-stage design will be applied with 12 patients accrued to ensure 80% power at a significance level of 0.05.

8.3 Accrual Estimates

The anticipated accrual rate is approximately 1-2 patients per month, leading to an estimated total accrual period of 20 months. Twelve (12) patients are anticipated to be enrolled in the neoadjuvant atezolizumab cohort, and 19 patients are anticipated to be enrolled in the SOC anti-PD-1 or anti-PD-L1 cohort. A total of 31 patients will be accrued.

8.4 Interim Analysis and Safety Stopping Rule

Interim analysis will be performed only for the SOC cohort (Cohort 2). After 8 patients are imaged at both baseline and post-treatment time points, the acquired PET/MR imaging results will be reviewed. If the post-treatment SUV_{max} increases by at least 2-fold compared to baseline SUV_{max} for at least one patient, the study will continue accrual for a total of 19 patients. If no patient is observed to have a post-treatment SUV_{max} that increases by at least 2-fold compared to baseline SUV_{max}, the study will be halted and the imaging protocol re-evaluated, with particular attention to the post-treatment imaging time point. Subsequently, the scan results will be analyzed on a continuous basis, and accrual may be halted to adjust imaging parameters on an as needed basis.

Complete safety data will also be analyzed at the time of interim analysis. Accrual will be halted after one serious adverse reaction attributable to [^{18}F]F-AraG is seen. If Grade 3 or higher toxicities are observed in more than 20% of all patients accrued which are attributable to [^{18}F]F-AraG, the study will be stopped and the dose of the of [^{18}F]F-AraG reexamined.

8.5 Analytic Plan

The median and interquartile range of SUV_{max} within the tumor and lymphoid tissues across all patients will be descriptively reported for baseline (before treatment) and post-treatment images, separately. The nonparametric paired Wilcoxon Signed-rank test will be used to assess differences in SUV_{max} before and after treatment. The log2 ratio of post-treatment versus baseline SUV_{max} within the tumor and lymphoid tissues will also be calculated.

To correlate change in SUV_{max} to clinical and/or pathologic response, patients will be divided into two groups: those who achieved clinical response and/or pathologic downs-staging, and those who did not. The median and interquartile range of change in SUV_{max} from baseline to pre-surgery in the different groups will be descriptively reported. For Cohort 1, clinical response will be determined by abdominal imaging performed $\leq$30 days after the last dose of atezolizumab prior to cystectomy compared to baseline pre-treatment imaging using RECIST v1.1 criteria, as specified in the companion treatment protocol (CC# 14524). For Cohort 1, pathologic response will be determined by evidence of down-staging (e.g. from muscle invasive to non-muscle invasive, or complete pathologic response) at the time of cystectomy.

Immunohistochemistry for immune infiltration will be performed in the Fong lab (Fong L et al. J

Natl Cancer Inst 2014). Briefly, 5-micron FFPE slides from archival tumor tissue or cystectomy tissue will be used for staining. For double stains, slides will first be incubated with antibody to CD8 and visualized with horseradish peroxidase using DAB+, followed by incubation with antibody to CD3 and visualized with alkaline phosphatase using Permanent Red. Tissues will be counterstained with hematoxyclin before analysis. Automatic cell counts for single- and double-stained cells will be determined using the Axiovision software (Zeiss, Peabody, MA). The correlation between change from baseline to post-treatment SUV_{max} on [^{18}F]F-AraG PET and CD3+ and CD3+CD8+ immune infiltration (#/μm^2) by IHC will be determined using Spearman's *rho* statistic, separately.

9 Study Management

9.1 Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF Institutional Review Board. Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form 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.

9.4 Changes in the Protocol

Once the protocol has been approved by the IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

10 Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

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Appendices

Appendix 1 Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity 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	Symptoms, but ambulatory Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work)	80	Normal activity with effort; some signs or symptoms of disease
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time Ambulatory and capable of all self-care, 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 his/her needs
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated Death not imminent
4	100% bedridden Completely disabled Cannot carry on any self-care Totally confined to bed or chair	20	Very sick, hospitalization indicated Death not imminent
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

Appendix 2 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study include:

- Review of subject data
- Review of suspected adverse reactions considered "serious"
- Monitoring every six months (depending on study accrual)
- Minimum of a yearly regulatory audit

Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and subject safety and discuss each subject's treatment at monthly Site Committee meetings. These discussions are documented in the Site Committee meeting minutes. The discussion will include the number of subjects, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase 2 or 3 studies are designated with a moderate risk assessment. The data is monitored twice per year with twenty percent of the subjects monitored (or at least three subjects if the calculated value is less than three).

Adverse Event Review and Monitoring

All grade(s) 3-5 adverse events, whether or not unexpected, and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

All grade(s) 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

In addition, all suspected adverse reactions considered "serious" entered into OnCore®, will be reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and it is determined to be related either to the study drug(s) or to a study procedure, the Investigator or his/her designee must notify the DSMC Chair within **1 business day** of knowledge of this event. The contact may be by phone or e-mail.

Increase in Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, a report should be submitted to the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Manager must be notified within 1 business day via e-mail. The DSMC must receive a formal letter within 10 business days and the IRB must be notified.

Data and Safety Monitoring Committee Contacts:

DSMC Chair: [redacted]
Phone:
Email:
Address:

DSMC Monitors
[redacted]
UCSF Helen Diller Family
Comprehensive Cancer Center
San Francisco, CA 94143

* DSMP approved by NCI 09/February2012

Appendix 3 UCSF Policy/Procedure for Required Regulatory Documents for a UCSF Investigator-Initiated Oncology Clinical Trials with an Investigator held Investigational New Drug (IND)

Purpose

This policy defines the required Regulatory Documents for Single Site and Multicenter Investigator Initiated Oncology Clinical Trials at the Helen Diller Family Comprehensive Cancer Center (HDFCCC) where the Principal Investigator (PI) holds the IND.

Background

The International Conference on Harmonization (ICH) Good Clinical Practices (GCP) Guidelines define Essential Regulatory Documents as those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of data produced. These documents serve to demonstrate compliance with standards of GCP and with all applicable regulatory requirements. Filing essential documents in a timely manner can greatly assist in the successful management of a clinical trial.

The Regulatory Documents will consist of electronic files in both iMedRIS and OnCore®, as well as paper files in the Regulatory Binders for both the Coordinating Site and the Participating Site(s) in the HDFCCC Investigator Initiated Oncology Clinical Trials.

Procedures

1. HDFCCC Essential Regulatory Documents

Documents Filed in iMedRIS:

- IRB approvals for initial submission of application, all modifications, and continuing annual renewals
- Current and prior approved protocol versions with signed protocol signature page(s)
- IRB approval letters and Informed Consent Form(s) (ICF)
- Current and prior versions of the Investigator Brochure (IB).
- Serious Adverse Event Reporting
- Protocol Violations and Single Patient Exception (SPE) Reports to IRB with supporting fax documentation

Documents Filed in OnCore®:

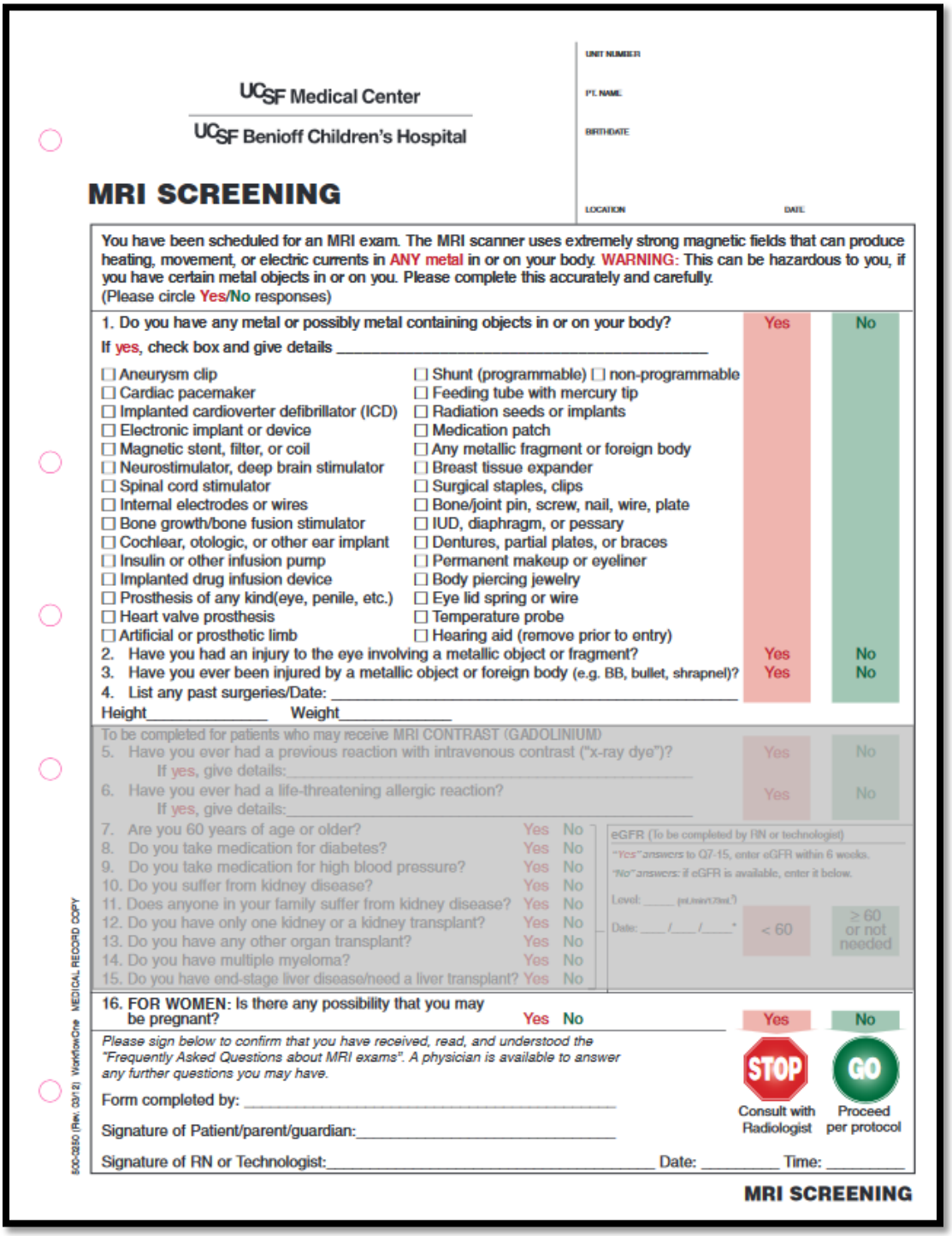
- Package Insert (if the study drug is commercial) or Investigator Brochure
- Protocol Review Committee (PRC) approved protocols, protocol amendments and Summary of Changes (SOC)
- Patient handouts
- Screening/enrollment log
- Data and Safety Monitoring Committee (DSMC) monitoring reports
- OnCore® Case Report Form (CRF) completion manual

Documents Filed in Regulatory Binder:

- Completed Food and Drug Administration (FDA) 1572 document with Principal Investigator's signature
- For all Principal Investigators and Sub-Investigators listed on the FDA 1572, will need Financial Disclosure Forms, CVs, MD Licenses, Drug Enforcement Agency (DEA) Licenses, and Staff Training Documents (i.e. Collaborative Institute Training Initiative (CITI), etc.)
- Site Initiation Visit (SIV) minutes and correspondence with participating site(s).
- As applicable, approvals for Biosafety Committee, Radiation Committee, and Infusion Center
- Serious Adverse Event (SAE) reports to IRB and sponsor.
- MedWatch reporting to FDA and sponsor
- Delegation of Authority Form
- Drug Destruction Standard Operating Procedure (SOP)
- For all laboratories listed on the FDA 1572, will need CLIA certifications, CAP certifications, lab licenses, CVs of Lab Directors, and laboratory reference ranges

Appendix 4 MRI Screening Form

Available online:
https://radiology.ucsf.edu/sites/radiology.ucsf.edu/files/wysiwyg/research/brainchange/MRI%20Screening%20Form-BrainChange.pdf



UCSF Medical Center

UCSF Benioff Children's Hospital

UNIT NUMBER
PT. NAME
BIRTHDATE
LOCATION
DATE

MRI SCREENING

You have been scheduled for an MRI exam. The MRI scanner uses extremely strong magnetic fields that can produce heating, movement, or electric currents in ANY metal in or on your body. WARNING: This can be hazardous to you, if you have certain metal objects in or on you. Please complete this accurately and carefully.
(Please circle Yes/No responses)

1. Do you have any metal or possibly metal containing objects in or on your body? Yes No

If yes, check box and give details _____

☐ Aneurysm clip	☐ Shunt (programmable) ☐ non-programmable
☐ Cardiac pacemaker	☐ Feeding tube with mercury tip
☐ Implanted cardioverter defibrillator (ICD)	☐ Radiation seeds or implants
☐ Electronic implant or device	☐ Medication patch
☐ Magnetic stent, filter, or coil	☐ Any metallic fragment or foreign body
☐ Neurostimulator, deep brain stimulator	☐ Breast tissue expander
☐ Spinal cord stimulator	☐ Surgical staples, clips
☐ Internal electrodes or wires	☐ Bone/joint pin, screw, nail, wire, plate
☐ Bone growth/bone fusion stimulator	☐ IUD, diaphragm, or pessary
☐ Cochlear, otologic, or other ear implant	☐ Dentures, partial plates, or braces
☐ Insulin or other infusion pump	☐ Permanent makeup or eyeliner
☐ Implanted drug infusion device	☐ Body piercing jewelry
☐ Prosthesis of any kind(eye, penile, etc.)	☐ Eye lid spring or wire
☐ Heart valve prosthesis	☐ Temperature probe
☐ Artificial or prosthetic limb	☐ Hearing aid (remove prior to entry)

2. Have you had an injury to the eye involving a metallic object or fragment? Yes No
3. Have you ever been injured by a metallic object or foreign body (e.g. BB, bullet, shrapnel)? Yes No
4. List any past surgeries/Date: _____

Height_____ Weight_____

To be completed for patients who may receive MRI CONTRAST (GADOLINIUM)

5. Have you ever had a previous reaction with intravenous contrast ("x-ray dye")? Yes No
   If yes, give details: _____
6. Have you ever had a life-threatening allergic reaction? Yes No
   If yes, give details: _____
7. Are you 60 years of age or older? Yes No
8. Do you take medication for diabetes? Yes No
9. Do you take medication for high blood pressure? Yes No
10. Do you suffer from kidney disease? Yes No
11. Does anyone in your family suffer from kidney disease? Yes No
12. Do you have only one kidney or a kidney transplant? Yes No
13. Do you have any other organ transplant? Yes No
14. Do you have multiple myeloma? Yes No
15. Do you have end-stage liver disease/need a liver transplant? Yes No

eGFR (To be completed by RN or technologist)
"Yes" answers to Q7-15, enter eGFR within 6 weeks.
"No" answers: if eGFR is available, enter it below.
Level: _____ (mL/min/1.73m²)
Date: ___/___/___*

< 60 | ≥ 60 or not needed

16. FOR WOMEN: Is there any possibility that you may be pregnant? Yes No

Yes: STOP — Consult with Radiologist
No: GO — Proceed per protocol

Please sign below to confirm that you have received, read, and understood the "Frequently Asked Questions about MRI exams". A physician is available to answer any further questions you may have.

Form completed by: _____

Signature of Patient/parent/guardian: _____

Signature of RN or Technologist: _____ Date: _____ Time: _____

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MRI SCREENING