STU 032018-078

A Prospective Study to Evaluate Quantitative Non-Contrast Perfusion using Arterial Spin Labeled MR Imaging for Assessment of Therapy Response in Metastatic Renal Cell Carcinoma

Principal Investigator:

Ananth Madhuranthakam, PhD
Director, MR Research
Department of Radiology and
Advanced Imaging Research Center
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX – 75390-9061
Phone: 214-648-7737
Fax: 214-648-7783
Ananth.Madhuranthakam@UTSouthwestern.edu

Sub-Investigator(s):

Ivan Pedrosa, MD, PhD
Department of Radiology and
Advanced Imaging Research Center

James Brugarolas, MD, PhD
Internal Medicine – Hematology/Oncology
Simmons Comprehensive Cancer Center

Hans Hammers, MD, PhD
Internal Medicine – Hematology/Oncology
Simmons Comprehensive Cancer Center

Kevin Courtney, MD, PhD
Internal Medicine – Hematology/Oncology
Simmons Comprehensive Cancer Center

Roderick McColl, PhD
Department of Radiology

Elena Vinogradov, PhD
Department of Radiology and
Advanced Imaging Research Center

Biostatistician:

Hong Zhu, PhD
Department of Clinical Science
Simmons Comprehensive Cancer Center
UT Southwestern Medical Center
5323 Harry Hines Blvd
Dallas, TX – 75390-8551
Phone: 214-648-7438
Hong.Zhu@UTSouthwestern.edu

Funding Source: NIH/NCI – U01CA207091

Initial version: 1.0 – March 30, 2018

Amended: **2.0 = August 27, 2019;**

3.0 = Feb. 26, 2021

UT Southwestern Medical Center (UTSW)
Harold C. Simmons Comprehensive Cancer Center
Attn: Clinical Research Office
5323 Harry Hines Blvd. MC 9179
Dallas, Texas 75390-9179

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Ananth Madhuranthakam, PhD

PI Signature: _____

Date:_____

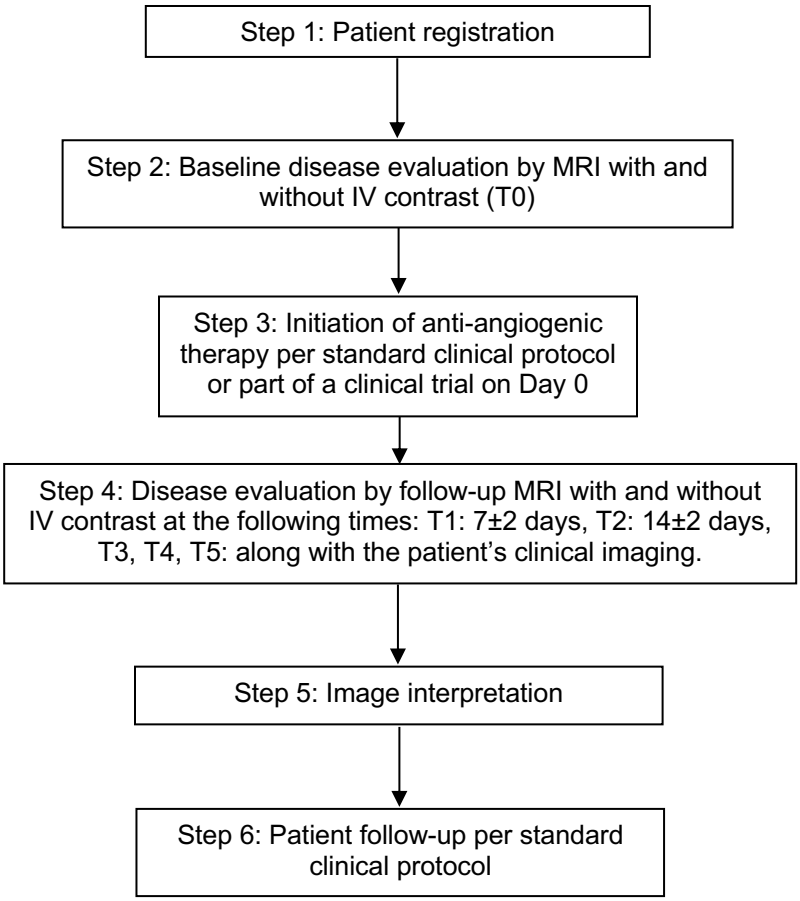
TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ASCO	American Society of Clinical Oncology
ASL	Arterial Spin Labeled
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CEST	Chemical Exchange Saturation Transfer
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSC	Dynamic Susceptibility Contrast
DSMB	Data and Safety Monitoring Board
DWI	Diffusion Weighted Imaging
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IDE	Investigational Device Exemption
IHC	Immunohistochemistry
IND	Investigational New Drug
IV (or iv)	Intravenously
MGMT	O6-methylguanine-DNA methyltransferase
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSF	Nephrogenic Systemic Fibrosis
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
pCR	Pathologic Complete Response
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival

p.o.	peros/by mouth/orally
PR	Partial Response
RANO	Response Assessment in Neuro-Oncology
RCB	Residual Cancer Burden
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCC	Simmons Comprehensive Cancer Center
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA



MRI including ASL will be performed before, during and after the treatment, in a total of 6 MRI sessions, or when progression is clinically indicated. The baseline MRI will be performed up to 7 days before the treatment initiation. The first two follow-up MRIs will be performed on day 7±2 and day 14±2 after treatment initiation, with the option of participating at both time points. The last three time points (*) will be performed along with the patient's clinical imaging. Thereafter, patients will be followed through standard clinical examinations for the next 3 years or until demise, whichever occurs first.

STUDY SUMMARY

Title	A Prospective Study to Evaluate Quantitative Non-Contrast Perfusion using Arterial Spin Labeled MR Imaging for Assessment of Therapy Response in Metastatic Renal Cell Carcinoma
Short Title	Quantitative MRI for therapy response assessment in metastatic RCC
Protocol Number	**STU 032018-078**
Phase	N/A
Methodology	Prospective study to evaluate quantitative MRI metrics for the assessment of treatment response
Study Duration	48 months
Study Center(s)	Single-center
Objectives	To prospectively determine whether ASL-measured perfusion can identify treatment response earlier than the currently used RECIST criteria.
Number of Subjects	90 (40 subjects with RCC and 50 healthy volunteers)
Diagnosis and Main Inclusion Criteria	Diagnosis: Locally advanced or metastatic renal cell carcinoma Main Inclusion Criteria: Patients with histologically proven clear cell RCC, scheduled to undergo anti-angiogenic treatment or immunotherapy (IO) who are 18 years of age and older and have no contraindication to MRI.
Study Product(s), Dose, Route, Regimen	N/A
Duration of administration	N/A
Reference therapy	N/A
Statistical Methodology	Primary end points for this study will include the absolute days of time to disease progression, progression free survival (PFS) and overall survival (OS) as well as disease status (progression versus not) at 7 months post treatment initiation. Progression will be determined according to the clinical RECIST criteria. One-sample correlation test will be used to determine the correlation between change in ASL measured tumor perfusion during and immediately after treatment and time to progression, and the correlation between change in ASL measured tumor perfusion and the corresponding tumor size change. The correlations will be measured and compared using Pearson's correlation coefficient along with 95% confidence interval. PFS and OS will be correlated with baseline perfusion and post-treatment changes at T1, T2 and T3 compared to baseline using univariable and multivariable Cox regression models. Univariable and multivariable logistic regression models will be used to predict responders from non-responders (progression versus not at 7 months) with ASL measurements at baseline and at earlier time points (T1 and T2) alone, and in combination with other MR imaging metrics.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

The incidence of kidney cancer has steadily increased over the past three to four decades and is among the 10 most frequently diagnosed cancers in the US. Approximately 63,990 new cases of kidney cancer are estimated in 2017 and the prognosis has been historically poor (1). The current 5-year survival rates are estimated at 74% overall, decreasing to 53% among patients with locally advanced diseases (2).

The most common form of kidney cancer, renal cell carcinoma (RCC), occurs in 90% of all kidney cancers. Among patients with localized RCC who are treated with nephrectomy, approximately one quarter have relapses in distant sites. Among patients with metastatic RCC, the 5-year survival rates are approximately 8%. With better understanding of the pathogenesis of the most common type of RCC, clear-cell renal cell carcinoma (ccRCC), newer treatment options with new agents are being developed to increase survival rates (3).

The high cost and potential risks associated with human trials for the newly developed experimental therapies have emphasized the need for sensitive monitoring of tumor response. Imaging approaches can play an important role in the evaluation and selection of potential new therapies with non-invasive longitudinal monitoring of treatment response (4). Currently, the radiological assessment of treatment outcomes predominantly relies on morphological (i.e. size) changes using the Response Evaluation Criteria in Solid Tumors (RECIST) and other similar scores (5). This is a major limiting factor as the effects of many therapeutic agents at the microscopic level precede the eventual changes in tumor size. One such tumor property that has gained increased attention is angiogenesis (6), which has been shown to support tumor proliferation and infiltration. Increasing numbers of clinical trials have begun targeting tumor vascular supplies by directly inhibiting angiogenesis (e.g. antiangiogenic therapy) (7). *Such clinical trials and the eventual clinical use of these therapies would be greatly assisted by the availability of robust imaging indicators of angiogenesis (i.e. tissue perfusion).*

Positron Emission Tomography (PET) using ^{15}O-labeled water (^{15}O-PET) is considered the gold standard for non-invasive measurement of tissue perfusion (8). However, the use of ^{15}O-PET requires a cyclotron in close proximity to PET to produce short lived ^{15}O-water (half life 2.4 min), limiting its applicability in clinical settings (9). Alternative imaging techniques include ultrasound using microbubbles, perfusion computed tomography (CT) using iodinated contrast agent and perfusion MRI using gadolinium based contrast agents (10). All of these techniques require exogenous agents, restricting their use in longitudinal monitoring of treatment response.

Arterial Spin Labeled (ASL) – MRI:

ASL-MRI has recently emerged as a quantitative imaging (QI) method to measure perfusion (or capillary blood flow) without the administration of exogenous contrast agents (11). ASL magnetically “labels” the highly permeable water in the blood as a tracer and measures their accumulation in the tissue of interest, without injecting any exogeneous contrast. Various versions of ASL have been validated in animals using microspheres (12), and in humans using ^{15}O-PET in the brain (13,14). ASL also has a number of advantages compared to dynamic contrast enhanced (DCE) and dynamic susceptibility contrast (DSC) based MR perfusion measurements. Specifically, ASL does not require exogenous agent alleviating the concerns of gadolinium accumulation (15,16) or nephrogenic systemic fibrosis (NSF) in patients with impaired renal function (17) and, unlike DCE/DSC, the contribution of vascular permeability to ASL measured perfusion is

negligible (18) enabling absolute perfusion quantification in physiological units (ml/100g/min).

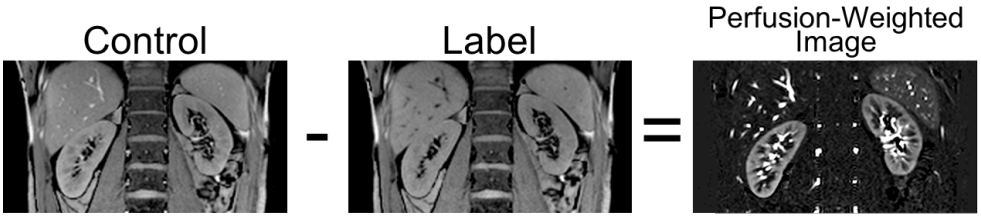
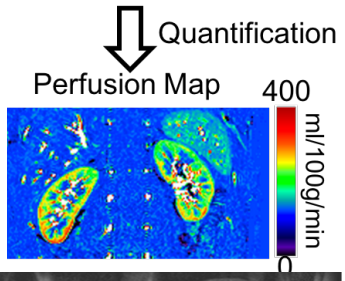


Figure 1. Schematic of an ASL acquired kidney perfusion. The acquisition includes a control image, where the magnetization is maintained at the equilibrium, and a label image, where the inflowing blood is selectively inverted. The subtraction between the control and the label image generates the perfusion-weighted image. Using a separately acquired proton-density image and the perfusion quantification model, absolute perfusion map in physiological values of ml/100g/min can be generated.



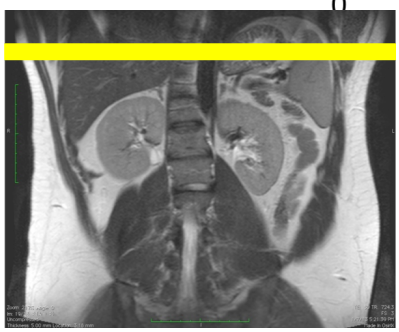


Figure 2. The yellow box shows the ASL labeling plane, across the abdominal aorta. Using MR principles including selective RF pulses and gradients, the inflowing blood in the abdominal aorta at this labeling plane is selectively inverted with ASL.

ASL-MRI consists of three distinct steps to achieve absolute quantification of tissue perfusion (Fig. 1). First, the acquisition of two images – a control image, where the blood and the static tissue is at its full magnetization and a label image, where only the inflowing blood is selectively inverted while the static tissue is maintained at its full magnetization. Second, the image reconstruction including the subtraction of labeled images from the control images to generate a perfusion-weighted image (PWI). Third, the perfusion quantification by modeling of PWI using a proton-density image and acquisition parameters to account for tissue characteristics to generate a quantitative perfusion map in physiological units of ml/100g/min. Both control and label images are acquired without administering any exogenous contrast agent, but using MR principles. The control image is acquired similar to other standard MR images. The label image is also acquired similar to other standard MR images, except that the inflowing blood such as the arterial blood in the abdominal aorta is selectively inverted using radiofrequency (RF) pulses and gradients (Fig. 2, yellow solid box). During the acquisition of control and label images, the subjects do not experience anything additional except the standard MR gradient noise and RF heating (that stays within the FDA guidelines) similar to any other standard MR examination.

1.2 Study Agent(s) Background and Associated Known Toxicities

This study will not investigate or focus on the role of any agents.

Gadolinium-based contrast agent for MRI such as Gadavist (generic Gadobutrol) or Dotarem (generic Gadoterate acid), are FDA-approved contrast agents for the diagnostic study and will be used in this study.

1.3 Other Agents

Not applicable (N/A).

1.4 Rationale

Recent discoveries in the biology of RCC have led to the development of targeted agents (e.g. vascular endothelial growth factor (VEGF)). Five of the FDA approved drugs for the treatment of metastatic RCC (bevacizumab, sunitinib, sorafenib, pazopanib, and axitinib) target either VEGF or its receptor. Clinically, these patients are followed every 2-3 months after therapy initiation and treatment response is primarily evaluated using size changes (i.e. Response Evaluation Criteria In Solid Tumors (RECIST)) (5). However, rapid changes in ASL measured perfusion may predict tumor targeting better than size change, allowing better patient management. This study is targeted to demonstrate this capability in metastatic RCC patients.

1.5 Correlative Studies

Standard clinical history including clinical histopathology will be collected and correlated.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To determine whether ASL-measured perfusion can identify treatment response (time to progression) earlier than the currently used RECIST criteria in patients undergoing anti-angiogenic treatment.

2.2 Secondary Objectives

2.2.1 To determine the correlation between ASL-measured baseline perfusion and the treatment response (PFS, OS).

2.2.2 To determine the correlation between post-treatment changes in ASL-measured perfusion at T1, T2 and T3 compared to baseline and the treatment response (PFS, OS).

2.2.3. To predict responders from non-responders (progression versus not at 7 months) with measurements at baseline and at earlier time points (T1 and T2) using:

a. ASL-measured perfusion alone
b. ASL-measured perfusion in combination with other MR imaging metrics such as diffusion weighted imaging (DWI) derived apparent diffusion coefficient (ADC), and chemical exchange saturation transfer (CEST) measured CEST effect.

2.3 Exploratory Objectives

2.3.1 To determine whether ASL-measured perfusion can identify treatment response (time to progression) earlier than the currently used RECIST criteria in patients undergoing IO.

2.4 Endpoints

Primary end points for this study will include the absolute days of progression free survival (PFS) and overall survival (OS). Additionally disease status (progression versus not) at 7 months and survival (dead or alive) at 24 months post-treatment initiation will also be documented. Progression will be determined based on the clinically accepted RECIST criteria.

3.0 Subject ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

3.1 Inclusion Criteria (RCC Subjects)

3.1.1 Diagnosis/disease status: Patients with locally advanced or metastatic renal cell carcinoma.

3.1.2 Patients scheduled to undergo anti-angiogenic treatment or IO.

3.1.3 Age ≥ 18 years.

3.1.4 Performance status: ECOG Status 0, 1 and 2.

3.1.5 Women of child-bearing potential must agree to undergo a urine pregnancy screening per standard Radiology departmental protocol, in place to prevent imaging of pregnant patients.

3.1.5.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.6 Ability to understand and the willingness to sign a written informed consent.

Inclusion Criteria (healthy controls)

3.1.7 Age ≥ 18 years.

3.1.8 Ability to understand and the willingness to sign a written informed consent.

3.2 Exclusion Criteria

3.2.1 Subjects may not be receiving any other anti-angiogenic agents, at the time of enrollment.

3.2.2 Subjects must not be pregnant since pregnancy is a contraindication to administration of gadolinium-based contrast agents.

3.2.3 Any contraindication to MRI per Radiology Department's routine protocol, e.g. MRI-incompatible objects, including but not limited to medical devices (e.g. pacemakers, AICD, etc.) and other foreign bodies.

3.2.4 Known severe allergic reaction to Gadolinium-based contrast agents.

3.2.5 Patients with sickle cell disease and patients with other hemolytic anemias (low red blood count in body).

3.2.6 Patients with uncontrollable claustrophobia, sever lower back pain, and uncontrollable tremors, to the point that it would render them unable to tolerate an MRI study.

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Not applicable.

4.2 Toxicities and Dosing Delays/Dose Modifications

Not applicable.

4.3 Concomitant Medications/Treatments

Not applicable.

4.4 Other Modalities or Procedures

Subjects will undergo treatment, as determined by the referring physician.

4.5 Duration of Therapy

Not applicable for this study.

4.6 Duration of Follow Up

After the conclusion of the study, subjects will be followed through standard clinical examinations for the next 3 years or until demise, whichever occurs first.

4.7 Removal of Subjects from Protocol Therapy

Subjects will be removed from the study when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator, and document the reason for study removal and the date the subject was removed in the Case Report Form. The subject should be followed-up per protocol.

4.8 Subject Replacement

If a subject is withdrawn from the study based on any criteria listed in Section 5.5, prior to completion of T2 MRI session, another subject may replace them and should undergo the entire study protocol.

5.0 STUDY PROCEDURES

5.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

5.1.1 *Informed Consent*

5.1.2 *Medical history*

Complete medical and surgical history, specific history regarding infections, trauma, foreign bodies, medical devices, and implants.

5.1.3 *Demographics*

Age, gender, race, ethnicity

5.1.4 *Review subject eligibility criteria (RCC Subjects only)*

Subjects will receive Group II gadolinium based contrast agents (GBCA) such as Gadavist (generic Gadobutrol) or Dotarem (generic Gadoterate acid) in this study. The risk of nephrogenic systemic fibrosis (NSF) for Group II GBCA is so low that the current clinical guidelines from the American College of Radiology (ACR) for use of these agents consider optional the screening of patient renal function – these were updated in 2017 (https://www.acr.org/Clinical-Resources/Contrast-Manual). The concern for gadolinium deposition is also lower for Group II agents and not related to renal function (i.e. associated to multiple exposures). Accordingly, patients receiving group II GBCA for clinical MRI are no longer screened for renal function impairment at UT Southwestern. Hence, a strict threshold based on renal function will not be applied to avoid gadolinium administration in patients enrolled in this study. Patients will be informed of the risks of gadolinium administration and offered to participate in the non-contrast portion of the MRI exam if preferred.

5.1.5 *Review previous and concomitant medications*

5.1.6 *Physical exam including vital signs, height and weight*

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 *Performance status (RCC Subjects only)*

Performance status evaluated prior to study entry.

5.1.8 *Adverse event assessment*

Baseline adverse events will be assessed. See section 7 for Adverse Event monitoring and reporting.

5.1.9 *Pregnancy test (for females of child bearing potential)*

See section 3.1.5.1 for definition.

5.1.10 *Tumor assessment (RCC Subjects only)*

Tumor measurements will be performed at baseline to identify metastatic tumors of ≥2.0 cm in at least one dimension on MRI.

5.2 Procedures During Treatment

All MR imaging will be performed during treatment.

5.3 Follow-up Procedures

After the conclusion of the study, subjects will be followed through standard clinical examinations for the next 3 years or until demise, whichever occurs first.

5.4 Time and Events Table

RCC Subjects

	Pre-study	Week 0 (T0) before initiation of anti-angiogenic therapy	Day 7±2 (T1)	Day 14±2 (T2)	T3	T4	T5	Follow-up (As indicated by clinical protocol)
Assessment	X							
Informed Consent	X							
History and PE	X							
Tumor Measurements	X							
MRI*		X	X	X	X	X	X	X

*Clinically, metastatic RCC patients are imaged every 2-3 months after the initiation of anti-angiogenic therapy, since morphological (i.e. size) changes are not anticipated earlier. However, our preliminary experience has shown functional changes including perfusion as early as 2-weeks after the initiation of the treatment (19). T0, T1, and T2 sessions will be performed for this proposal, while T3, T4, and T5 will be performed along with the clinical imaging sessions. The research MR imaging may take approximately an additional 15 minutes per each imaging session, when done in conjunction with the clinical imaging. The T0, T1, and T2 research MR imaging sessions will be performed additionally for the purpose of this study, with each taking approximately one hour.

The ASL portion of the study does not require contrast. Clinically, the subjects will also receive gadolinium based contrast injection for the MRI study to measure the blood flow to the tumors. This is done at the clinical imaging time points of T3, T4, and T5. Similar to this, the contrast agent will also be administered during the research portion of the study at T0, T1 and T2 time points, to compare the blood flow measured with ASL-MRI.

MRI including ASL will be performed before, during and after the treatment, in a total of 6 MRI sessions until 7 months after the first session, or when progression is clinically indicated. Thereafter, patients will be followed through standard clinical examinations for the next 3 years or until demise, whichever occurs first.

Healthy Volunteers

	Pre-study	Week 0	Week 3±1 (T3)
Assessment	X		
Informed Consent	X		
History and PE	X		
Research MRI		X	X

5.5 Removal of Subjects from Study

Subjects can be taken off the study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.5.1 Subject voluntarily withdraws from the study (follow-up permitted);

5.5.2 Subject withdraws consent (termination of study and follow-up);

5.5.3 Subject is unable to comply with protocol requirements;

5.5.4 Subject experiences toxicity that makes continuation in the protocol unsafe;

5.5.5 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event) AND pregnancy prevents the subject to undergo follow up studies, then subject will be removed from the study.

5.5.6 Development of second malignancy that requires treatment, which would interfere with this study;

5.5.7 Lost to follow-up. *If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.*

6.0 Measurement of Effect

6.1 Antitumor Effect- Solid Tumors

This study is designed to monitor therapy response in metastatic RCC using MRI with both conventional methods and ASL. Hence, the standard clinical assessment will be performed using RECIST criteria with conventional MRI. The ASL defined therapy response is currently developmental and not yet defined. Based on prior studies, a coefficient of variance (COV) of 7% was observed in ASL measured perfusion within the same subject imaged at two different time points (21). Thus, we will use a threshold of >10% difference in ASL measured perfusion compared to baseline to define ASL measured therapy response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST v1.1 criteria.

6.1.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with MRI. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Previously irradiated lesions are non-measurable except in cases of documented progression of the lesion since the completion of radiation therapy.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with MRI), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 3 lesions per organ and 6 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

6.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

MRI should be performed with cuts of 10 mm or less in slice thickness contiguously.

6.1.3 Response Criteria

6.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

6.1.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

6.1.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the

treatment started). The subjects best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

6.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.5 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.2 Antitumor Effect - Hematologic Tumors

Not applicable for this study.

6.3 Safety/tolerability

Not applicable for this study.

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

Not applicable

7.2 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

[Inserted from Adverse Event Definitions and Reporting Section – Appendix IB SCCC DSMC Plan]

7.2.1 Definition

Adverse Events will be reported as indicated by the appropriate following table (see below).

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, clinical event, or disease, temporarily associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) and version number specified in the protocol. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild

- Grade 2: Moderate
- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

ICH Guideline E2A and the UTSW IRB define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- Results in death
- Immediately life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect
- Based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring overnight hospitalization would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The term "unanticipated problem" is found, but not defined in the regulations for the Protection of Human Subjects at 45 CFR 46, and the FDA regulations at 21 CFR 56. Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ***each*** of the following criteria:

- Unexpected (in terms of nature, severity or frequency) ***AND***
- Definitely or probably related to participation in the research ***AND***
- Serious or a possible unexpected problem in that the research places subjects or others at greater risk of harm than was previously known or recognized. Note: Any serious adverse event would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.2.3 Reporting

The UTSW IRB requires reporting of all UPIRSOs according to the guidance below. For participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events. All SAEs occurring during the protocol-specified monitoring period should be submitted to the UTSW study team within 2 business days of the center learning of the event.

7.2.3.1 UPIRSOs occurring on the study require expedited reporting, and are submitted to the UTSW IRB through the UTSW eIRB by the UTSW study team and to the SCCC DSMC Coordinator. Hardcopies or electronic versions of the eIRB report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the UTSW study team and will be forwarded to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix IV of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized when a sponsor form is unavailable and SAE submission to the eIRB is not required).*

All serious adverse events which occur on research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. Hardcopies or electronic versions of the FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be forwarded to the DSMC Coordinator.

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Cancer Center, the DOT Manager or lead coordinator ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all serious adverse events upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: Ananth Madhuranthakam, PhD Phone: 214-645-1568
Written reports to: Ananth Madhuranthakam, PhD UT Southwestern Medical Center Department of Radiology 5323 Harry Hines Blvd, Dallas, TX 75390-9061 Fax 214-648-7783 UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit via eIRB with a copy of the final sponsor report as attached supporting documentation

1. SAEs

Serious adverse events (SAEs) for studies where the SCCC DSMC is the DSMC of record require reporting to the DSMC coordinator within 2 working days of PI awareness,

or as described in the protocol.

2. Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs)

Local Serious Adverse Event UPIRSOs require reporting to the UTSW IRB within 48 hours of PI awareness of the event (life threatening or fatal events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction).

Local UPIRSOs (non-serious events experienced by subjects enrolled by the investigator(s) under UTSW IRB jurisdiction) require reporting to the UTSW IRB within 5 business days of PI awareness of the event.

External UPIRSOs including those that occur as non-local events require reporting to the UTSW IRB within 10 working days of PI awareness of the event.

For further guidance for Investigators regarding safety reporting requirements for INDs and BA/BE studies, refer to FDA Draft Guidance document: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

7.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v4).

Step 2: Grade the adverse event using the NCI CTCAE v4.

Step 3: Determine whether the adverse event is related to the protocol therapy
Attribution categories are as follows:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.
Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

7.4 Unblinding Procedures

Patient information is not blinded and all information obtained from the imaging studies performed for the purposes of the study will be available to all clinics treating the patient.

7.5 Stopping Rules

This study does not contain any stopping rules as it does not include treatment for patients.

8.0 DRUG/TREATMENT INFORMATION

Not applicable.

9.0 CORRELATIVES/SPECIAL STUDIES

Standard clinical history including clinical histopathology will be collected and correlated. No additional correlative studies are collected.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a prospective, single-centered study, designed to address the following primary objective:

1. To determine whether ASL-measured perfusion can identify treatment response (time to progression) earlier than the currently used RECIST criteria (tumor size). *Hypothesis: Greater reduction in ASL measured tumor perfusion during and immediately after treatment is a marker of tumor responsiveness prior to size changes.*

Primary end points for this study will include the absolute days of time to disease progression, PFS and OS as well as disease status (progression versus not) at 7 months post treatment initiation. Progression will be determined based on clinically accepted RECIST criteria (20).

10.2 Sample Size and Accrual

The sample size is calculated based on the primary objective. A significant correlation of 0.75 was observed between one month ASL perfusion change and time to progression in our RCC patients, whereas the corresponding tumor size change was not correlated with time to progression (19). We expect approximately 50% of RCC patients to progress within 7 months of imaging protocol. Beyond this time point, patients will be followed according to their clinical scans for the next 3 years or until death. Using such information, we target 40 subjects for this study and anticipate approximately 20 subjects to progress within the 7 months period. This sample size would provide more than 95% power to detect a correlation of 0.75 between earlier perfusion changes (at T2 and T6) and time to progression, using two-sided correlation test at a significance level of 0.05.

10.3 Data Analyses Plans

The perfusion difference images and the absolute quantified images will be converted to DICOM and transferred to a DICOM database (e.g. iPACS, OsiriX). A semi-automated segmentation algorithm and region of interest (ROI) based measures will be performed to extract perfusion measures. Percentage changes in perfusion within each ROI will be calculated at each follow-up MRI compared to the baseline image. The semi-automated tumor ROIs will be compared to expert segmentation by Dr. Pedrosa in all cases, who will also supervise the trainee (to be recruited) in the analysis. Additionally, morphological changes will also be calculated according to RECIST and 10% reduction in the sum of the largest diameters (20).

Among patients with disease progression, one-sample correlation test will be used to determine the correlation between change in ASL measured tumor perfusion during and immediately after treatment and time to progression, and the correlation between change in ASL measured tumor perfusion during and immediately after treatment and the corresponding tumor size change. The correlations will be measured and compared using Pearson's correlation coefficient along with 95% confidence interval. PFS and OS will be correlated with baseline perfusion and post-treatment changes at T1 and T2

compared to baseline using univariable and multivariable Cox regression models. We used PFS at 7 months as a cutoff point to divide patients into “responders” versus “non-responders” in this study. Univariable and multivariable logistic regression models will be used to predict responders from non-responders with ASL measurements at baseline and at earlier time points (T1 and T2) alone, and in combination with other MR imaging metrics. The statistical analysis will also be performed separately for male and female subjects to evaluate sex as a biological variable.

11.0 STUDY MANAGEMENT

11.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient’s participation in the trial, the written informed consent form should be signed and personally dated by the subject or legally authorized representative and by the person who conducted the informed consent discussion.

11.3 Registration Procedures

All subjects must be registered with the Radiology Clinical Trials Office before enrollment to study. Prior to registration, eligibility criteria must be confirmed with the Radiology Clinical Trials Office Study Coordinator. To register a subject, call 214-645-1568 Monday through Friday, 9:00AM-5:00PM.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to be enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for this and all SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements.

Trial monitoring will be conducted no less than annually and refers to a regular interval review of trial related activity and documentation performed by the DOT, which includes but is not limited to accuracy of case report forms, protocol compliance, timeless and accuracy of Velos entries and AE/SAE management and reporting. Documentation of trial monitoring will be maintained along with other protocol related documents and will be reviewed during internal audit.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all local serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The QAC works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

11.5.2 Other Protocol Deviations/Violations

All other planned deviations from the protocol must have prior approval by the Principal Investigator and the IRB. According to the IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs

- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs without prior approval from the Principal Investigator, the guidelines below will be followed:

Protocol Deviations: Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Study personnel should report violations within two (2) weeks of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. When an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

11.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

12.0 REFERENCES

1. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. April 2017. Accessed on April 11, 2018. Available at: https://seer.cancer.gov/statfacts/html/kidrp.html.
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary C, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis D, Chen H, Feuer E, Cronin K. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. April 2017. Accessed on April 11, 2018. Available at: https://seer.cancer.gov/csr/1975_2014/.
3. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. The New England journal of medicine 2017;376(4):354-366.
4. Clarke LP, Nordstrom RJ, Zhang H, Tandon P, Zhang Y, Redmond G, Farahani K, Kelloff G, Henderson L, Shankar L, Deye J, Capala J, Jacobs P. The Quantitative Imaging Network: NCI's Historical Perspective and Planned Goals. Translational oncology 2014;7(1):1-4.
5. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer 2009;45(2):228-247.
6. Folkman J. Role of angiogenesis in tumor growth and metastasis. Seminars in oncology 2002;29(6 Suppl 16):15-18.
7. Al-Husein B, Abdalla M, Trepte M, Deremer DL, Somanath PR. Antiangiogenic therapy for cancer: an update. Pharmacotherapy 2012;32(12):1095-1111.
8. Cai W, Chen X. Multimodality molecular imaging of tumor angiogenesis. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2008;49 Suppl 2:113S-128S.
9. Lodge MA, Jacene HA, Pili R, Wahl RL. Reproducibility of tumor blood flow quantification with 15O-water PET. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2008;49(10):1620-1627.
10. Jeswani T, Padhani AR. Imaging tumour angiogenesis. Cancer imaging : the official publication of the International Cancer Imaging Society 2005;5:131-138.
11. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, Lu H, MacIntosh BJ, Parkes LM, Smits M, van Osch MJ, Wang DJ, Wong EC, Zaharchuk G. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2015;73(1):102-116.
12. Walsh EG, Minematsu K, Leppo J, Moore SC. Radioactive microsphere validation of a volume localized continuous saturation perfusion measurement. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 1994;31(2):147-153.

13. Ye FQ, Berman KF, Ellmore T, Esposito G, van Horn JD, Yang Y, Duyn J, Smith AM, Frank JA, Weinberger DR, McLaughlin AC. H(2)(15)O PET validation of steady-state arterial spin tagging cerebral blood flow measurements in humans. Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine 2000;44(3):450-456.
14. Xu G, Rowley HA, Wu G, Alsop DC, Shankaranarayanan A, Dowling M, Christian BT, Oakes TR, Johnson SC. Reliability and precision of pseudo-continuous arterial spin labeling perfusion MRI on 3.0 T and comparison with 15O-water PET in elderly subjects at risk for Alzheimer's disease. NMR in biomedicine 2010;23(3):286-293.
15. Kanal E, Tweedle MF. Residual or retained gadolinium: practical implications for radiologists and our patients. Radiology 2015;275(3):630-634.
16. McDonald RJ, McDonald JS, Kallmes DF, Jentoft ME, Murray DL, Thielen KR, Williamson EE, Eckel LJ. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology 2015;275(3):772-782.
17. Saleh L, Juneman E, Movahed MR. The use of gadolinium in patients with contrast allergy or renal failure requiring coronary angiography, coronary intervention, or vascular procedure. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 2011;78(5):747-754.
18. Wolf RL, Wang J, Wang S, Melhem ER, O'Rourke DM, Judy KD, Detre JA. Grading of CNS neoplasms using continuous arterial spin labeled perfusion MR imaging at 3 Tesla. Journal of magnetic resonance imaging : JMRI 2005;22(4):475-482.
19. de Bazelaire C, Alsop DC, George D, Pedrosa I, Wang Y, Michaelson MD, Rofsky NM. Magnetic resonance imaging-measured blood flow change after antiangiogenic therapy with PTK787/ZK 222584 correlates with clinical outcome in metastatic renal cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2008;14(17):5548-5554.
20. Krajewski KM, Guo M, Van den Abbeele AD, Yap J, Ramaiya N, Jagannathan J, Heng DY, Atkins MB, McDermott DF, Schutz FA, Pedrosa I, Choueiri TK. Comparison of four early posttherapy imaging changes (EPTIC; RECIST 1.0, tumor shrinkage, computed tomography tumor density, Choi criteria) in assessing outcome to vascular endothelial growth factor-targeted therapy in patients with advanced renal cell carcinoma. European urology 2011;59(5):856-862.

13.0 APPENDICES