SUMMARY OF CHANGES

For Protocol Amendment # to: A Randomized Phase 2 Study of MK-2206 in Comparison with Everolimus in Refractory Renal Cell Carcinoma

NCI Protocol #: 8727
Local Protocol #: 2010-0247

NCI Version Date: June 11, 2018
Protocol Date: June 11, 2018

#	Section	Page(s)	Change
1	Header	All	Rationale: The header date is being updated Old Text: ~~November 8, 2016~~ New Text : June 11, 2018

2	Comprehensive Adverse Events and Potential Risks list (CAEPR) for Everolimus (RAD-001, NSC 733504)	42 through 45	Rationale: The Comprehensive Adverse Events and Potential Risks list (CAEPR) for Everolimus (RAD-001, NSC 733504) is being updated with the most recent version number (Version 2.3, June 30, 2016[1]). Old Text [1]~~This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.~~ [2]~~Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.~~ [3]~~Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.~~ [4]~~Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.~~ [5]~~Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.~~ [6]~~Hyperglycemia may result in either exacerbation of or development new-onset diabetes mellitus.~~ [7]~~Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.~~ [8]~~Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.~~ [9]~~Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.~~ ~~Adverse events reported on Everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Everolimus (RAD-001) caused the adverse event:~~ ~~CARDIAC DISORDERS - Atrial fibrillation; Chest pain - cardiac; Heart failure; Myocardial infarction; Sinus tachycardia~~ ~~ENDOCRINE DISORDERS - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels)~~ ~~EYE DISORDERS - Blurred vision; Conjunctivitis~~ ~~GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Dysphagia; Flatulence; Hemorrhoids; Oral pain; Periodontal disease~~ ~~GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Irritability; Non-cardiac chest pain; Pain~~ ~~HEPATOBILIARY DISORDERS - Hepatic failure~~ ~~IMMUNE SYSTEM DISORDERS - Allergic reaction~~ ~~INVESTIGATIONS - Blood bilirubin increased; CPK increased; GGT increased; Investigations - Other (increased lactate dehydrogenase)~~ ~~METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypernatremia; Hyponatremia; Metabolism and nutrition disorders - Other (hyperlipidemia)~~ ~~MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms)~~ ~~NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)~~ ~~NERVOUS SYSTEM DISORDERS - Paresthesia~~ ~~PSYCHIATRIC DISORDERS - Agitation; Anxiety[8]; Depression~~ ~~RENAL AND URINARY DISORDERS - Proteinuria; Urinary frequency~~ ~~REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dysmenorrhea; Irregular menstruation; Menorrhagia; Vaginal hemorrhage~~ ~~RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Sore throat~~ ~~SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (angioedema)[9]; Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration~~ ~~VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (hemorrhage)~~ ~~Note: Everolimus (RAD-001) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.~~

New Text:

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3033 patients.* Below is the CAEPR for Everolimus (RAD-001).

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July10, 2017[1]

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			*Anemia (Gr 2)*
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea[2]			*Diarrhea[2] (Gr 2)*
Mucositis oral[3]			*Mucositis oral[3] (Gr 2)*
	Nausea		*Nausea (Gr 2)*
	Vomiting		*Vomiting (Gr 2)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		*Edema limbs (Gr 2)*
Fatigue			*Fatigue (Gr 2)*
	Fever		*Fever (Gr 2)*
INFECTIONS AND INFESTATIONS			
	Infection[4]		*Infection[4] (Gr 2)*
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		*Alanine aminotransferase increased (Gr 2)*
	Alkaline phosphatase increased		*Alkaline phosphatase increased (Gr 2)*
	Aspartate aminotransferase increased		*Aspartate aminotransferase increased (Gr 2)*
	Cholesterol high		*Cholesterol high (Gr 2)*
	Creatinine increased		*Creatinine increased (Gr 2)*
	Lymphocyte count decreased		*Lymphocyte count decreased (Gr 2)*
	Neutrophil count decreased		*Neutrophil count decreased (Gr 2)*
	Platelet count decreased		*Platelet count decreased (Gr 2)*

	Weight loss		
	White blood cell decreased		*White blood cell decreased (Gr 2)*
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		*Anorexia (Gr 2)*
	Hyperglycemia[6]		*Hyperglycemia[6] (Gr 2)*
	Hypertriglyceridemia		*Hypertriglyceridemia (Gr 2)*
	Hypophosphatemia		*Hypophosphatemia (Gr 2)*
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		*Headache (Gr 2)*
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		*Cough (Gr 2)*
	Dyspnea		*Dyspnea (Gr 2)*
	Epistaxis		*Epistaxis (Gr 2)*
	Pneumonitis[7]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		
Rash maculo-papular			*Rash maculo-papular (Gr 2)*

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

[3]Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

[4]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.

[6]Hyperglycemia may result in either exacerbation of or development new onset diabetes mellitus.

[7]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.

[8]Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.

[9]Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obsessive compulsive disorder.

Adverse events reported on Everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Everolimus (RAD-001) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (thrombotic microangiopathy)

#	Section	Page(s)	Change
			CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (myocardial abnormality); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia ENDOCRINE DISORDERS - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels); Endocrine disorders - Other (low testosterone); Hypothyroidism EYE DISORDERS - Blurred vision; Conjunctivitis; Keratitis GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Hemorrhoids; Intra-abdominal hemorrhage; Oral pain; Pancreatitis; Periodontal disease; Toothache GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Irritability; Non-cardiac chest pain; Pain HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly) IMMUNE SYSTEM DISORDERS - Allergic reaction INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CPK increased; GGT increased; INR increased; Investigations - Other (bicarbonate decreased); Investigations - Other (increased lactate dehydrogenase); Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia) METABOLISM AND NUTRITION DISORDERS - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia); Metabolism and nutrition disorders - Other (hyperlipidemia) MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts) NERVOUS SYSTEM DISORDERS - Dizziness; Encephalopathy; Hydrocephalus; Lethargy; Paresthesia PSYCHIATRIC DISORDERS - Agitation; Anxiety[8]; Delirium; Depression; Insomnia; Mania RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Urinary frequency REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dysmenorrhea; Genital edema; Irregular menstruation; Menorrhagia; Vaginal hemorrhage RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (rales); Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea); Sore throat; Voice alteration SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema)[9]; Skin and subcutaneous tissue disorders - Other (nail disorder); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (acute bowel ischemia); Vascular disorders - Other (hemorrhage) Note: Everolimus (RAD-001) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

#	Section	Page(s)	Change
3	7.2 Adverse Event Characteristics	45	Rationale: Current ongoing protocol transitioning from CTCAE v4.0 to v5.0 with v5.0 start date only. Old Text: ~~CTCAE term (AE description) and grade: CTCAE term (AE description) and grade: NCI Common Terminology Criteria for Adverse Events (CTCAE) v.4 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic applications/ctc.htm. All appropriate treatment areas should have access to a copy of CTCAE v4.~~ New Text: CTCAE term (AE description) and grade: **The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be version utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment /electronic applications/ctc.htm**.
4	7.3 Expedited Adverse Event Reporting	46	Rationale: Section 7.3.3 Phase 2 and 3 Trials Reporting Guidelines – CTEP-AERS Progressive disease Example from CTEP Generic Protocol Template Old Text: Note: ~~All~~ death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided. New Text: Note: **A** death on study requires **both** routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided. Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted. Pregnancy loss Example: Pregnancy loss • Pregnancy loss is defined in CTCAE as "Death in utero • Any pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. • A pregnancy loss should NOT be reported as a Grade 5 event under • the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS • recognizes this event as a patient death. Death neonatal Example: A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

NCI Protocol #: 8727

Local Protocol #: 2010-0247

TITLE: A Randomized Phase 2 Study of MK-2206 in Comparison with Everolimus in Refractory Renal Cell Carcinoma

Coordinating Center: The University of Texas M. D. Anderson Cancer Center

***Principal Investigator:**
Eric Jonasch, M.D.
Department of GU Medical Oncology
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
ejonasch@mdanderson.org

Co-Investigators:

Amado Zurita, M.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
azurita@mdanderson.org

Ana Aparicio, M.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
aaparicio@mdanderson.org

John Araujo, M.D., Ph.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
johna@mdanderson.org

Padmanee Sharma, M.D., Ph.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
padsharma@mdanderson.org

Paul Corn, M.D., Ph.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
pcorn@mdanderson.org

Shi-Ming Tu, M.D., Ph.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
stu@mdanderson.org

Nizar Tannir, M.D.
1155 Pressler Street, Unit 1374
Houston TX 77030
713-792-2830
713-745-1625
ntannir@mdanderson.org

Pheroze Tamboli, M.D. *Associate Investigator is NOT responsible for patient care and therefore does not require a current registration packet.*
1515 Pressler Street, Unit 0085
Houston TX 77030
713-794-5445
713-745-3740
ptamboli@mdanderson.org

Przemyslaw Twardowski MD
City of Hope (COH PI)
1500 E. Duarte Rd
Duarte, CA 91010
626-256-HOPE (4673) x 62307
626-301-8233
ptwardowski@coh.org

David I. Quinn MD PhD FRACP
University of Southern California (USC PI)
1441 Eastlake Ave #3453
Los Angeles CA 90033
323-865-3956 /323-865-3000
323-865-0061
diquinn@usc.edu

Primo N. Lara, Jr., MD
UC Davis Cancer Center (UCD PI)
4501 X Street
Sacramento, CA 95817
916-734-3772
916-734-7946
primo.lara@ucdmc.ucdavis.edu

Leonard J. Appleman, MD, PhD
University of Pittsburgh Cancer Institute (UOP PI)
UPMC Cancer Pavilion, 5th Floor
5150 Center Avenue
Pittsburgh, PA 15232
412-648-6507
412-648-6579
applemanlj@upmc.edu

Joseph J. Drabick MD FACP
Penn State Milton S. Hershey Medical Center (PSU PI)
500 University Drive CH46
Hershey, PA 17033-0850
717-531-8678
717-531-5076
jdrabick@psu.edu

Mark McNamara, MD
City of Hope Medical Group, Inc., (COHMG)
50 Bellefontaine Street
Pasadena, CA 91105
626-396-2900
626-396-2911
mmcnamara@coh.org

Solomon Hamburg, MD
Tower Cancer Research Foundation (TOW)
9090 Wilshire Blvd., 2nd Floor
Beverly Hills, CA 90211
310-285-7427
310-285-7298
hamburghs@toweroncology.com

NCI Supplied Agent(s): MK-2206 (NSC 749607; IND # 109493)

IND Sponsor: NCI

Protocol Type / Version # / Version Date: Revision/ Local Version June 11, 2018

SCHEMA

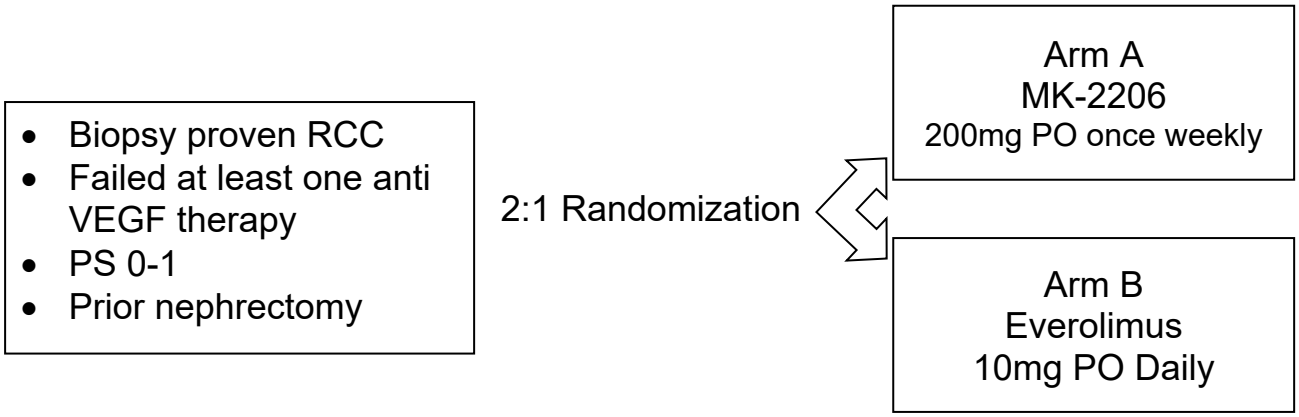
Biopsy proven RCC
Failed at least one anti VEGF therapy
PS 0-1
Prior nephrectomy
2:1 Randomization
Arm A
MK-2206
200mg PO once weekly
Arm B
Everolimus
10mg PO Daily

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess progression free survival (PFS) of vascular endothelial growth factor (VEGF) therapy refractory renal cell carcinoma (RCC) patients who receive either MK-2206 or everolimus.

1. To assess safety of MK-2206 in patients with VEGF therapy refractory RCC

1.2 Secondary Objectives

Clinical:

1. To assess overall response rate (ORR) and overall survival (OS)
2. To assess time to treatment failure (TTF)

Pre-clinical/Exploratory:

1. To determine whether baseline AKT activation is predictive for clinical benefit after treatment with MK-2206 or everolimus.
2. To determine whether circulating cytokines and angiogenic factors predict for clinical benefit after treatment with MK-2206 or everolimus.
3. To assess impact of karyotype on outcome in patients treated with MK-2206 or everolimus.

2. BACKGROUND

2.1 Study Disease

Renal cell carcinoma (RCC) comprises more than 90 percent of all kidney cancer cases and accounts for approximately 3 percent of all adult malignancies. It affected more than 40,000 individuals in the USA in 2009, and was directly responsible for approximately 13,000 deaths. Nearly one third of patients with RCC present with metastases at the time of diagnosis, and up to 50 percent develop recurrence after nephrectomy for localized disease. Surgical removal of the primary lesion is the only clearly effective therapy in the non-metastatic setting. No adjuvant therapy has been shown to be effective in patients with RCC post-nephrectomy in the non-metastatic setting.

If metastases develop, cure is difficult, and most patients ultimately succumb to their disease. Commonly available clinical and laboratory parameters can be used to stratify patients into different risk groups. Investigators at Memorial Sloan Kettering Cancer Center (MSKCC) demonstrated that patients who went on to receive immunotherapy could be categorized into three discrete risk categories, using five variables: Karnofsky performance status of less than 80; time from diagnosis to treatment of less than one year; lactate dehydrogenase levels one and a half times the upper limit of normal, anemia, and hypercalcemia. A recent analysis in patients who received anti-VEGF inhibitors came up with a similar list. Unfortunately the mechanism underpinning these risk factors is poorly understood, and they cannot easily be used as predictive biomarkers.

A number of different approaches are taken to control metastatic RCC. In patients with oligometastatic disease, metastasectomy is associated with long term disease free survival. Systemic therapy options include immunotherapy, with modest overall survival (OS) increases seen in patients treated with interferon alpha , and a small but consistent rate of complete responses (CR) seen in patients treated with high-dose interleukin 2 (IL-2). As the molecular biology of RCC was elucidated, it became apparent that clear cell RCC (CCRCC) was frequently associated with mutations in the von Hippel Lindau (VHL) gene. Mutated VHL resulted in unbridled hypoxia inducible factor (HIF) driven transcription of various proangiogenic factors, including VEGF, transforming growth factor alpha, platelet derived growth factor, GLUT1, and carbonic anhydrase nine. Inhibitors of inappropriate angiogenesis were developed and tested, including sorafenib (Nexavar, Bayer AG), sunitinib (Sutent, Pfizer Corp), bevacizumab (Avastin, Roche AG), and pazopanib (Votrient, Glaxo Smith Kline PLC). Each of these agents was Food and Drug Administration (FDA) approved for advanced RCC between 2005 and 2009. Most patients on these studies were diagnosed with CCRCC, had good or intermediate MSKCC risk criteria, and had prior nephrectomy.

At the same time, clinical experience with the mammalian target of rapamycin (mTOR) inhibitor sirolimus ester temsirolimus (Torisel, Pfizer Corp) suggested a clinical signal in patients with cytokine refractory RCC. Subset analysis suggested that patients with poor risk features may have derived differential benefit from this agent. A phase III study was performed recruiting patients with three or more of six risk factors, which included the five MSKCC risk criteria and the presence of at least two organ sites of disease. The patient population also differed in that only two thirds had undergone prior nephrectomy, and only 80 percent had clear cell histology. The OS of temsirolimus treated patients was significantly longer than in the IFN treated population, and a combination temsirolimus-IFN arm ended up with outcomes somewhere in between the monotherapy arms. Everolimus (Afinitor, Novartis AG), an orally administered sirolimus ester, was tested against placebo in patients who had failed either sorafenib or sunitinib, and showed a 4.0 month PFS versus 1.9 months in the placebo arm. Both agents are FDA approved, with temsirolimus approved for advanced RCC, and everolimus approved in sorafenib and sunitinib refractory patients.

2.2 CTEP Supplied Investigational Agent(s)

MK-2206

The PI3K/AKT pathway is downstream of the common growth factor tyrosine kinase receptors (TKR), including EGFR, HER2, IGFR, *etc.*, and is a likely driver of tumor progression in most carcinomas (Altomare and Testa, 2005; Hennessy *et al.*, 2005; Steelman *et al.*, 2008). AKT protein kinase is activated in a substantial proportion of human solid tumors (breast, endometrial, ovarian, prostate, pancreatic, colon, gastric, and non-small cell lung cancer [NSCLC]). Upregulation of AKT can be caused by direct amplification/mutation of *AKT*, or by overexpression of TKRs, PI3K and RAS, and/or by inactivation of the tumor suppressor PTEN. Because of its key function in cell survival,

AKT plays a pivotal role in rendering tumor cells insensitive or resistant to chemotherapy or targeted agents.

The rationale for the use of an AKT inhibitor in treatment of various malignancies is included in the following references (Staal, 1987; Shayesteh *et al.*, 1999; Fry, 2001; Tanno *et al.*, 2001; Testa and Bellacosa, 2001; Hu *et al.*, 2002; Rahman *et al.*, 2002; Min *et al.*, 2003; Lee *et al.*, 2004; St-Germain *et al.*, 2004; Altomare and Testa, 2005; Hennessy *et al.*, 2005; Kirkegaard *et al.*, 2005; Nakanishi *et al.*, 2005; Oki *et al.*, 2005; Saal *et al.*, 2005; Shoman *et al.*, 2005; Vestey *et al.*, 2005; Wolf and Slomovitz, 2005; Konecny *et al.*, 2006; Kornblau *et al.*, 2006; Nakayama *et al.*, 2006; Oza, 2006; Uddin *et al.*, 2006; Sosman *et al.*, 2007; Cejka *et al.*, 2008; Engelman *et al.*, 2008; Han *et al.*, 2008; Kinkade *et al.*, 2008; Steelman *et al.*, 2008; Kawauchi *et al.*, 2009; Salvesen *et al.*, 2009).

MK-2206 is the first allosteric inhibitor of AKT to enter clinical development (Investigator's Brochure, 2009). MK-2206 demonstrated AKT inhibition and antiproliferative activity as single agent and in combination with other agents in multiple human cancer cell lines, such as breast, ovarian, lung, and prostate. MK-2206 synergized antitumor effects of docetaxel, erlotinib, and carboplatin *in vivo* in various human tumor xenograft models.

Mechanism of Action

MK-2206 is a selective allosteric inhibitor of AKT (Investigator's Brochure, 2009). MK-2206 does not bind to the active site of AKT, and consequently does not compete with either ATP or peptide substrate for binding to AKT. It is equally potent against the two human AKT isoforms, AKT1 and AKT2, and ~5-fold less potent against AKT3.

Nonclinical Studies

In Vitro Activity Studies

In vitro single-agent activity of MK-2206

In an *in vitro* kinase assay with GSK3 alpha peptide as substrate, MK-2206 strongly inhibited kinase activity of the three human isoforms of AKT, AKT1, 2, and 3, with 50% inhibitory concentration (IC_{50}) values of 8, 12, and 65 nM, respectively. MK-2206 exhibited no inhibition (IC_{50}>50 micromol/L (mcM) against the (pleckstrin-homology domain) deletion mutants of AKT, indicating that this domain is essential for binding MK-2206 to AKT. Apart from AKT, MK-2206 was tested at a single concentration of 1 mcM against a panel of ~250 kinases without demonstrating significant (≥50%) inhibition against any kinase.

The antiproliferative potency of MK-2206 was evaluated against a panel of tumor cell lines using *in vitro* proliferation and viability assays. Among 52 cell lines, 18 cell lines were highly sensitive (IC_{50}<1 mcM), 7 were moderately sensitive (IC_{50}=1-5 mcM), and

27 cell lines were insensitive (IC_{50}>5 mcM) to MK-2206. Highly sensitive cell lines included breast, ovarian, prostate, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), gastric, and endometrial cancer. At least one of the following genetic defects was represented in the majority of sensitive cell lines: *PTEN* mutation, *PI3KCA* mutation, *AKT* amplification, or genomic amplification of *HER2* or *MET*. Nine of 27 cell lines that were insensitive to MK-2206 had either *PTEN* or *PI3KCA* mutation, or were deficient in PTEN protein. Among eight cell lines carrying *RAS* or *BRAF* activating mutation, six were insensitive to MK-2206.

MK-2206 activity in combination with other agents

In a proliferation/viability assay, various degrees of synergism between MK-2206 and lapatinib (a dual EGFR/HER2 inhibitor) were observed in eight breast cancer cell lines. MK-2206 and docetaxel demonstrated additive to synergistic antiproliferative activity against nine breast-cancer cell lines, however, the effects were dependent on agent sequence. Enhancement of antitumor activity occurred only when cells were treated first with docetaxel and then exposed to MK-2206. In contrast, co-administration of the two agents resulted in antagonism. Combination of MK-2206 with erlotinib produced various degrees of synergism in nine NSCLC cell lines, including A431 epidermoid cells overexpressing EGFR.

MK-2206 synergized antitumor activity of carboplatin, gemcitabine, doxorubicin, camptothecin, or 5-FU in ovarian, prostate and NSCLC cell lines. Antitumor activity of MK-2206/carboplatin, demonstrated in the ovarian cell line A2780, was accompanied with enhanced apoptosis (cleavage of caspases 3 and 7). However, the effect was dependent on the sequence of agent administration, as it occurred only when cells were exposed to carboplatin before or simultaneously with MK-2206. Enhancement of apoptosis did not occur when MK-2206 preceded carboplatin.

In Vivo Activity Studies

MK-2206 monotherapy administered as a single dose (10-240 mg/kg) to mice bearing human ovarian tumor (A2780) potently inhibited phosphorylation of AKT1/2 in blood as well as in tumor tissue. After a single dose of 30, 120, or 240 mg/kg of MK-2206, ≥80% inhibition of AKT1/2 was achieved in peripheral blood; inhibition persisted at this level for 6 and 24 hours at the 120- and 240-mg/kg dose, respectively. Pronounced inhibition (70-90%) of phosphorylation of AKT1/2 (pAKT1/2), lasting for at least 24 hours, was detected also in tumor tissue following the single 120- or 240- mg/kg dose. MK-2206 combinations with docetaxel, carboplatin, or erlotinib exhibited significantly more potent antitumor activity than each agent in monotherapy settings. For example, a combination of MK-2206 and docetaxel, administered for 4 weeks as one weekly intravenous (IV) dose of docetaxel (30 mg/kg) followed 24 hours later by MK-2206 (240 or 480 mg/kg) given orally (PO) once a week (QW), produced strong antitumor responses in the A2780 ovarian-cancer xenograft mouse model. MK-2206 monotherapy was ineffective at all doses. Although the combination was significantly more effective than docetaxel monotherapy, responses did not endure beyond the treatment period. Tumor regression

was also observed in PC-3 prostate xenograft model following sequential treatment with docetaxel and MK-2206 (24 hours later). MK-2206 (120 mg/kg) was given three times per week (days 1, 3, 5) and docetaxel (5 mg/kg) once weekly on day 0. Inhibition of tumor growth was also enhanced when MK-2206 was combined with carboplatin and erlotinib in the NSCLC H460 and H292 xenograft models, respectively. Overall, the agents' combinations were well-tolerated at the effective dose levels, although transient 10-20%-weight loss was observed in some animals.

Pharmacokinetics

Pharmacokinetic (PK) parameters of MK-2206 in the rat, dog, and monkey are summarized in Table 1. Across the species, MK-2206 showed moderate plasma clearance (Cl) and high volume of distribution at steady state (Vd_{ss}) and elimination half-life ($t_{1/2}$) ranging from 4 hours in rats to >12 hours in dogs and monkeys.

Table 1. **Summary of nonclinical pharmacokinetics for MK-2206**

IV Route								PO Route	
Species	**Dose (mpk)**	**Cl (mL/min/kg)**	**Vd_{ss} (L/kg)**	**$t_{1/2}$ (h)**	**Dose (mpk)**	**AUC (mcM·h)**	**C_{max} (mcM)**	**t_{max} (h)**	**F (%)**
Rat	2	27.6	9	4.2	10	2.1	0.29	5	20
					100	35.2	2.76	2.7	35
Dog	0.5	7.7	8	12.5	2	8.89	0.38	4	83
Rhesus	0.5	10.8	11	14					

Cl: clearance; Vd_{ss}: volume of distribution at steady state; $t_{1/2}$: elimination half-life; AUC: the area under the time-concentration curve; C_{max}: maximum drug concentration in plasma; t_{max}: time needed to achieve C_{max}; F: oral availability; mcM: micromol/L; mpk: mg per kg;
Vehicle: intravenous (IV): DMSO, oral route (PO): 0.5% methylcellulose (10 mpk), 30% Captisol (100 mpk), or 1% methylcellulose (3 mpk)

MK-2206 was significantly bound to plasma proteins (ranged from 96% to 88% in mice>rats>dogs>monkeys>humans) with moderate Cl in rats, but relatively low Cl in dogs and monkeys.

The oral availability of MK-2206 was acceptable in rats (20%-35%) and better in dogs (83%). Plasma Cl in rats occurred primarily by direct glucuronidation with <3% of MK-2206 excreted in feces. In dogs, elimination occurred via multiple metabolic pathways including oxidation followed by glucuronidation, direct glucuronidation, and formation of a carbamoyl glucuronide. Relative to rats, a higher fraction (30%) of parent compound MK-2206 was excreted (urine, bile, and feces) in dogs. Significant intestinal secretion was observed in dogs. No metabolites of MK-2206 with biologic activity were noted.

MK-2206 was also metabolized by oxidation in human liver microsomes, primarily via the 3A4 isoenzyme of the P450 cytochrome (CYP) enzyme complex. MK-2206 was neither a potent inhibitor nor inducer of human CYPs, although at clinically relevant concentrations, it appeared to slightly induce CYP3A4. Transport experiments in the P-

glycoprotein (P-gp)-transfected cell lines (L-MDR1) suggested that MK-2206 could be a P-gp substrate. In addition, MK-2206 demonstrated weak inhibition of vectorial transport of digoxin in L-MDR1 cells (IC_{50} of 13.4 mcM).

Toxicology

In the 10-day tolerability studies, dose-limiting toxicities (DLTs) were observed at the dose of ≥200 mg/kg/day and ≥15 mg/kg/day in rats and dogs, respectively. In a 4-week safety study in dogs, MK-2206 was administered at 2.5, 5, or 10 mg/kg PO every-other-day (QOD) followed by a 2-week recovery period. The 10-mg/kg dose was poorly tolerated as manifested by severe body-weight loss and other physical and histomorphological signs of toxicity, which required cessation of dosing by the end of the second week of treatment. The 5-mg/kg dose was tolerated and although treatment-related toxicities occurred, they were transient. As no significant toxicities were observed in dogs at the 2.5-mg/kg dose, this dose was defined as NOAEL (no observed adverse effect level). Exposure at this level characterized by the maximum plasma concentration (C_{max}) and the area under the time-concentration curve (AUC_{0-48h}) corresponded to 0.37 mcM and 8.52 mcM·h, respectively. A potential safety concern associated with MK-2206 therapy is prolongation of the QT-corrected (QTc) interval, which seemed to be dose-dependent. While QTc-prolongation was persistent in dogs at the 10-mg/kg dose, it declined and returned to baseline between 24 to 72 hours post-dosing at 5 and 2.5 mg/kg. No cardiovascular changes were observed at the 1-mg/kg dose of MK-2206 (C_{max} of 0.092 mcM and AUC_{0-24h} of 1.6 mcM) within 48 hours following dosing in dogs.

A tissue distribution study demonstrated that [^{14}C] MK-2206 was widely distributed in Sprague Dawley (albino) and Long Evans (pigmented) rats except for the central nervous system. The majority of the radioactivity went into the muscle, liver and skin shortly after dosing. In Sprague Dawley and Long Evans rats, the radioactivity in most tissues was comparable. It declined in parallel to that in blood and became negligible 3 days post-dose. However, the radioactivity was more sustained at higher levels in the skin and the uveal tract of the eye in Long Evans than in Sprague Dawley rats. The concentration (ng equivalent [^{14}C]MK-2206/g tissue) in the skin and the uveal tract of Long Evans rats was 37- and 84-fold higher than that in the respective tissues of Sprague Dawley rats 24 hours post-dose.

An additional safety concern involves MK-2206-induced hyperglycemia and hyperinsulinemia. MK-2206 induced hyperglycemia in all preclinical species tested. In the most sensitive species, the dog, the glucose level was elevated by 24%-35%, when MK-2206 was administered at 5 mg/kg QOD for 4 weeks (AUC_{0-48} of 19.6 mcM·h and C_{max} of 0.73 mcM). Such exposure is expected to correspond with human exposures achievable at the upper MK-2206 dosing range.

Results from genetic toxicology assays demonstrated that MK-2206 was neither genotoxic nor mutagenic.

Clinical Development of MK-2206

Preliminary clinical PK/pharmacodynamic and safety experience is derived from a Merck-sponsored phase 1 study in healthy volunteers (HVs) and company phase 1 studies in patients with advanced solid tumors.

Projections derived from preclinical PK and metabolism studies in dogs suggested that the target exposure corresponding to a plasma concentration of ≥100 nM MK-2206 over 8 hours and $AUC_{0\text{-}48h}$ of ~2 mcM·h in humans could be attained by MK-2206 dosed at 30-70 mg QOD on a 28-day cycle schedule. Clinical PK/pharmacodynamic data confirmed that the MK-2206 dose of 60 mg QOD conferred substantial and lasting inhibition of AKT as measured in tumor biopsies from cancer patients. The 60-mg QOD dose level is being currently investigated as the maximum tolerated dose (MTD) in the expanded cohort of patients.

Based on preclinical and clinical experience from Merck-sponsored studies, PK modeling and simulation analysis suggests potential benefit of a less frequent dosing schedule (*i.e.*, QW). It is potentially feasible to administer MK-2206 at higher dose levels on a less frequent dosing schedule to maximize significant or peak target inhibition. This approach may also alleviate DLTs (*e.g.*, skin rash) associated with accumulated exposure to MK-2206. Dose escalation on a QW schedule is currently being evaluated at the MK-2206 doses ranging from 90-300 mg.

Clinical Pharmacokinetics

The clinical PK for MK-2206 was evaluated in HVs receiving a single dose (0.25-100 mg) and in cancer patients given a 30-, 45-, 60-, 75-, or 90-mg dose on the QOD schedule or 90-, 135-, 200-, 250-, or 300-mg dose on the QW schedule.

Although Day 1 $AUC_{0\text{-}48h}$ and C_{max} values achieved at ≤ 90 mg in cancer patients overlapped with the ranges observed in HVs, overall, MK-2206 exposures in cancer patients trended on average somewhat higher than those observed in HVs. In all cohorts evaluated at ≤ 200 mg QW, exposures after the first and last dose in Cycle 1 were below the dog NOAEL $AUC_{0\text{-}48h}$ and C_{max} values of 8.52 mcM•h and 365 nM, respectively. The mean first dose MK-2206 $AUC_{0\text{-}48h}$ and C_{max} were 1.77 μM•h and 62.2 nM, respectively, for 60 mg QOD, and 14.8 μM•h and 466 nM, respectively, for 300 mg QW. The dog NOAEL exposures were exceeded in humans following the first dose of 300 mg QW.

The variability in $AUC_{0\text{-}48h}$ and C_{max} following the first dose, where it could be assessed, was low to moderate across all dose levels, with the coefficient of variation (CV) values ranging from approximately 10%–60%. There does not appear to be a substantial or consistent departure from dose proportionality for either $AUC_{0\text{-}48hr}$ or C_{max} following the first dose up to the 300-mg dose level, except for an apparent plateau in exposures observed at 200 mg (n=3). Dose proportionality could not be reliably assessed beyond 135 mg (n=4) due to limited numbers of patients at each dose level.

T_{max} and apparent terminal $t_{1/2}$ values from cancer patients were generally within the ranges observed in HVs. Median T_{max} values ranged from 4–10 hours across all dose regimens and harmonic mean apparent terminal half-life ($t_{1/2}$) values ranged from approximately 60–80 hours, with the exception of the 90mg QOD cohort. At 90 mg QOD, apparent terminal $t_{1/2}$ was assessable in one patient and was approximately 50 hours.

Clinical Efficacy/Pharmacodynamics

Preliminary pharmacodynamic results in cancer patients indicate that phosphorylation of AKT in whole blood is substantially inhibited at all dose levels evaluated on the QOD and QW schedule. Additionally, preliminary results indicate that substantial pAKT inhibition was demonstrated in tumor tissue at 60 mg QOD. As there is a causal relationship between the development of hyperglycemia/hyperinsulinemia and mechanism of AKT inhibition, such events could potentially implicate pharmacodynamic activity of MK-2206. In cancer patients, reversible grade 1/2 hyperglycemia was observed across all dose levels in a total of 59 patients. Hyperinsulinemia occurred in 26 patients who received MK-2206 60 mg QOD. From a preliminary analysis, these adverse events (AEs) do not appear to be dose-dependent. Neither hyperglycemia nor hyperinsulinemia was observed at any single dose in HVs.

Thus far, no formal efficacy studies have been performed with MK-2206; however, in patients with advanced solid tumors, early indications of antitumor activity included substantial decreases in CA125 in some patients with ovarian cancer and PSA stabilization in some prostate cancer patients. Minor RECIST responses, *e.g.*, <30% decreases in tumor size, have also been observed in a patient with melanoma (16%), a patient with pancreatic cancer (23%), and in a patient with neuroendocrine tumor (20%). No partial responses, *e.g.*, confirmed >30% decreases in tumor size, have been observed.

Clinical Toxicology

Preclinical efficacy and safety studies and preliminary safety data from the clinical studies support the use of MK-2206 via the oral route, both as monotherapy and in combination with other anticancer agents.

Overall, MK-2206 has been generally well-tolerated when administered as a single PO dose (0.25-100 mg) to HVs, or to cancer patients as the 30-60 mg PO dose on the QOD schedule and the 90-200 mg PO dose on the QW schedule. Mild-to-moderate skin rash was observed in 21 of 42 patients (50.0%) and severe skin rash was observed in 5 of 42 patients (11.9%) at the dose of 60 mg QOD. Skin rash resolved following the 1- to 2-week therapy break. The higher doses evaluated in oncology patients (*i.e.,* 75 and 90 mg QOD and 300 mg QW) were not tolerated and resulted in DLT of grade 3/grade 4 skin rash.

Mild to moderate mucositis and conjunctivitis were associated with rash. The supportive-care measures included hydration, topical steroid preparations, oral corticosteroids, oral antihistamines, and oral antibiotics. Other common AEs included nausea, fatigue, vomiting, and diarrhea. These AEs were mild to moderate and in most cases were resolved by the standard supportive care and did not require therapy modifications. Hyperglycemia and hyperinsulinemia, both expected mechanism-based AEs, were observed in approximately 76% and 57% of patients, respectively, receiving MK-2206 on the QOD schedule. Episodes were generally mild, transient, and did not require therapeutic intervention. Importantly, administration of insulin may not counteract MK-2206-induced hyperglycemia due to mechanism-based insulin resistance. In this case, hydration and oral antihyperglycemic agents can be used as the supportive-care measures. Grade 3 hyperglycemia occurred in 1 patient who received 60 mg QOD and required treatment with PO antihyperglycemic medication. Grade 4 hyperglycemia was reported in one patient who received MK-2206 45 mg QOD in combination with erlotinib. In addition to supportive care measures, blood glucose management included administration of insulin and PO antihyperglycemic medication.

Grade 1/grade 2 prolongation of QTc-interval was observed in 14 out of 64 patients (21.9%) with available 12-lead ECG data. Prolongations ≥30 msec but <60 msec occurred in 4 of these patients. Grade 3 QTc prolongation was reported in one patient who received 135 mg QW. Episodes of QTc interval prolongation were in general isolated with no apparent dependency on dose or exposure levels, and were not considered clinically significant by investigators and were not reported as adverse experiences. Eleven patients experienced sinus bradycardia (<50 bpm) during Holter or ECG monitoring. These events were asymptomatic and were not clinically significant. While a causal relationship between these events and administration of MK-2206 is uncertain, similar side effects were seen preclinically in conscious dogs. Consequently, patients with a history or current evidence of heart disease should be excluded from enrollment on MK-2206 trials. Standard 12-lead ECG measurements should be performed at the protocol-specified time-points.

Developmental/Reproductive Toxicity

Developmental and reproductive toxicity studies of MK-2206 have not been performed thus far. MK-2206 was not tested in pregnant or breast-feeding women. Women of child-bearing potential and men participating in clinical studies of MK-2206 must use appropriate contraception, including abstinence and double-barrier methods, throughout MK-2206 therapy. In preclinical mutagenicity studies, MK-2206 was neither genotoxic or mutagenic.

Drug Interactions

No clinical drug interaction studies have been performed with MK-2206. Oxidative metabolism of MK-2206 in human liver microsomes was catalyzed primarily by CYP3A4. MK-2206 was not an inhibitor of the major CYPs. Human hepatocyte induction data suggested a low potential as an inducer of CYP3A for MK-2206 at clinically relevant concentrations. MK-2206 was shown to be a P-gp substrate.

2.3 Other Agent(s)

Everolimus:

RAD001 (everolimus) Everolimus is a novel oral derivative of rapamycin. Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation and has obtained marketing authorization (Certican®) for prophylaxis of rejection in renal and cardiac transplantation in a number of countries, including the majority of the European Union. Everolimus has been in development for patients with various malignancies since 2002. Everolimus is being investigated as an anticancer agent based on its potential to act:

- Directly on the tumor cells by inhibiting tumor cell growth and proliferation
- Indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell HIF-1 activity, VEGF production and VEGF-induced proliferation of endothelial cells). The role of angiogenesis in the maintenance of solid tumor growth is well established, and the mTOR pathway has been implicated in the regulation of tumor production of proangiogenic factors as well as modulation of VEGFR signaling in endothelial cells.

At weekly and daily schedules and at various doses explored, everolimus is generally well tolerated. The most frequent adverse events (rash, mucositis, fatigue and headache) associated with everolimus therapy are manageable. Non-infectious pneumonitis has been reported with mTOR inhibitors but is commonly low-grade and reversible.

2.3.1 mTOR Pathway and Mechanism of Action

At cellular and molecular level everolimus acts as a signal transduction inhibitor. Everolimus selectively inhibits mTOR (mammalian target of rapamycin), a key and a highly conservative serine-threonine kinase, which is present in all cells and is a central regulator of protein synthesis and ultimately cell growth, cell proliferation, angiogenesis and cell survival. mTOR is the only currently known target of everolimus (Reviewed in Boulay and Lane, 2007). mTOR is downstream of PI3K/AKT pathway, a pathway known to be deregulated in a wide spectrum of human cancers (e.g. through loss/mutation of the PTEN negative regulator; through PI3K mutation/amplification; through AKT/PKB overexpression/overactivation; through modulation of TSC1/TSC2 tumor suppressors). In addition, activation of the PI3K/AKT/mTOR pathway is frequently a characteristic of worsening prognosis through increased aggressiveness, resistance to treatment and progression. The main known functions of mTOR include the following (Bjornsti and Houghton 2004; Boulay and Lane, 2007):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1 to S phase in appropriate growth conditions.

- The PI3K-mTOR pathway itself is frequently activated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- Through inactivating eukaryotic initiation factor 4E binding proteins (4E-BP1) and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates translation of important massages, including those encoding the HIF-1 proteins, c-myc, ornithine decarboxylase, and cyclin D1, as well as ribosomal proteins themselves.
- The activation of mTOR pathway leads to the increased production of pro-angiogenic factors (i.e., VEGF) in tumors and to tumor, endothelial and smooth muscle cell growth and proliferation.
- The regulation of mTOR signaling is complex and involves positive regulators, such as AKT that phosphorylate and inactivate negative regulators such as the Tuberous Sclerosis Complex (TSC1/TSC2).

mTOR is represented by two structurally and functionally distinct multiprotein signaling complexes, mTORC1 (mTOR complex 1, rapamycin sensitive) and mTORC2 (mTOR complex 2, rapamycin insensitive) (Wullschleger, Loewith and Hall 2006). mTORC1 is mainly activated via the PI3 kinase pathway through AKT (also known as PKB, protein kinase B) and the tuberous sclerosis complex (TSC1/TSC2) (Bjornsti and Houghton 2004). Activated AKT phosphorylates TSC2, which lead to the dissociation of TSC1/TSC2 complex, thus inhibiting the ability of TSC2 to act as a GTPase activating protein. This allows Rheb, a small G-protein, to remain in a GTP bound state and to activate mTORC1. AKT can also activate mTORC1 by PRAS40 phosphorylation, thereby relieving the PRAS40-mediated inhibition of mTORC1 (Manning and Cantley 2007; Wang at al 2007). mTORC2 (mTOR complex 2) is activated through a currently unknown mechanism, possibly by receptor tyrosine kinase (RTK) signalling (Manning and Cantley 2007). It has been suggested that mTORC2 phosphorylates and activates a different pool of AKT, that is not upstream of mTORC1. PHLPP phospatase plays a role of a negative regulator. mTORC2 is rapamycin insensitive and is required for the organization of the actin cytoskeleton (Wullschleger, Loewith and Hall 2006). mTORC1-mediated signaling is subject to modulation by the macrocyclic lactone rapamycin and its derivatives, such as everolimus. Once these agents bind to the 12 kDa cytosolic FK506- binding protein immunophilin FKBP12, the resulting rapamycin- FKBP12 complexes bind to a specific site near the catalytic domain of mTORC1 and inhibit phosphorylation of mTOR substrates. As a consequence, downstream signaling events involved in regulation of the G1 to S-phase transition are inhibited. This mechanism is thought to be responsible for the immunosuppressive effects of rapamycin as well as its putative antineoplastic activity (Witzig, et al 2005). As many cancers are characterized by dysregulation of G1 transit (for example, overexpression of cyclin or cyclin-dependent kinases), inhibition of mTOR becomes an intriguing target for inducing cytostasis (Bjornsti and Houghton 2004).

2.3.2 Preclinical Studies

Pre-clinical investigations have demonstrated that everolimus is a potent inhibitor of the proliferation of a range of human tumor cell lines *in-vitro* with IC50s ranging from sub/low nM to μM concentrations, concentrations capable of being reached in patients at the doses used in clinical trials. Everolimus was shown to have activity in human tumor cell lines originating from lung, breast, prostate, colon, kidney, melanoma and glioblastoma. Everolimus was also shown to have activity in human pancreatic neuroendocrine cells, where induction of apoptosis was reported (Zitzmann, et al 2007), as well as in acute myeloid leukemia cells (Zeng, et al 2007), adult T-cell leukemia cells (Ikezoe, et al 2007), diffuse large B cell lymphoma cells (DLBCL; Wanner, et al 2006), pancreatic tumor cells (Tuncyurek, et al 2007), ovarian cancer cells (Treeck, et al 2006, Mabuchi, et al 2007) and hepatocellular carcinoma cells (Sieghart, et al 2007). As a single agent, everolimus inhibited proliferation in three mantle cell lymphoma cell lines (Jeko1, SP49 and NCEB1) approximately 40–65% compared to control cells. This was associated with G1 cell-cycle arrest and reduced phosphorylation of the mTOR downstream target, 4E-BP1 (Haritunians, et al 2007). In a clonogenic assay using cells derived from 81 patient-derived tumor xenografts never cultured *in vitro* (11 human tumor types with 3 to 24 tumors each: bladder, colon, gastric, NSCLC [adeno, squamous epithelium and large cell], SCLC, breast, ovary, pancreatic, renal, melanoma, and pleuramesothelioma), everolimus inhibited colony formation in a concentration-dependent manner. In addition, normal hematopoetic stem cells were insensitive to everolimus, with an IC50 about 15 fold higher than the tumor lines. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS), with particular potency against VEGF induced proliferation. The inhibition of endothelial proliferation and antiangiogenic activity of everolimus was confirmed *in vivo*, as everolimus selectively inhibited VEGF-dependent angiogenic response. Mice with primary and metastatic tumors treated with everolimus showed a significant reduction in blood vessel density when compared to controls at well tolerated doses. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis. Everolimus also inhibits tumor growth *in-vivo* in xenografted, syngeneic and orthotopic animal models, residing longer in tumor tissue than in plasma and demonstrating high tumor penetration in a rat pancreatic tumor model. These effects occurred within the dose range of 2.5 to 10 mg/kg p.o. daily. Typically, the antitumor activity of everolimus monotherapy was that of reduction of tumor growth rates rather than producing regressions or stable disease. Everolimus, administered p.o., was a potent inhibitor of tumor growth and well tolerated in:

- s.c. mouse xenograft model, established from a variety of tumor cell lines of diverse histotypes (NSCLC, pancreatic, colon, melanoma, epidermoid), including a Pgp170 over-expressing multi-drug resistant tumor line
- a series of low-passage tumor xenografts established directly from human tumor material, maintained only *in vivo* and considered highly predictive of

therapeutic outcome in patients. These included breast (5 lines), colorectal (9 lines), gastric (3 lines), lung (22 lines including adenocarcinomas, epidermoid cell, large cell and small cell histotypes), melanoma (6 lines), ovarian (4 lines), pancreatic (3 lines) and renal (6 lines)
- two syngeneic models (CA20948 rat pancreatic, B16/Bl6 mouse orthotopic melanoma)

Taken together, these data indicate the broad anti-proliferative potential of everolimus. It is not clear which molecular determinants predict responsiveness of tumor cells to everolimus. Molecular analysis has revealed that relative sensitivity to everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein. PTEN status alone may not be predictive of everolimus relative *in vitro* sensitivity, however in some cases (i.e., GBM) there is also a correlation with PTEN status. In preclinical models, the administration of everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (pS6) and p4EBP1, and occasionally with an increase in phosphorylation AKT (pAKT).

2.3.3 Pre-clinical Safety

In safety pharmacology studies, everolimus was devoid of relevant effects on vital functions including the cardiovascular, respiratory and nervous systems. Everolimus had no influence on QT interval prolongation. Furthermore, everolimus showed no antigenic potential. Although everolimus passes the blood-brain barrier, there was no indication of relevant changes in the behavior of rodents, even after single oral doses up to 2000mg/kg or after repeated administration at up to 40 mg/kg/day. Based on these findings, the potential of everolimus to affect vital functions in patients is considered to be low.

Everolimus is considered to have no genotoxicity or carcinogenicity potential. All significant adverse events observed in preclinical toxicology studies with everolimus in mice, rats, monkeys and minipigs were consistent with its anticipated pharmacologic action as an antiproliferative and immunosuppressant and at least in part reversible after a 2- or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes. Ocular effects (lenticular disorders) observed in rats were not observed in any other species and are considered to be a species specific disorder.

2.3.4 Clinical experience

Everolimus Pharmacokinetics

Everolimus is rapidly absorbed with a median tmax of 1-2 hours. The bioavailability of the drug is believed to be 11% or greater. The AUC0-τ is dose-proportional over the dose range between 5 to 70 mg in the weekly regimen and 5 and 10 mg in the daily regimen. Cmax is dose-proportional between 5 and 10 mg for both the weekly and daily regimens. At doses of 20 mg/week and higher, the increase in Cmax is less than dose-proportional. The coefficient of variation

between patients is approximately 50%. Trough levels (24 hour post-dose) correlate well with AUC0-τ at steady-state during daily administration. In whole blood, at a daily dose of 10 mg, about 20% of everolimus is confined in plasma with 26% being unbound. The remaining 80% is sequestered in blood cells. Everolimus is extensively metabolized in the liver and eliminated in the bile. Major metabolites are inactive. Elimination half-life is approximately 30 hours. The clearance of everolimus is approximately halved in patients with mild-moderate hepatic impairment (Child-Pugh Class A or B), while renal impairment has little or no impact on the pharmacokinetics of everolimus. Age, weight and gender in the adult population do not affect the pharmacokinetics of everolimus to a clinically relevant extent. The clearance of everolimus is reduced in children. Pharmacokinetic characteristics are not notably different between Caucasian and Japanese subjects, whereas in Black patient populations pharmacokinetic studies have shown an average 20% higher clearance. A high-fat meal altered the absorption of everolimus with 1.3 hour delay in tmax, a 60% reduction in Cmax and a 16% reduction in AUC. Everolimus is a substrate of CYP3A4 and a substrate and a moderate inhibitor of the multi-drug efflux pump P-glycoprotein (PgP, MDR1, ABCB1). Hence, its metabolism is sensitive to drugs which modify these enzymes (substrates, inducers, or inhibitors of these enzymes). Competitive inhibition could occur when everolimus is combined with drugs which are also CYP3A4 or Pglycoprotein substrates. Appendix C lists examples of clinically relevant CYP3A inhibitors and inducers and a list of P Glycoprotein substrates can be accessed at the following link: http://www.genemedrx.com/PGPtable.php. Please refer to Appendix C and/or the everolimus prescribing information for more information on the concomitant use of CYP3A4 inhibitors/inducers and other medications.

Everolimus Pharmacodynamic Studies
Pharmacokinetic/pharmacodynamic modeling based on inhibition of the biomarker p70S6 kinase 1 [S6K1] in peripheral blood mononuclear cells [PBMC]) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition ([Study C2101] / [Study 2102], Lane, et al 2003). Furthermore, molecular pharmacodynamic (MPD) studies, using immunocytochemistry (IHC) in biopsied tumor tissue, assessed the degree of inhibition and its duration for pS6, p4E-BP1 and pAKT expression with the daily and weekly dosing. There was high inhibition of the downstream markers S6K1 and 4E-BP1 at 5mg/day, which was complete at 10 mg/day, while preliminary results suggest increase in pAKT expression with maximal effect at 10 mg daily ([Study C2107], Tabernero, et al 2005).

Clinical Experience with Everolimus
Everolimus has been investigated as a component of multi-drug immunosuppression in solid organ transplantation since 1996 and was approved for the indication of prophylaxis of organ rejection in adult patients receiving an allogeneic renal or cardiac transplant on 8 Jul 2003 by the European Union under the trade name of Certican®. The most frequent adverse drug reactions in this

context are highly specific to the transplant context. However, certain events are generalizable, most notably myelosuppression, skin disorders and increases in blood lipid levels. Everolimus has been in development for patients with cancer since 2002. Approximately 4000 patients with various malignancies have been treated in either Novartis sponsored or non-Novartis sponsored, and 3 healthy volunteer clinical studies as of 31 Aug 2008. Overall, Novartis sponsored a total of 28 studies of everolimus administered either as single-agent (n=13), or in combination with other anti-tumor agents (n=15). Ongoing or completed Investigator sponsored studies also enrolled over 1000 patients globally.

Eight single-agent Novartis sponsored trials have or are being conducted in various advanced malignancies. Five Phase I studies evaluated several escalating doses with either weekly or daily administration (Studies C2101/02, C2106, C2107, C1101) of everolimus with the objective to identify an optimal regimen and dosage, based on safety, pharmacokinetics and knowledge of the drug's molecular effects on various tumors. The 10 mg/day and 50-70 mg/week dosages were proposed for further studies, when using everolimus as a single agent, and as a target maximum dose in combination studies. In addition the Phase I studies, conducted in prostate cancer (Study C2106) and in Japanese patients with advanced cancers (Study C1101), evaluated the safety and the molecular changes in tumor, associated with the administration of everolimus. Two Phase II monotherapy studies were designed to evaluate the safety and efficacy of a single dose of 10 mg administered daily including Study C2235 in advanced NSCLC (n=81) and Study C2239 in advanced pancreatic neuroendocrine tumors (n=160). A Phase III, randomized, double blind, placebo controlled study in patients with mRCC who progressed on a VEGFr TKI demonstrated that everolimus, administered daily at an oral dose of 10 mg, was superior to placebo for the primary endpoint of progression free survival. Median PFS was prolonged from 1.9 months for patients receiving placebo to 4.9 months for everolimus treated patients, assessed by central independent review blinded to clinical data (hazard ratio 0.33, 95% CI 0.25-0.43, $p<0.001$) (Kay et al, 2009). On 30 March 2009 everolimus was approved for use in the United States for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. Overall, the most frequent adverse effects suspected to be related to everolimus have been stomatitis, rash, anemia, fatigue, asthenia, diarrhea, anorexia, nausea, hypercholesterolemia, mucosal inflammation, vomiting, hypertriglyceridemia, cough, peripheral edema, dry skin, epistaxis, pruritus and dyspnea. The most common Grade 3 or 4 adverse reactions suspected to be related to treatment were anemia, infections, hyperglycemia, stomatitis, fatigue, lymphopenia, hypercholesterolemia, pneumonitis, and elevated gammaglutamyltransferase concentrations. Non-infectious low-Grade (Grade 1/2) pneumonitis has led to development of treatment guidelines for the disorder (Section 6, Table 5). The primary DLT has been severe (Grade 3) stomatitis, and occasionally fatigue, hyperglycemia, and neutropenia.

2.3.5 Everolimus Safety Profile

Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, and diarrhea. Infections have not been notably frequent or severe. Non-infectious pneumonitis has also been observed. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2). Overall, the most frequently observed laboratory abnormalities include reduced blood counts, hyperlipidemia mostly reported as hypercholesterolemia and/or hypertriglyceridemia. The principal DLT in Phase 1 trials has been Grade 3 stomatitis. For guidance on management of stomatitis refer to Section 6. Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side-effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations. Monitoring of blood lipid levels requires patients to be fasting so that this aspect must be verified when interpreting results. For guidance on management of hyperlipidemia refer to Section 6. Hyperglycemia was reported as a serious adverse reaction. Similarly, the fasting state of patients should be verified when interpreting results. For guidance on management of hyperglycemia refer to Section 6. Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, non-malignant infiltration in the lungs, which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy which may or may not be symptomatic. Advice on the management of pneumonitis has been provided in Section 6 (table 5).

In oncology studies with everolimus, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alveolar hemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each). One fatal case of drug-related pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which developed approximately two months after starting everolimus. Cytology for both the pleural and pericardial fluids was positive for malignancy. The death was considered possibly related to the underlying late stage tumor and study drug. Additionally, one patient treated with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung.

Along with the cases of non-infectious pneumonitis, serious opportunistic infections have also been reported in cancer patients treated with everolimus:

mycobactrium, aspergillus, and fatal candidal sepsis, and fatal pneumocystis carnii in particular. Because everolimus, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts, treatment with everolimus must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co-medications. Outcome may be fatal in case of serious infections. A reduction in blood cell counts is frequent when everolimus therapy is initiated. Without clinical significance and infrequently, anemia and thrombocytopenia have been reported. In heavily pretreated patients with aggressive lymphoma, the incidence of grade 3 anemia, neutropenia, and thrombocytopenia was reported to be 11%, 16%, and 30%, respectively. Serious, suspected drug related hemorrhages have been exceptional. Nevertheless, everolimus should be considered as predisposing patients to hemorrhage, potentially fatal, should they develop severe drug related thrombocytopenia. Discrete, reversible changes in liver enzymes have been found to occur in numerous patients during treatment with everolimus in oncology clinical studies, and in a study in rheumatoid arthritis. In oncology studies, these changes may be evident only in patients without severe underlying morbidity. The increase in transaminases (AST and ALT) generally appears after 4 weeks of treatment. In all but a few cases it does not exceed Grade 1 (≤ 2.5 x ULN). Similarly, mild increases in alkaline phosphatases can coexist. Spontaneous corrections or intermittent correction with continued treatment can occur. Serum bilirubin is not increased. In studies of patients with advanced cancers, clinically relevant changes in liver enzymes have been invariably associated with the presence of liver metastases and/or progression of the underlying cancer. Renal failure has been reported in five suspected cases to date. One patient with no alternative explanation made a complete recovery following study drug adjustment and no treatment/therapy for the event. The rest or the patients had concurrent morbidities, which might have contributed to the reported events. Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported as serious adverse reactions. Electrolytes should be monitored in patients treated with everolimus. Table 4 and 5 provide general recommendations for the management of patients, with suspected drug toxicities while on treatment with everolimus as single-agent therapy.

2.4 Rationale

Several studies show that upregulation of the PI3K pathway is associated with poorer prognosis in patients with nonmetastatic RCC. Our data show that RCC patients treated with anti-VEGF therapy who have upregulation of components of the PI3K pathway have shorter PFS. In an 80 patient CTEP sponsored study of patients who received sorafenib or sorafenib plus IFN, AKT S473 was the single strongest predictor for clinical outcome in a panel of clinical and tissue variables. Similarly, analysis of nephrectomy samples in patients who received presurgical bevacizumab showed that upregulation of AKT was associated with a shorter PFS and poorer overall survival. We hypothesize that blockade

of AKT in patients who are refractory to anti VEGF therapy will eliminate one of the key drivers of tumor growth and proangiogenic signaling, and will result in prolongation of PFS.

2.5 Correlative Studies Background

Tissue Microarrays (TMA) to assess PI3K pathway protein levels: We have extensive experience in the generation and analysis of TMA in patients with RCC. Our recently published CTEP sponsored randomized phase II study of sorafenib vs sorafenib plus IFN used this technique on 40 formalin fixed, paraffin embedded nephrectomy specimens from patients on the study. We hypothesize that (1) upregulated AKT in nephrectomy specimens, including T308 and especially S473, will predict for response to MK2206 and (2) patients with baseline upregulated S473 will not show short PFS after treatment with the TORC1 inhibitor everolimus.

We assume that patterns seen in primary tumors are reflective of those expressed in metastatic sites. This assumption is supported by evidence that the karyotype and transcriptome is relatively similar when primary and metastatic disease is compared, and by unpublished observations from our group that protein expression in primary and metastatic sites is the same.

Cytokines and Angiogenesis Factors (CAF) in RCC: Analysis of the circulating miroenvironment will provide insight into baseline and induced biomarkers associated with response and resistance to AKT inhibition. We have analyzed CAF from patient on the CTEP sorafenib trial, and have demonstrated biologically plausible associations with several factors, including VEGF and osteopontin. A five factor signature permitted discrimination between patients who benefitted from sorafenib plus IFN versus patients who benefitted from sorafenib monotherapy (Clin Ca Res, submitted). The purpose of the current study is to generate a similar set of observations in patients receiving TORC1 or AKT blockade.

We hypothesize that baseline and induced levels of CAF will be predictive for a response signature that identifies individuals who benefit from AKT blockade. Comparison between patterns in patients who receive an AKT blocking agent versus those who receive a TORC1 blocking agent will provide valuable information on the endocrine effects of AKT versus TORC1 blockade. These patterns may provide mechanistic insight into downstream pathways differentially affected by these two agents.

Virtual Karyotyping as a Predictive Biomarker in RCC: RCC karyotypic changes have been associated with clinical outcome in primary RCC. Preliminary data suggest that a specific karyotypic profile is associated with response and resistance to antiangiogenic therapy (abstracts, manuscript in preparation). Evaluation of chromosomal regions to elucidate mechanisms behind the karyotypic observations is underway. The purpose of the current study is to confirm our observations in a cohort of patients previously treated with anti-VEGF therapy, and to determine whether karyotypic patterns are predictive for response or resistance in TORC1 or AKT blocking agents.

We hypothesize that (1) Patients who showed a short PFS on prior anti-VEGF therapy will have a distinct karyotype, (2) These patients will show benefit to AKT blocking agents, and (3) Further karyotypic discrimination will be possible between patients who benefit from AKT blockade versus mTOR blockade.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed metastatic or unresectable RCC. All histologies are permitted. Patient should have undergone nephrectomy.

3.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan. See Section 11 for the evaluation of measurable disease.

3.1.3 Patients must have received, and progressed on an anti-VEGF therapy, including bevacizumab, sorafenib, sunitinib or pazopanib.

3.1.4 Because no dosing or adverse event data are currently available on the use of MK-2206 or everolimus in patients < 18 years of age, children are excluded from this study but will be eligible for future pediatric phase 2 trials.

3.1.5 ECOG performance status ≤1.

3.1.6 Patients must have normal organ and marrow function as defined below:

- leukocytes ≥ 3,000/mcL
- absolute neutrophil count ≥ 1,500/mcL
- platelets ≥ 100,000/mcL
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional upper limit of normal
- Serum creatinine ≤ 1.5 x ULN

3.1.7 INR and PTT ≤ 1.5 x ULN. Therapeutic anticoagulation with warfarin is allowed if target INR ≤ 3 on a stable dose of warfarin or on a stable dose of LMW heparin for > 2 weeks at time of randomization.

3.1.8 The effects of MK-2206 and/or everolimus on the developing human fetus at the recommended therapeutic dose are unknown. For this reason, women of childbearing potential and men must use two forms of contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and for 8 weeks after the last dose of study drug. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, the patient should inform the treating physician immediately.

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

3.1.10 Serum pregnancy test in female patients of childbearing potential must be negative within 24 hours of enrolling on this study.

3.2 Exclusion Criteria

3.2.1 Patients who received oral TKIs (sorafenib, sunitinib, or pazopanib) within 2 weeks prior to entering the study, radiotherapy, immunotherapy or chemotherapy within 4 weeks prior to entering the study, bevacizumab within 4 weeks prior to entering the study, or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier (recovered to ≤ Grade 1).

3.2.2 Patients may not be receiving any other investigational agents. Patients may not have received an mTOR inhibitor.

3.2.3 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MK-2206 or other agents used in the study.

3.2.5 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP 450 3A4 are ineligible. Lists including medications and substances known or with the potential to interact with the CYP 450 3A4 isoenzymes are provided in Appendix C.

3.2.6 Patient should have a Hemoglobin A1C value of < 8%. Preclinical studies demonstrated the potential of MK-2206 for induction of hyperglycemia in all preclinical species tested. Studies also demonstrate a risk of hyperglycemia, hyperlipidemia and hypertriglyceridemia associated with everolimus therapy. Patients with diabetes or in risk for hyperglycemia, hyperlipidemia and/or hypertriglyceridemia should not be excluded from trials with MK-2206 or everolimus, but the patient should be well controlled on oral agents (recent (i.e. within 3 months) HbA1C ≤ 7.0) before the patient enters the trial.

3.2.7 Preclinical studies indicated transient changes in QTc interval during MK-2206 treatment. Prolongation of QTc interval is potentially a safety concern while on MK-2206 therapy. Cardiovascular: baseline QTcF > 450 msec (male) or QTcF > 470 msec (female) will exclude patients from entry on study. A list of medications that may cause QTc interval prolongation are listed in Appendix D, and should be avoided by patients entering on trial.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant women are excluded from this study because MK-2206 and/or everolimus are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MK-2206 and/or everolimus, breastfeeding should be discontinued if the mother is treated with MK-2206 or everolimus.

3.2.10 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with MK-2206 or everolimus. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.11 Individuals who are diagnosed with an intercurrent cancer are excluded, with the exception of non-melanoma skin cancers, and other cancers where curative treatment was completed at least two years ago.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	2	+	12	=	14

Not Hispanic or Latino	28	+	72	=	100
Ethnic Category: Total of all subjects	30 (A1)	+	84 (B1)	=	114 (C1)
Racial Category					
American Indian or Alaskan Native	1	+	1	=	2
Asian	0	+	0	=	0
Black or African American	6	+	6	=	12
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	23	+	77	=	100
Racial Category: Total of all subjects	30 (A2)	+	84 (B2)	=	114 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

4. REGISTRATION PROCEDURES

4.1 General Guidelines

See Appendix K: Multi-Center Study Management Plan

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) except for Group studies.

4.2 Registration Process

Before an institution may begin participation in a M.D. Anderson protocol, all the required steps outlined in Section 3.3 of Appendix K concerning regulatory documents, must be fulfilled.

Prior to protocol enrollment and initiation of treatment, subjects must sign and date an Institutional Review Board (IRB) approved consent form. Patients at participating institutions should be registered with their institutional central registration first, following each institution's established policies. All patients must then be registered in the M.D. Anderson database, Clinical Oncology Research System (CORe) before beginning treatment. CORe is a clinical research information management system supporting clinical research trials at U.T. M.D. Anderson Cancer Center and collaborative sites across the nation.

At the time of registration, the registrant will be requested to verify the patient's eligibility in

CORe by answering a series of inclusion/exclusion protocol questions and the name of the registering physician. Once patient eligibility has been established, the patient will then be automatically registered and randomized to the appropriate treatment arm. Therapy may then be initiated per protocol guidelines.

Please see Section 3.3 of Appendix K for registration requirements and data collection guidelines.

5. TREATMENT PLAN

5.1 Agent Administration

Patients will be randomized 2:1 to one of two treatment arms (i.e. Arm A: MK-2206; Arm B: Everolimus). Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for MK-2206 and everolimus are described in Section 7. Appropriate dose modifications for MK-2206 and everolimus are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course. Patients should be instructed to record doses as they take them and not to enter them in batches at a later time.

5.1.1 *MK-2206 (Arm A)*

There is no specific guidance available regarding overdose due to the lack of clinical experience. In case of an acute overdose, it is recommended that activated charcoal be administered orally to reduce the absorption of MK-2206.

MK-2206 is an oral drug that may be administered once weekly (QW). Patients should take MK-2206 at a starting dose of 200mg PO once weekly 2 hours before or after a meal. The phase 1 clinical pharmacology study of MK-2206 in volunteers included a panel of 8 patients who were administered MK-2206 after a high-fat breakfast. The results indicated a moderate increase in AUC and a slight increase in Cmax relative to that of fasted patients.

A study cycle will be 4 weeks in length. Patients who are progression free after 1 year may be given a 12 week (+/- 7 days) study drug supply.

5.1.2 *Everolimus (Arm B)*

Everolimus is an oral drug that will be administered once daily. Patients should take everolimus at a staring dose of 10 mg orally once daily. Patients will be instructed to take everolimus in the morning, at the same time each day.

A study cycle will be 4 weeks in length.

5.2 Screening and Evaluation On-Study

Within four weeks of study entry:

- All the participants must have signed a consent form agreeing to participate in the study.
- Radiological studies shall include a chest X-ray, and CT scans of the chest and abdomen for the baseline tumor measurement, a CT or MRI of the brain, and a bone scan. Appropriate additional studies should be obtained to fully define the extent and severity of existing or suspected malignant disease.
- A MRI of the spine should be obtained, if there is suspicion of evolving cord or nerve root compression. Spinal cord or nerve root compression syndromes should be managed before trial entry.
- A skeletal survey and a CT scan of the pelvis will be ordered as clinically indicated.
- A 12-lead electrocardiogram

Within two weeks of study entry:

- All patients must undergo a complete history and physical examination, including vital signs, ECOG performance status, recent weight loss, height, and current weight.
- Concurrent non-malignant disease and medical therapy must be documented. On-study forms must be filled out completely.
- All prior anti-cancer treatment must be recorded in proper detail. Any residual toxicity from prior therapies should be recorded by using the grading schema in NCI Common Toxicity Criteria v4.0.
- Patient's MSKCC prognostic criteria will be recorded. (Appendix J).
- Laboratory studies shall include CBC w/differential, platelet count, chemistry panel (total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, magnesium, glucose), amylase, lipase, PT and PTT, and urinalysis (pH, specific gravity, ketones, RBC, WBC, bilirubin, and protein). T4, TSH will be obtained. Hemoglobin A1C, fasting glucose, lipid panel and triglycerides will be obtained. Serum pregnancy test in female patients of childbearing potential will also be included and must be negative within 24 hours of enrolling on this study.

Optional studies with patient consent:

- Nephrectomy blocks will be acquired to: a) generate tissue microarray (TMA) to stain for PI3K pathway components and other biologically relevant pathways and molecules and b) perform virtual karyotyping.
- Baseline blood will be drawn for a) plasma and serum analysis of cytokines and angiogenesis factors b) circulating monocytic cells.

Evaluation During Treatment:
On-study evaluations will consist of the following study activities every four weeks +/- four days (Patients who are progression free after 1 year may have the following performed every 12 weeks +/- 7days):

- History and physical exam by physician, or mid-level provider at each scheduled visit.
- Vital signs (including weight) and ECOG performance status
- Serum chemistry including total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, magnesium, and glucose at each scheduled visit (+/- 4 days). Hematology including CBC with differential and platelet counts and PT and PTT at each scheduled visit (+/- 4 days). T4, TSH, will be obtained at each scheduled visit (+/- 4 days). Amylase and lipase will be repeated at each scheduled visit as clinically indicated. Fasting lipid panel and glucose will be done every 4 weeks for the first 8 weeks and every 8 weeks thereafter. Cycle 1 Day 1 blood tests will not be done if screening labs were done in the previous 7 days.
- Serum glucose level monitoring for patients every 7 days +/- 2 days for patients on MK2206 during the first cycle of therapy. These measurements do not have to be performed at the study site, but data must be provided to the study team by the patient.
- Hemoglobin A1c levels need to be monitored at the beginning of each cycle for patients on MK2206 who require antihyperglycemic medication.
- Record concomitant medications at each scheduled visit.
- Monitor for adverse events. Treatment-related toxicity (acute and cumulative) will be performed every scheduled visit.
- On C1D1 only, patients randomized to MK-2206 will have an ECG within 4 hours of taking study drug.

Optional studies with patient consent:

- Blood will be drawn for a) plasma and serum analysis of cytokines and angiogenesis factors and b) circulating monocytic cells.

In addition to the above, the following will be performed every eight weeks+/- 7 days (Patients who are progression free after 1 year may have the following performed every 12 weeks +/- 7days)**:**

- Repeat radiologic studies (CT, MRI, Chest x-ray and bone scan as indicated) to evaluate disease progression or response (in accordance with restaging of disease). Studies to confirm a complete response or document progressive disease will be performed as needed.
- 12-lead electrocardiogram (ECG)

End of Treatment

The following study activities will be completed after treatment has been discontinued for any reason:

- Physical exam.
- Vital Signs including weight
- Radiologic assessment and assessment of response.
- 12-lead electrocardiogram.
- Urinalysis to include: pH, specific gravity, ketones, RBC, WBC, bilirubin, protein, and glucose.
- Serum chemistry including total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, magnesium, and glucose
- TSH, T4.
- Hematology to include: CBC with differential and platelet count, PT and PTT.
- Record for concomitant medications.
- Monitor for adverse events.

Optional studies with patient consent:

- Blood will be drawn for a) plasma and serum analysis of cytokines and angiogenesis factors b) circulating monocytic cells

5.3 General Concomitant Medication and Supportive Care Guidelines

Because MK-2206 is metabolized by CYP3A4, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. A list of agents known to interact with the CYP3A4 isoform is listed in Appendix C.

Drugs known that may prolong the QTc interval should be avoided.

Everolimus is a substrate of CYP3A4 and a substrate and inhibitor of P-glycoprotein. Everolimus metabolism may be affected by drugs that are substrates or strong inhibitors or inducers of CYP3A4 or P-glycoprotein. A list of agents known to interact with the CYP3A4 and P-glycoprotein are listed in Appendix C.

5.4 Definition of Dose-Limiting Toxicity

A dose limiting toxicity is any grade 3 or 4 hematological or nonhematological toxicity, as well as the following:

1. Grade 3 hyperglycemia that can be brought down to grade 1 within a week (both

agents).
2. Persistent refractory grade 2 rash (MK2206) despite dose withholding followed by reinitiation at same dose.
3. Persistent refractory grade 2 nonhematological toxicity (everolimus) that persists despite dose withdholding followed by reinitiation at same dose
4. Persistent refractory grade 2 thrombocytopenia (everolimus) that persists despite dose withdholding followed by reinitiation at same dose
5. Grade 2 pneumonitis (everolimus)

The following will not be considered a dose limiting toxicity

6. Asymptomatic hyperuricemia any grade
7. Asymptomatic lymphopenia, any grade

Management and dose modifications associated with dose limiting toxicities are outlined in Section 6.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Pregnancy

5.6 Duration of Follow Up

Patients will be followed for every 3 months (by telephone, e-mail, clinic visit, or medical record review) after removal from study until death, whichever occurs first. Follow up of a treatment arm will cease once median OS has been reached for that arm. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

If a patient becomes pregnant while on trial and withdraws, the outcome of the pregnancy will be recorded, including the newborn if the pregnancy is carried to full term.

5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and dose modification for MK2206 and for everolimus are outlined in the following sections. Dose withholding, dose reduction or treatment discontinuation will be performed for clinically important grade 3 and 4 toxicities. Dose withholding and/or dose reduction will be performed for selected grade 2 toxicities summarized in Section 5.4 and outlined in detail below.

6.1 MK-2206

Dose Level	MK2206 Dose
-2	90 mg PO weekly
-1	135 mg PO weekly
0 (starting dose)	200 mg PO weekly

Clinically significant Grade 3 side effects attributable to MK2206 will require dose withholding until grade 1 levels of toxicity are reached. At that point drug can be restarted at the next lower dose level. If after four weeks the toxicity remains completely controlled, dose re-escalation can be attempted at the treating physician's discretion.

If toxicity does not resolve to a grade 1 or lower levels within four weeks of drug discontinuation, the patient will be taken off study.

Clinically significant Grade 4 side effects attributable to MK2206 which are considered medically relevant will result in patient being taken off study.

Management of Hyperglycemia

Grade 3 hyperglycemic events (>250 mg/dL) should lead to consultation with an endocrinologist or other specialist. If glucose levels do no return to grade 1 or lower within one week of appropriate therapy, patients should be considered to have a DLT.
Appropriate therapy will usually involve oral antihyperglycemic agents, since the inhibition of glucose transport into the cell by AKT/mTOR inhibitors may render insulin ineffective. The goal of therapy is to keep fasting glucose <150 mg/dL, random blood glucose levels <180 mg/dL, and Hemoglobin A1c <8%. Glucose monitoring should be performed weekly, during the first cycle of therapy, and on day 1 of subsequent cycles, prior to drug administration. Hemoglobin A1c monitoring, for patients requiring treatment of hyperglycemia, should be

performed with each cycle of MK-2206 therapy.

Management of Rash

Patients who develop grade 3 rash will have treatment withheld as outlined above. For patients with persistent grade 2 rash that does not respond to conservative measures, and which in the opinion of the treating physician is significantly compromising quality of life, dose can be held, and once rash reaches grade 1 intensity or lower, MK2206 can be restarted at the same dose level. If a second dose withholding is required for redevelopment of persistent refractory grade 2 rash, dose can be withheld and then restarted at one dose level lower once rash reaches a grade 1 or lower level. MK2206 re-escalation can be attempted after 4 weeks if in the judgment of the treating physician the patient's side effect profile warrants re-escalation.

6.2 Everolimus

Table 3 Everolimus dose level modification guidelines
Dose level Dose and schedule

Dose Level	Dose and schedule
0 (starting dose)	**10 mg daily**
-1	**5 mg daily**
-2	**5mg every other day**

Table 4 Criteria for dose-modification in case of suspected toxicity and reinitiation of everolimus treatment

Toxicity	Actions
Non-hematological toxicity Grade 2 (pneumonitis – refer to Table 5) Grade 3 (hyperlipidemia*) (pneumonitis – refer to Table 5) Grade 4	 If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt everolimus until recovery to grade ≤1. Then reintroduce everolimus at same dose. If event returns to grade 2, then interrupt everolimus until recovery to grade ≤1. Then reintroduce everolimus at the lower dose level. Interrupt study drug until recovery to grade ≤1. Then reintroduce everolimus at the lower dose level. For pneumonitis consider the use of a short course of corticosteroids. Discontinue everolimus.
Hematological toxicity Grade 2 Thrombocytopenia (platelets <75, ≥ 50x10^9/L)	Interrupt study drug until recovery to grade ≤1 (>75 x109/L). Then reintroduce study drug at initial dose. If thrombocytopenia again returns to grade 2, interrupt study drug until recovery to grade ≤1. Then reintroduce study drug at the lower dose level.

Grade 3 Thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt study drug until recovery to grade ≤1 (platelets ≥ 75 x109/L). Then resume study drug at one dose level lower. If grade 3 thrombocytopenia recurs, discontinue study drug.
Grade 4 Thrombocytopenia (platelets < 25x10^9/L)	Discontinue study drug.
Grade 3 Neutropenia (neutrophils <1, ≥0.5x10^9/L)	Interrupt study drug until recovery to grade ≤1 (neutrophils ≥ 1.5 x 109/L). Then resume study drug at the initial dose. If ANC again returns to Grade 3, hold study drug until the ANC ≥ 1.5 x 109/L. Then resume study drug dosing at the lower dose level. Discontinue patient from study therapy for a third episode of grade 3 neutropenia.
Grade 4 Neutropenia (neutrophils < 0.5 x10^9/L)	Interrupt study drug until recovery to grade ≤ 1 (neutrophils ≥ 1.5 x 109/L). Then resume study drug at the lower dose level. If grade 3 or grade 4 neutropenia occurs despite this dose reduction, discontinue study drug.
Grade 3 febrile neutropenia (not life-threatening)	Interrupt study drug until resolution of fever and neutropenia to grade ≤ 1. Hold further study drug until the ANC ≥ 1,500/mm3 and fever has resolved. Then resume study drug at the lower dose level. If febrile neutropenia recurs, discontinue study drug.
Grade 4 febrile neutropenia (life-threatening)	Discontinue study drug.
Any hematological or non-hematological toxicity requiring interruption for ≥ 4 weeks	Discontinue study drug.

* Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies.

Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers due to study drug should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with study drug as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), use conservative measures such as **non-alcoholic mouth wash or salt water (0.9%) mouth wash** several times a day until resolution.
2. For more severe toxicity (Grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are **topical analgesic**

mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride,menthol, or phenol) with or without **topical corticosteroids,** such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of metabolism of study drugs, thereby leading to higher drug level exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed. Note: Stomatitis/oral mucositis should be appropriately graded using the functional grading given on the NCI-CTC for adverse events, version 4.0.

Management of hyperlipidemia and hyperglycemia
Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 hypercholesterolemia (> 300 mg/dL or 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) should be treated with a 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitor (e.g., atorvastatin, pravastatin) or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Grade 3 **hyperglycemia** has been observed in patients receiving everolimus therapy. It is suggested that optimal glucose control should be achieved before starting a patient on everolimus and should be monitored during everolimus therapy.

Table 5 - Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
Grade 1	CT scans with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat chest x-ray/CT scan every 2 Cycles until return to baseline.	No specific therapy is required	Administer 100% of everolimus dose.
Grade 2	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Consider bronchoscopy *	Symptomatic only. Prescribe corticosteroids if cough is troublesome.	Hold everolimus dose until recovery to ≤ Grade 1. Restart everolimus at a reduced dose (only if patient recovers to Grade 1 within 3 weeks and only if the patient shows evidence of clinical benefit from the agent) Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 3	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Hold treatment until recovery to ≤ Grade 1. May restart protocol treatment within 3 weeks at a reduced dose (by one level) if evidence of clinical benefit. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 within 3 weeks.
Grade 4	CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to baseline. Bronchoscopy is recommended *.	Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.	Discontinue treatment.

*A bronchoscopy with biopsy and/or bronchoalveolar lavage is recommended.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited (via CTEP-AERS) reporting in addition to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

7.1.1 CAEPR for MK-2206

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MK-2206 (NSC 749607)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 245 patients.* Below is the CAEPR for MK-2206.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, June 16, 2015[1]

Adverse Events with Possible Relationship to MK-2206 (CTCAE 4.0 Term) [n= 245]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
	Sinus bradycardia		***Sinus bradycardia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 3)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Creatinine increased		
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 2)***
	Hemoglobin increased		
	Investigations - Other (eosinophilia)		***Investigations - Other (eosinophilia) (Gr 2)***
	Investigations - Other (insulin c-peptide increased)		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***

Adverse Events with Possible Relationship to MK-2206 (CTCAE 4.0 Term) [n= 245]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
	Hypocalcemia		
	Hyponatremia		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		***Headache (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		***Dry skin (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on MK-2206 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-2206 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis; Hemolytic uremic syndrome; Leukocytosis
CARDIAC DISORDERS - Atrioventricular block complete; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vertigo
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blepharitis); Eye disorders - Other (eye swelling); Eye disorders - Other (foreign body sensation in eyes); Eye disorders - Other (iritis); Eye disorders - Other (mydriasis); Eye disorders - Other (visual acuity reduced); Eye pain; Floaters; Keratitis; Photophobia; Retinal detachment; Uveitis
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Cheilitis; Colonic perforation; Constipation; Dry mouth; Dyspepsia; Dysphagia; Gastritis; Gastrointestinal disorders - Other (oropharyngeal pain); Lip pain; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Flu like symptoms; General disorders and administration site conditions - Other (throat tightness); Injection site reaction; Irritability; Localized edema; Non-cardiac chest pain; Pain
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (herpetic vesicular rash [due to herpes zoster infection]); Infections and infestations - Other (oral herpes); Lung infection; Nail infection; Paronychia; Pharyngitis; Rhinitis infective; Sepsis; Sinusitis; Skin infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; INR increased; Investigations - Other (blood LDH increased); Investigations - Other (hyperinsulinemia); Lipase increased; Serum amylase increased; Weight gain

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Generalized muscle weakness; Myalgia; Neck pain; Pain in extremity
NERVOUS SYSTEM DISORDERS - Akathisia; Dizziness; Encephalopathy; Lethargy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (renal tubular necrosis); Renal and urinary disorders - Other (glucose urine present); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Gynecomastia; Vaginal hemorrhage; Vaginal perforation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchial obstruction; Cough; Dyspnea; Epistaxis; Hypoxia; Pneumonitis; Pulmonary edema; Respiratory failure; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Erythroderma; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (skin irritation); Stevens-Johnson syndrome; Urticaria
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Thromboembolic event

Note: MK-2206 in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.2 CAEPR for Everolimus (RAD-001, NSC 733504)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Everolimus (RAD-001, NSC 733504)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3033 patients.* Below is the CAEPR for Everolimus (RAD-001).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, July 10, 2017[1]

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Constipation		
Diarrhea[2]			***Diarrhea[2] (Gr 2)***
Mucositis oral[3]			***Mucositis oral[3] (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Cholesterol high		***Cholesterol high (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hyperglycemia[6]		***Hyperglycemia[6] (Gr 2)***
	Hypertriglyceridemia		***Hypertriglyceridemia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dysgeusia		
	Headache		***Headache (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 2)***
	Pneumonitis[7]		

Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Pruritus		
Rash maculo-papular			***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (angioedema)[8]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Includes diarrhea, enteritis, enterocolitis, colitis, defecation urgency, and steatorrhea.

[3]Includes stomatitis, aphthous stomatitis, gingival pain/swelling/ulceration, glossitis, glossodynia, lip ulceration, mouth ulceration, tongue ulceration, and mucosal inflammation.

[4]Infection includes all 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[5]Everolimus delays wound healing and increases the occurrence of wound-related complications like wound dehiscence, wound infection, incisional hernia, lymphocele, and seroma.

[6]Hyperglycemia may result in either exacerbation of or development new onset diabetes mellitus.

[7]Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease.

[8]Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema
[9] Includes agitation, anxiety, panic attack, aggression, abnormal behavior, and obesessive compulsive disorder.
Adverse events reported on Everolimus (RAD-001) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Everolimus (RAD-001) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (thrombotic microangiopathy)
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (myocardial abnormality); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
ENDOCRINE DISORDERS - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels); Endocrine disorders - Other (low testosterone); Hypothyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Keratitis
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Hemorrhoids; Intra-abdominal hemorrhage; Oral pain; Pancreatitis; Periodontal disease; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema trunk; Flu like symptoms; Irritability; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)

IMMUNE SYSTEM DISORDERS - Allergic reaction
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CPK increased; GGT increased; INR increased; Investigations - Other (bicarbonate decreased); Investigations - Other (increased lactate dehydrogenase); Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia)
METABOLISM AND NUTRITION DISORDERS - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia); Metabolism and nutrition disorders - Other (hyperlipidemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)
NERVOUS SYSTEM DISORDERS - Dizziness; Encephalopathy; Hydrocephalus; Lethargy; Paresthesia
PSYCHIATRIC DISORDERS - Agitation; Anxiety[8]; Delirium; Depression; Insomnia; Mania
RENAL AND URINARY DISORDERS - Hematuria; Proteinuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Dysmenorrhea; Genital edema; Irregular menstruation; Menorrhagia; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (rales); Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea); Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema)[9]; Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration
VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; Vascular disorders - Other (acute bowel ischemia); Vascular disorders - Other (hemorrhage)

Note: Everolimus (RAD-001) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site **http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm**.

- **'Expectedness'**: **AEs can be 'Unexpected'** or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1.1).

- **Attribution** of the AE:
- 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.

- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 7.3.3).

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

7.3.2 Multi-Institutional Studies

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Phase 2 and 3 Trials Expedited Reporting Guidelines – CTEP-AERS

Reporting Requirements for Adverse Events that occur within 30 Days1 of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	**Grade 2**	**Grade 2**	**Grade 3**		**Grade 3**		**Grades 4 & 5[2]**	**Grades 4 & 5[2]**
				Unexpected		**Expected**			
	Unexpected and Expected	**Unex-pected**	**Expected**	**with Hospitali-zation**	**without Hospitali-zation**	**with Hospitali-zation**	**without Hospitali-zation**	**Unex-pected**	**Expected**
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: A death on study require <u>both</u> routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within <u>24 hours</u> of learning of the event followed by a complete CTEP-AERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected.

  - Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Pregnancy loss Example:

Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero
- Any pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.
- A pregnancy loss should NOT be reported as a Grade 5 event under
- the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEPAERS
- recognizes this event as a patient death.

Death neonatal Example:

A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the

General disorders and administration SOC.

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Secondary AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols via CTEP-AERS. Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

8. PHARMACEUTICAL INFORMATION

8.1 CTEP-Supplied Investigational Agents

8.1.1 *MK-2206 (NSC 749607)*

Chemical Name or Amino Acid Sequence: 8-[4-(1-aminocyclobutyl)phenyl]-9-phenyl-1,2,4-triazolo[3,4-*f*]-1,6-naphthyridin-3(2*H*)-one mono-hydrochloride salt

Other Names: N/A

Classification: Akt inhibitor

Molecular Formula: $C_{25}H_{22}N_5OCl$ **M.W.:** 443.93

Approximate Solubility: Soluble in water (7.54 mg/mL; pH = 6.) but less soluble in acetonitrile (1.4 mg/mL) and ethanol (2 mg/mL). Its mono-hydrochloride salt is slightly hygroscopic (absorbs 1.9 wt% water up to 95% relative humidity).

Mode of Action: The PI3K/AKT pathway is downstream of EGFR, HER2, IGF1R, and cMet, and is a suspected driver of tumor progression in most cancers. Overexpression or activating mutations in TKRs, PI3K and RAS, inactivation of the tumor suppressor PTEN, or amplification or mutation of AKT can activate AKT protein kinase in most human carcinomas. It is believed that AKT inhibitors that target the pathway downstream of the most common mutations have broader utility and provide less resistance in the clinic.

Description: A highly selective non-ATP competitive allosteric AKT inhibitor.

How Supplied: MK-2206 tablets are supplied by Merck and distributed by the DCTD, NCI. The 5 mg and 25 mg bottles contain 10 and 20 tablets, respectively. The 200-mg

bottles contain 5 tablets each. The pharmaceutical collaborator does not have stability data to support repackaging MK-2206 tablets in any container other than what is provided.

The white film (Opadry® 20A18273) coating consists of hydroxypropyl cellulose, hydroxypropyl methylcellulose and titanium dioxide.

Inactive ingredients consist of microcrystalline cellulose (Avicel PH102®), calcium phosphate dibasic anhydrous (ATAB®), crosscarmellose sodium, and magnesium stearate.

Storage: Store intact bottles at room temperature, not to exceed 30ºC.

Stability: Shelf life of MK-2206 is up to 24 months.

Route*(s)* of Administration: Oral

Method of Administration: Take MK-2206 tablets 2 hours before or after food.

Potential Drug Interactions: MK-2206 is a substrate for P-glycoprotein (P-gp) mediated transport.

Patient Care Implications: In acute overdose, use activated charcoal to reduce the absorption of MK-2206. If additional measures are needed, consider emptying the stomach. Administer specific medical therapy as clinically appropriate.

8.1.2 *Agent Ordering*

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability call (240) 276-6575 Monday through Friday between

8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.3 *Agent Accountability*

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

8.2 Commercial Agent: Everolimus

Refer to the FDA-approved product package insert for comprehensive information.

How Supplied: Everolimus is commercially available as 5 mg and 10 mg tables in blisters of 28 tablets. Each carton contains 4 blister cards of 7 tablets each.

Storage: Store everolimus tablets at 25° C (77°F); excursions permitted between 15°–30°C (59°–86°F). Store in the original container, protect from light and moisture.

Stability: Everolimus tablets are stable, when stored as indicated, until the expiration date identified on the package label.

Route of Administration: Oral

9. CORRELATIVE/SPECIAL STUDIES

As described in Section 2.5, tissue microarrays (TMAs), cytokine-angiogenesis factor (CAF) analysis and virtual karyotyping will be performed on tissue and blood samples from patients on this study.

The tissue microarrays will be performed at the University of Texas M. D. Anderson Cancer Center (UTMDACC) in the Genitourinary Center core facility. The CAF analysis will be performed in collaboration with Dr. Amado Zurita and Dr. John Heymach at UTMDACC. The virtual karyotyping will be perfomed at UTMDACC core facility.

For details on sample collection, shipment and analysis, refer to the following appendices:

Appendix G: Virtual karyotype analysis
Appendix H: TMA analysis
Appendix I: CAF analysis

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 2 week prior to start of protocol therapy. Scans and x-rays must be done ≤ 4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Screening	Every 4 weeks[k]	Every 8 Weeks[k]	Early Withdrawal/ End of Study
Informed consent	x[a]			
Medical history	x[b]	x		
Physical exam	x[b]	x		x
Vital signs	x[b]	x		x
Performance status	x[b]	x		
Weight	x[b]	x		x
Height	x[b]			
Concurrent meds	x[b]	x		x
CBC w/diff, plts	x[b]	x		x
Serum chemistry	x[b, e]	x[e, f]		x
HGB A1C	x[b]			
Fasting Glucose, Fasting Lipid Panel, and triglycerides	x[b]	x[i]	x[i]	
B-HCG	x[b, c]			
PT/PTT	x[b]	x		x
T4, TSH	x[b]	x		x
Amylase, Lipase	x[b]	x[h]		
Hemoglobin A1C		x[g]		
Urinalysis	x[b]	x		x
EKG	x[a]	x[j]	x	x
Adverse event evaluation	<----------			---------->
Chest X-Ray	x[a]		x	x
CT Scan Chest/Abdomen	x[a]		x	x

MRI or CT of Brain	x[a]		x	x
Bone Scan	x[a]		x	x
Other Radiological Scans	x[a, d]		x	x
Optional Correlative Blood	x	x		x
Optional Archived Tissue Collection	x			

a Within 4 weeks of study entry

b Within 2 weeks of study entry

c Within 24 hours of study entry

d MRI spine should be obtained if suspicion of evolving cored or nerve root compression. A skeletal survey and/or a CT scan of the pelvis will be ordered as clinically indicated.

e Serum chemistry will include total protein, albumin, alkaline phosphatase, AST and/or ALT, calcium, LDH, total bilirubin, BUN, creatinine, phosphorus, uric acid, sodium, potassium, chloride, carbon dioxide, glucose, and magnesium.

f Serum glucose testing will be done every 7 days for the first cycle of treatment for those patients receiving MK-2206. This can be done at a local physician's office.

g Only for patients on MK-2206 who require anti-hyperglycemic medication.

h Repeated only if indicated

i Fasting glucose and lipid panel will be done every 4 weeks for the first 8 weeks and every 8 weeks thereafter.

j Course 1 Day 1 post-treatment (only for patients randomized to MK-2206).

k Patients who are progression free after 1 year may have the following performed every 12 weeks +/- 7days

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every _eight weeks. In addition to a baseline scan, confirmatory scans should also be obtained *not* less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009].

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with MK-2206.

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) as $\geq$ 20 mm by chest x-ray, as $\geq$10 mm with CT scan, or $\geq$10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be $\geq$15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with $\geqslant$ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

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 by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions

(longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 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 4 weeks 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor

evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

d. AKT inhibition inhibits cellular membrane glucose transporters, so that alterations in FDG uptake may demonstrate a pharmacodynamic activity of MK-2206, but may not correlate with antitumor activity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: 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. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall

disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 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 patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients 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.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 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 progressive 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, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from randomization to time of progression or death, whichever occurs first.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP-AERS, must be reported via CDUS.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CDUS data and/or data forms to the

Coordinating Center quarterly to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.).

The Coordinating Center is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (Study Coordinator) and the procedures for auditing are presented in Appendix B.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (*PIO@ctep.nci.nih.gov*) except for Group studies.

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, Agent-CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as a "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the

access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used, and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open-label, multi-center, randomized phase II study. Patients will be randomized using 2:1 ratio to receive either MK2206 or everolimus. The primary endpoint of the study is progression-free survival (PFS), where an event is defined as either disease progression or death. The anticipated median PFS is 4.9 months and 8.2 months for the everolimus and MK2206 arms, respectively. The secondary endpoints include safety, overall survival (OS), overall response rate (ORR) and time to failure (TTF). For the primary endpoint, one interim futility analysis will be performed when a total of 38 events have occurred. The O'Brien-Fleming stopping boundaries using Lan-DeMets spending function will be used for early rejection of H1 (futility boundaries). At the interim look, if the nominal critical point (Z-scale) is less than 0.051, we will terminate trial, reject H1, and conclude that MK2206 has no significant effect on improving PFS. Assuming that the alternative hypothesis holds and trial is continued to completion without interim analysis, 105 patients with 75 events provide 81% power to reject null hypothesis. Since this trial has one interim analysis, 105 patients with 75 events provide 80% power to reject null hypothesis. Please see the detail information for power calculation in section 13.2 sample size / power calculation.

Additionally, toxicity will be monitored for the MK2206 arm. For the purpose of implementing this safety rule, toxicity will be defined as Grade 3 or greater toxicity that requires treatment discontinuation. The method of Thall, Simon and Estey (1995, 1996) will be used. Denoting the probability of toxicity by p, the trial will be stopped early if for the MK2206 arm, Prob(p > 0.30|data) > .93. That is, if at any time during the trial, we determine that there is more than 93% chance that the toxicity rate for the MK2206 arm is greater than 30%, we will stop the trial. Assuming a beta(0.6, .1.4) priori for p, the above decision criterion implies that we will stop the trial if [# patients with toxicities in the MK2206 arm]/ [# patients evaluated in the MK2206 arm] >/= 3/4, 4/5, 5/7, 6/9, 7/12, 8/14, 9/17, 10/20, 11/22, 12/25, 13/28, 14/30, 15/33, 16/36, 17/39, 18/42, 19/44, 20/47, 21/50, 22/53, 23/56, 24/59, 25/62, 26/65, 27/68. The operating characteristics for this toxicity monitoring rule are illustrated in Table 6.

Table 6. Operating Characteristics for Toxicity Monitoring Rule.

True toxicity rate	Prob (stop the trial early)	Sample Size 25th, 50th and 75th percentiles

0.10	0.005	70, 70, 70
0.20	0.047	70, 70, 70
0.30	0.288	41, 70, 70
0.40	0.784	8, 24, 61
0.50	0.990	4, 10, 19

This study will be monitored by the MDACC DSMB.

13.2 Sample Size/ Power Calculation

Assuming that the median progression-free survival (PFS) is 4.9 months and 8.2 months for the everolimus and MK2206 arm, respectively and patients will be randomized with 2:1 ratio into the MK2206 arm and the everolimus arm, then with a total of 75 events (i.e., disease progression or death), we will have an 80% power to detect such a 67% increase in median PFS using one-sided log-rank test and at a 0.10 significance level. The total number of patients to be enrolled will be 105, with 35 on the everolimus arm and 70 on the MK2206 arm. The above calculation also assumes an accrual rate of 4 patients per month, thus it will take 26.3 months to accrue all 105 patients. The maximum study duration will be around 29 months, which include patients' accrual period and a follow-up period. East5 software was used for the sample size/power calculation.

13.3 Stratification Factors

Patients will be stratified by the MSKCC criteria (Appendix J) and type of prior therapy before being randomized into the MK2206 arm and the everolimus arm using a ratio of 2:1. The stratified randomization will be conducted through the Clinical Trial Conduct (CTC) website (https://biostatistics.mdanderson.org/ClinicalTrialConduct) maintained by the Department of Biostatistics of the University of Texas, M. D. Anderson Cancer Center.

13.4 Statistical Analysis Plan

The primary endpoint, progression-free survival (PFS), is defined as the time interval between date of treatment and date of disease progression, date of death or last follow-up date, whichever occurred first. The probability of PFS be estimated using the Kaplan-Meier method and will be compared between the two treatment arms using stratified log-rank test. Patients' safety data will be summarized by treatment arm, category, severity and relevance.

For secondary analyses, the Kaplan-Meier method will be used to estimate overall survival (OS) and time to failure (TTF), and stratified log-rank test will be used to compare between the two treatment arms. The OS is defined as the time interval between the date of treatment and the date of death or last follow-up, whichever occurred first. The TTF is defined as the time interval between the date of treatment and the date of disease progression, date of death, date of treatment discontinuation due to severe toxicity or last follow-up date, whichever occurred first. Overall response (OR) is defined as CR+PR and logistic regression model will be fit to assess the effect of treatment on the rate of OR.

Since the correlative studies being performed are by nature exploratory, and have not been

performed before in patients with RCC receiving mTOR inhibitors or AKT inhibitors, powering of these endpoints is not possible. Clinical benefit is defined as CR+PR+SD and again, we will fit logistic regression models to assess the effects of treatment, AKT activation, circulating cytokines and angiogenic factors, and karyotype on clinical benefit. The interaction effect between treatment and these exploratory factors will also be evaluated.

For virtual karyotyping, technique specific statistical analyses are outlined in Appendix G.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with MK-2206.

13.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

REFERENCES

1 Altomare, D.A., and J.R. Testa. (2005). Perturbations of the AKT signaling pathway in human cancer. *Oncogene*. 24:7455-7464.

2 Cejka, D., M. Preusser, A. Woehrer*, et al.* (2008). Everolimus (RAD001) and anti-angiogenic cyclophosphamide show long-term control of gastric cancer growth in vivo. *Cancer Biol Ther*. 7:1377-1385.

3 Engelman, J.A., L. Chen, X. Tan*, et al.* (2008). Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat Med*. 14:1351-1356.

4 Fry, M.J. (2001). Phosphoinositide 3-kinase signalling in breast cancer: how big a role might it play? *Breast Cancer Research*. 3:304-312.

5 Han, Z., K. Wu, H. Shen*, et al.* (2008). Akt1/protein Kinase Bα is Involved in Gastric Cancer Progression and Cell Proliferation. *Digest Dis and Sci*. 53:1801-1810.

6 Hennessy, B.T., D.L. Smith, P.T. Ram*, et al.* (2005). Exploiting the PI3K/AKT pathway for cancer drug discovery. *Nat Rev Drug Discov*. 4:988-1004.

7 Hu, L., J. Hofmann, Y. Lu*, et al.* (2002). Inhibition of phosphatidylinositol 3'-kinase increases efficacy of paclitaxel in in vitro and in vivo ovarian cancer models. *Cancer Res*. 62:1087-1092.

8 Investigator's Brochure. (2008). MK-2206. *Merck & Co, Inc*.

9 Kawauchi, K., T. Ogasawara, M. Yasuyama*, et al.* (2009). The PI3K/Akt pathway as a target in the treatment of hematologic malignancies. *Anti-cancer Ag Medicin Chem*. 9:550.

10 Kinkade, C.W., M. Castillo-Martin, A. Puzio-Kuter*, et al.* (2008). Targeting AKT/mTOR and ERK MAPK signaling inhibits hormone-refractory prostate cancer in a preclinical mouse model. *J Clin Invest*. 118:3051.

11 Kirkegaard, T., C.J. Witton, L.M. McGlynn*, et al.* (2005). AKT activation predicts outcome in breast cancer patients treated with tamoxifen. *J Pathol*. 207:139-146.

12 Konecny, G.E., M.D. Pegram, N. Venkatesan*, et al.* (2006). Activity of the Dual Kinase Inhibitor Lapatinib (GW572016) against HER-2-Overexpressing and Trastuzumab-Treated Breast Cancer Cells. *Cancer Res*. 66:1630-1639.

13 Kornblau, S.M., M. Womble, Y.H. Qiu*, et al.* (2006). Simultaneous activation of multiple signal transduction pathways confers poor prognosis in acute myelogenous leukemia. *Blood*. 108:2358-2365.

14 Lee, J.W., Y.H. Soung, S.Y. Kim*, et al.* (2004). PIK3CA gene is frequently mutated in breast carcinomas and hepatocellular carcinomas. *Oncogene*. 24:1477-1480.

15 Min, Y.H., J.I. Eom, J.W. Cheong*, et al.* (2003). Constitutive phosphorylation of Akt//PKB protein in acute myeloid leukemia: its significance as a prognostic variable. *Leukemia*. 17:995-997.

16 Nakanishi, K., M. Sakamoto, S. Yamasaki*, et al.* (2005). Akt phosphorylation is a risk factor for early disease recurrence and poor prognosis in hepatocellular carcinoma. *Cancer*. 103:307-312.

17 Nakayama, K., N. Nakayama, R.J. Kurman*, et al.* (2006). Sequence mutations and amplification of PIK3CA and AKT2 genes in purified ovarian serous neoplasms. *Cancer Biol Ther*. 5:779-785.

18 Oki, E., B. Baba, E. Tokunaga*, et al.* (2005). Akt phosphorylation associates with LOH of PTEN and leads to chemoresistance for gastric cancer. *Int J Cancer*. 117:376-380.

19 Oza, A.M. (2006). Molecular correlates associated with a phase II study of temsirolimus (CCI-779) in patients with metastatic or recurrent endometrial cancer–NCIC IND 160. *J Clin Oncol*. 24:A3003.

20 Rahman, M.A., D.K. Ioannis, O. Takashi*, et al.* (2002). Impact of PTEN expression on the outcome of hepatitis C virus-positive cirrhotic hepatocellular carcinoma patients: Possible relationship with COX II and inducible nitric oxide synthase. *Int J Cancer*. 100:152-157.

21 Saal, L.H., K. Holm, M. Maurer*, et al.* (2005). PIK3CA mutations correlate with hormone receptors, node metastasis, and ERBB2, and are mutually exclusive with PTEN loss in human breast carcinoma. *Cancer Res*. 65:2554-2559.

22 Salvesen, H.B., S.L. Carter, M. Mannelqvist*, et al.* (2009). Integrated genomic profiling of endometrial carcinoma associates aggressive tumors with indicators of PI3 kinase activation. *PNAS*. 106:4834-4839.

23 Shayesteh, L., Y. Lu, W.L. Kuo*, et al.* (1999). PIK3CA is implicated as an oncogene in ovarian cancer. *Nat Genet*. 21:99-102.

24 Shoman, N., S. Klassen, A. McFadden*, et al.* (2005). Reduced PTEN expression predicts relapse in patients with breast carcinoma treated by tamoxifen. *Mod Pathol*. 18:250-259.

25 Sosman, J.A., I. Puzanov, and M.B. Atkins. (2007). Opportunities and Obstacles to Combination Targeted Therapy in Renal Cell Cancer. *Clin Cancer Res*. 13:764s-769.

26 St-Germain, M.-E., V. Gagnon, S. Parent, and E. Asselin. (2004). Regulation of COX-2 protein expression by Akt in endometrial cancer cells is mediated through NF-kappaB/IkappaB pathway. *Mol Cancer*. 3:7.

27 Staal, S.P. (1987). Molecular cloning of the akt oncogene and its human homologues AKT1 and AKT2: amplification of AKT1 in a primary human gastric adenocarcinoma. *PNAS.* 84:5034-5037.

28 Steelman, L.S., K.M. Stadelman, W.H. Chappell*, et al.* (2008). Akt as a therapeutic target in cancer. *Exp Opin Ther Targ*. 12:1139-1165.

29 Tanno, S., S. Tanno, Y. Mitsuuchi*, et al.* (2001). AKT activation up-regulates insulin-like growth factor I receptor expression and promotes invasiveness of human pancreatic cancer cells. *Cancer Res*. 61:589-593.

30 Testa, J.R., and A. Bellacosa. (2001). AKT plays a central role in tumorigenesis. *PNAS.* 98:10983-10985.

31 Uddin, S., A.R. Hussain, A.K. Siraj*, et al.* (2006). Role of phosphatidylinositol 3'-kinase/AKT pathway in diffuse large B-cell lymphoma survival. *Blood*. 108:4178-4186.

32 Vestey, S.B., C. Sen, C.J. Calder*, et al.* (2005). Activated Akt expression in breast cancer: correlation with p53, Hdm2 and patient outcome. *Eur J Cancer*. 41:1017-1025.

33 Wolf, J., and B.M. Slomovitz. (2005). Novel biologic therapies for the treatment of endometrial cancer. *Int J Gyn Cancer*. 15:411-411

34 Thall, PF, Simon, R, Estey, EH: Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. *Statistics in Medicine* 14:357-379, 1995.

35 Thall, PF, Simon, R, Estey, EH: New statistical strategy for monitoring safety and efficacy in single-arm clinical trials. *J. Clinical Oncology* 14:296-303, 1996.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of AE reports. There are two options for AE reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit AE reports to the Protocol Chair for timely review.
- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how AEs will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX C LIST OF CYP3A4 INHIBITORS AND INDUCERS

CYP3A4 Inhibitors

Acetominophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan	Progesterone
Amiodarone	Diltiazem	Lovastatin	Propofol
Amlodipine	Disulfiram	Mefloquine	Propoxyphene
Amprenavir	Docetaxel	Mestranol	Quinidine
Anastrozole	Doxorubicin	Methadone	Quinine
Aprepitant	Doxycycline	Methimazole	Quinupristin
Atazanavir	Drospirenone	Methoxsalen	Rabeprazole
Atorvastatin	Efavirenz	Methylprednisolone	Ranolazine
Azelastine	Enoxacin	Metronidazole	Risperidone
Azithromycin	Entacapone	Miconazole	Ritonavir
Betamethasone	Ergotamine	Midazolam	Saquinavir
Bortezomib	Erythromycin	Mifepristone	Selegiline
Bromocriptine	Ethinyl estradiol	Mirtazapine	Sertraline
Caffeine	Etoposide	Mitoxantrone	Sildenafil
Cerivastatin	Felodipine	Modafinil	Sirolimus
Chloramphenicol	Fentanyl	Nefazodone	Sulconazole
Chlorzoxazone	Fluconazole	Nelfinavir	Tacrolimus
Cimetidine	Fluoxetine	Nevirapine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nicardipine	Telithromycin
Cisapride	Fluvoxamine	Nifedipine	Teniposide
Clarithromycin	Fosamprenavir	Nisoldipine	Testosterone
Clemastine	Glyburide	Nizatidine	Tetracycline
Clofazimine	Grapefruit juice (2)	Norfloxacin	Ticlopidine
Clotrimazole	Haloperidol	Olanzapine	Tranylcypromine
Clozapine	Hydralazine	Omeprazole	Trazodone
Cocaine	Ifosfamide	Orphenadrine	Troleandomycin
Conivaptan	Imatinib	Oxybutynin	Valproic acid
Cyclophosphamide	Indinavir	Paroxetine	Venlafaxine
Cyclosporine	Irbesartan	Pentamidine	Verapamil
Danazol	Isoniazid	Pergolide	Vinblastine
Dasatinib (1)	Isradipine	Phencyclidine	Vincristine
Delavirdine	Itraconazole	Pilocarpine	Vinorelbine
Desipramine	Ketoconazole	Pimozide	Voriconazole
Dexmedetomidine	Lansoprazole	Pravastatin	Zafirlukast
Diazepam	Lidocaine	Prednisolone	Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

When MK-2206 is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of MK-2206 is the potential outcome. The co-administration of 'inducers' would potentially lower plasma MK-2206 concentrations.

Everolimus is a substrate of CYP3A4 and a substrate and inhibitor of P-glycoprotein. Everolimus metabolism may be affected by drugs that are substrates or strong inhibitors or inducers of CYP3A4 or P-glycoprotein.

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15TH ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.
Only major substrates and effective inducers are listed.

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

(1) Investigator's Brochure: MK-2206. Merck. January 2009.

(2) Malhotra et al*. (2001). Clin Pharmacol Ther. 69:14-23.*

(3) Mathijssen et al*. (2002). J Natl Cancer Inst. 94:1247-1249.*
Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329.

Updated on May 1, 2007

APPENDIX D MEDICATIONS THAT MAY CAUSE QTC PROLONGATION

The following table presents a list of drugs that may prolong the QTc. These drugs are prohibited during the study. MK-2206 may be administered after a 5 half-life washout period elapses following the use of these drugs. Washout period is based on roughly 5 half-lives and rounded to a convenient interval.

Compound	Compound Half Life	Possible Washout Period - Hours	Possible Washout Period - Days
Alfuzocin	~10 hours		7
Amantadine	17 +/- 4 hours (10-25)		4
Amiodarone (cordarone)	58 days (15-142) 36 days (active metabolite)		180
Amitriptyline*	> 24 hours, wide interpatient variability		
Arsenic trioxide	Not characterized		
Azithromycin	40 hours		
Bepridil	42 hr (26-64)		10
Chloral hydrate	Readily converted to Trichloroethanol (active metabolite $T_{1/2}$=7-10 hour)	48	
Chloroquine	Prolonged (days to weeks)		
Chlorpromazine	30 +/- 7 hours		7
Cisapride	6 – 12 hour, up to 20 hour	60	
Clarithromycin	Non linear PK3-4 hr (250mg Q12) 5-7 hr (500mg Q12)	36	
Cloroquine	6 to 60 days; mean 20 days		
Desipramine*	> 24 hours, wide interpatient variability		
Disopyramide	6.7 hr (4-10)	36	
Dofetilide	10 hr	48	
Dolesetron	8.1 hr		
Domperidone	7-8 hr	48	
Doxepin*	> 24 hours, wide interpatient variability		
Droperidol	2.2 hours	10	
Erythromycin	* Each salt form has different Half life*		
Felbamate	20-23 hr		5
Flecainide	20 hr (12-27)		5
Foscarnet	87.5+/-41.8 hours *distribution and release from bone*		20
Fosphenytoin	12-29 hr		6
Gatifloxacin	7-14 hr	48	
Gemifloxacin	7 hours	48	
Grepafloxacin	16 hr		3
Halofantrine	6-10 days (variable among individual)		45
Haloperidol	18 +/-5 hr		5
Ibutilide	6 hours (2-12) * variable among subject*	36	
Imipramine*	> 24 hours, wide interpatient variability		
Indapamide	14 hours (biphasic elimination)		3
Isradipine	8 hours (multiple metabolites)	48	
Levofloxacin	6-8 hours	48	
Levomethadyl	Multiple compartment PK with active metabolite 2.6 day for LAAM, 2 day for nor-LAAM, 4 day for dinor-LAAM		20

Lithium	24 hour (10-50)		7
Compound	**Compound Half Life**	**Possible Washout Period - Hours**	**Possible Washout Period - Days**
Mesoridazine	24-48 hours (animal study)		10
Methadone	15-30 hours		7
Moexipril/HCTZ	2-9 hour (include active metabolite) for moexipril; 5.6-14.8 hours for HCTZ	48	
Moxifloxacin	12 +/-1.3 hours	72	
Naratriptan	6 hours	36	
Nicardipine	~ 2 hour post IV infusion	12	
Nortriptyline*	> 24 hours, wide interpatient variability		
Octreotide	1.7 hours	12	
Ofloxacin	5 to 7.5 hours		2
Ondansetron	4 hours (IV/IM); 3 hours (PO)		1 to 3
Pentamidine	6.4+/-1.3 hours	36	
Pimozide	55 hours		10
Procainamide	3-4 hour for PA and NAPA (active metabolite)	24	
Protiptyline*	> 24 hours, wide interpatient variability		
Quetiapine	6 hours	36	
Quinidine	6-8 hours in adult; 3-4 hours in children	36	
Quinine	4-5 hours		
Risperidone	3-20 hours (extensive to poor metabolizer) 9-hydroxyrisperidone (active metabolite) T ½ =21-30 hours (extensive to poor metabolizer)		4
Salmeterol	5.5 hours (only one datum)	36	
Sotalol	12 hours	72	
Sparfloxacin	20 hours (16-30)		4
Sumatriptan	2.5 hours	12	
Tacrolimus	~34 hours in healthy; ~19 hours in Kidney transplant		7
Tamoxifen	5-7 days (biphasic)		30
Telithromycin	2-3 hr	24	
Thioridazine	20-40 hours (Phenothiazines)		7
Tizanidine	2.5 hours	12	
Vardenifil	4 to 5 hours		
Venlaflaxine	5 +/-2 hours for parent comp. 11+-2 hours for OVD (active metabolite)	60	
Voriconizole	6 hours; dose dependent		
Ziprasidone	7 hr	36	
Zolmitriptan	2.8-3.7 hours (higher in female)	18	

***** Weakly associated with Torsades de Pointes and/or QT prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in patients without other risk factors (*e.g.*, concomitant QT prolonging drugs, bradycardia, electrolyte disturbances, congenital long QT syndrome, concomitant drugs that inhibit metabolism).

References:

1. **Physician's Desk Reference 2002**
2. **Facts and Comparisons (update to June 2005)**
3. **The Pharmacological Basis of Therapeutics 9th Edition, 1996**

APPENDIX E PATIENT'S MEDICATION DIARY

CTEP-assigned Protocol #_____

Local Protocol # _____

Today's date _____ **Agent: MK-2206**

Patient Name_____(*initials acceptable)* **Patient Study ID**

_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take MK-2206 tablets via mouth once weekly. You should take the tablets 2 hours before or after a meal
   Dose: take ___ mg tablets, ___ mg tablets, and ___ mg tablets.
3. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of MK-2206 tablets when you return for each appointment.

Day	Date	Time of dose	# of tablets taken			Comments
			mg	mg	mg	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
25						
26						
27						
28						

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment
2. Date patient was removed from study
3. Patient's planned total daily dose
4. Total number of tablets taken this month
5. Physician/Nurse/Data Manager's Signature

APPENDIX F PATIENT'S MEDICATION DIARY

CTEP-assigned Protocol #_____

Local Protocol # _____

Today's date _____ **Agent: Everolimus**

Patient Name_____(*initials acceptable)* **Patient Study ID**

_____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle of treatment.
2. You will take Everolimus 10 mg every day at the same time with or without food.
   Dose: take 2 (5 mg tablets) or 1 (10mg tablet)
3. Record the date, the number of tablets of each size of tablet that you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please bring this form and your bottles of MK-2206 tablets when you return for each appointment.

Day	Date	Time of dose	# of tablets taken	Comments
			5 or 10 mg	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Patient's signature _____

Physician's Office will complete this section:

1. Date patient started protocol treatment
2. Date patient was removed from study
3. Patient's planned total daily dose

4. Total number of tablets taken this month
5. Physician/Nurse/Data Manager's Signature

APPENDIX G SNP ANALYSIS

1. **Collection of Specimen(s)**
   If patient consents to optional procedure(s), at least 2 and as many as 5 formalin fixed paraffin embedded blocks from nephrectomy will be acquired from each patient participating in the study. These blocks will be used for TMA analysis and for virtual karyotyping. A detailed laboratory manual will be provided.

2. **Handling of Specimens(s)**
   Specimens need to be kept at ambient temperatures, and reasonable efforts should be undertaken to avoid exposure to temperature extremes. If necessary, samples may be shipped on gel packs to avoid extreme temperatures.

3. **Shipping of Specimen(s)**
   Samples will be batch shipped to the University of Texas M. D. Anderson Cancer Center. All samples will be transported according to applicable IATA regulations.

   Samples will be shipped to:

   Sherie Hodges
   University of Texas M. D. Anderson Cancer Center
   1220 Holcombe Blvd, Room ACB7.2408
   Houston, TX 77030
   Tel 713-563-3173
   Fax 713-563-0572
   GuClinicalResearchLab@mdanderson.org

   Once received, samples will be distributed to UTMDACC core facility for analysis.

4. **Site(s) Performing Correlative Study**
   The analysis will be performed at UTMDACC core facility.

5. **Methods in brief:** An area with at least 80% tumor content will be marked on the H&E slide from paraffin embedded patient tissue, and this area will be manually microdissected from unstained slides. DNA extractions from the microdissected tissue will be performed with the Qiagen DNA Easy Kit (Qiagen, Valencia, CA) with modifications for FFPE tissue. DNA will be analyzed for chromosome copy number (CCN) changes and loss of heterozygosity (LOH) with the Affymetrix 250K Nsp SNP Genotyping arrays (Affy250KNsp) following a modified protocol.

   Data acquired from the Affymetrix GeneChip Operating System v4.0 (GCOS) will be analyzed using Affymetrix's Genotyping Console v2.1. The quality control parameters for each sample will be signal detection rate (the percentage of features in the array that show adequate fluorescence intensity) and the SNP call rate (rate of successful allele identification). LOH and copy number estimates will be obtained using a publicly available analysis package: Copy Number Analyzer for Affymetrix GeneChip arrays (CNAG v3.3).

Chromosomal gains and losses will be determined by the copy number estimates assigned by the hidden Markov model (HMM) in CNAG. LOH will be determined based on the LOH likelihood score as determined with CNAG with a threshold likelihood of 12. Extent and boundaries of the chromosomal lesions will be recorded for each lesion in all tumor samples.

6. **Statistical Analysis:** Univariate and multivariate Cox proportional hazards regression will be performed to model the effects of various chromosomal abnormalities, nuclear grade, pathologic stage, and clinical outcome (PFS, OS). Kaplan-Meier analysis and Cox regression will be performed using Stata 10 (College Station, TX).

   Classification analysis will also be performed to identify profiles of chromosomal abnormalities that predict progression and death. Chromosomal abnormalities that are informative for classification will be identified by filtering with a Mahalanobis distance-based greedy plus-take-away-1 heuristic based on a sequential forward-backward stepwise procedure. Performance and area under the curve (AUC) will be compared by using k nearest neighbor, naive Bayes, linear/quadratic/Fisher's discriminant analysis, random forests, linear vector quantization, kernel regression, support vector machines, particle swarm optimization, and artificial neural networks. Random forests will be applied to pre-selected features, so the results will essentially represent the 0.632 bootstrap method.

   For sample size determination, using PASS 2008 (Kaysville, UT) and a one-sided logrank test, for a sample size of N=60 (N=30 in the response group and N=30 in the non-response group), a median PFS of 3.5 months for non-response and 7.5 months for response, the hazard ratio is 2.14 and the power to reject the null hypothesis (one-sided alternative) that response PFS is equal to or more than median non-response PFS is 86.5%. Based on the patients proposed for this study and survival projections, we should be able to attain statistical power > 90%.

7. **Method Performance:** The detection of chromosomal gains and losses in human tumors and other genetic diseases is medically important and has diagnostic, prognostic and therapeutic implications. We have shown that virtual karyotyping with Affymetrix SNP arrays is a robust and reliable alternative for chromosomal analysis of FFPE tissues showing high concordance with frozen tissues (1) and chromosomal analysis by conventional cytogenetics (2), and that it is useful in the identification of chromosomal abnormalities for classification of renal tumors (3). In our experience with more than 400 FFPE samples, the Affymetrix SNP arrays have demonstrated excellent performance and reproducibility with the 250K Nsp platform. We have shown that this technology can reliably detect chromosome copy number, LOH and aUPD in at least 76% of archival FFPE cases. Assay failure was linked to three major factors: older age of the sample, exposure to non-controlled temperature environments and sample institutional origin (4).

1. Lyons-Weiler MA, Hagenkord JM, Sciulli CM, Dhir R, and Monzon FA. Optimization of the Affymetrix GeneChip Mapping 10K 2.0 Assay for Routine Clinical Use on Formalin Fixed Paraffin Embedded Tissues. Diag Mol Path 2008, 17: 3-13. PMID: 18303412
2. Monzon FA, Alvarez K, Gatalica Z, Bridge JA, Nelson M, Kim HJ, Hagenkord JM. Detection of chromosomal aberrations in renal tumors: a comparative study of conventional cytogenetics and

virtual karyotyping with SNP microarrays. Arch Pathol Lab Med. 2009 Dec;133(12):1917-22. PMID: 19961245

3. Kim HJ, Shen SS, Ayala AG, Ro JY, Truong LD, Alvarez K, Bridge JA, Gatalica Z, Gonzalez-Berjon JM & Monzon FA. Virtual-Karyotyping with SNP microarrays in morphologically challenging renal cell neoplasms: a practical and useful diagnostic modality. Am J Surg Pathol. 2009 Sep;33(9):1276-86 PMID: 19461508
4. Alvarez K, Kash SF, Lyons-Weiler MA, Kim HJ, Mathai B, Hagenkord JM and Monzon FA. Reproducibility and Performance of Virtual Karyotyping with SNP Microarrays for the Detection of Chromosomal Imbalances in Formalin-Fixed Paraffin Embedded Tissues. Diagn Mol Pathol (in press)

APPENDIX H TISSUE MICROARRAY (TMA)

1. **Collection of Specimen(s)**
   If patient consents to optional procedure(s), at least 2 and as many as 5 formalin fixed paraffin embedded blocks from nephrectomy will be acquired from each patient participating in the study. These blocks will be used for TMA analysis and for virtual karyotyping. A detailed laboratory manual will be provided.

2. **Handling of Specimens(s)**
   Specimens need to be kept at ambient temperatures, and reasonable efforts should be undertaken to avoid exposure to temperature extremes. If necessary, samples may be shipped on gel packs to avoid extreme temperatures.

3. **Shipping of Specimen(s)**
   Samples will be batch shipped to the University of Texas M. D. Anderson Cancer Center. All samples will be transported according to applicable IATA regulations.

   Samples will be shipped to:

   Sherie Hodges
   University of Texas M. D. Anderson Cancer Center
   1220 Holcombe Blvd, Room ACB7.2408
   Houston, TX 77030
   Tel 713-563-3173
   Fax 713-563-0572
   GuClinicalResearchLab@mdanderson.org

4. **Site(s) Performing Correlative Study**
   The analysis will be performed at the University of Texas M. D. Anderson Cancer Center.

5. **Tissue Microarray Methods**
   Archival paraffin-embedded tissue will be evaluated by the PI or a dedicated pathologist, to select for areas containing viable cells. These areas will be used to construct TMAs. Technical work will be performed by a dedicated technician under the supervision of the PI and the pathologist.

   Arrays will be constructed from 3 sites within each tissue block. The impact of heterogeneity on TMA readout validity has been assessed in other tissue types, with TMAs demonstrating comparable readout quality to standard immunohistochemical slides by using triplicate samples. Using a Beecher TMA device, three 0.6mm cores will be punched into each donor block, and transferred to a custom generated paraffin recipient block. Five micron-thick sections will be placed on a standard glass slide and will be stained using standard immunohistochemical techniques. Five □m TMA sections will be mounted on slides, deparaffinized and hydrated. Section is then blocked and steamed, and appropriate antibody titer is applied overnight, rinsed, and appropriate secondary antibody is applied, followed by more rinses. DAB+ is then applied followed by rinse and DAB+ enhancer. The slide is then

placed in Hematoxylin followed by rinsing and bluing. Section is dehydrated; coverslip is placed.

Arrays created as outlined in will be stained with antibodies against the following proteins and others that may be deemed clinically relevant: Total AKT, AKT^{S473}, AKT^{T308}, p70 S6K, S6, phospho S6, p27, NFkB, mTOR, phospho mTOR. RCC-specific antibody optimization has already been performed by our lab.

6. Sample Analysis

Once staining has been performed, sample quantitation will be performed using an Ariol Image analysis system. Areas of viable tumor will be gated, and necrotic and nonviable regions masked. Acquisition characteristics will be set by the PI and the core facility staff. Percentage involvement of core by stain of interest will be captured as a continuous variable. Averaging of triplicate samples will be performed for each case. In the situation where significant outliers exist, scanning quality will be assessed and samples discarded if variability is due to low sample quality.

7. Statistical Analysis

Statistical Analysis will be performed according to guidelines in Section 13.4 of the protocol.

APPENDIX I CYTOKINE AND ANGIOGENESIS FACTOR ANALYSIS: AMADO ZURITA, COLLABORATOR

1. Collection of Specimen(s)

Venous blood will be collected for Cytokine and Angiogenic factors as outlined below.

Collect blood into 1x 10ml EDTA vacutainer (BD# 366457), 1 x 10ml SST vacutainer (BD# 367985), and 2 x 8ml Sodium Citrate CPT vacutainers (BD# 362761) following institutional procedures. All samples should be clearly labeled with the NCI Protocol Number, Subject Number, Specimen, and Timepoint using an indelible marker. A detailed laboratory manual will be provided.

2. Handling of Specimens(s)

Serum and EDTA treated Plasma Samples:
Allow the SST vacutainer to clot for approximately 20 minutes at room temperature prior to centrifugation. Centrifuge the SST and EDTA vacutainers at 1200xg for 20 minutes at 4°C. Remove the serum and plasma layers, respectively, and transfer to cryovials. Freeze serum and plasma samples at or below -80°C until shipment.

Sodium Citrated Plasma and Peripheral Blood Mononuclear Cell Layer (PBMC) Samples:
Within two hours of collection, centrifuge the Sodium Citrate CPT vacutainers at 1500xg for 20 minutes at 25°C using only a swing-out head rotor. (Spinning CPT vacutaienrs in a fixed angle rotor may cause tube breakage). Without disturbing the mononuclear cell layer (cloudy white layer) remove the upper plasma layer and transfer to cryovials. Freeze plasma samples at or below -80°C until shipment. Next, remove 1.5ml of the mononuclear layer and divide among two cryovials. Add an equal volume of freezing media to each cryovial. (Freezing media consists of 80% RPMI-1640 (Cambrex 12-167F) and 20% DMSO (Sigma D8418). Mix thoroughly. Freeze PBMC cryovials overnight at -80°C using a controlled rate freezing container (Mr. Frosty™, Nalgene 5100-0001). After 24 hours at-80°C, PBMC samples will be transferred to a liquid nitrogen freezer for long-term storage until shipment. **Note: Sites that do not have access to liquid nitrogen storage will submit serum and plasma samples only.**

3. Shipping of Specimen(s)

Samples will be batch shipped on dry ice to the University of Texas M. D. Anderson Cancer Center. All samples will be transported according to applicable IATA regulations. A detailed laboratory manual, as well as sample collection kits/shipping supplies, will be provided.

Samples will be shipped to:

Sherie Hodges
University of Texas M. D. Anderson Cancer Center
1220 Holcombe Blvd, Room ACB7.2408

Houston, TX 77030
Tel 713-563-3173
Fax 713-563-0572
GuClinicalResearchLab@mdanderson.org

4. Site Performing Correlative Study:
Samples will be analyzed at the University of Texas M. D. Anderson Cancer Center.

5. Brief description of methods.

Multiplex bead assays (MBAs) will be analyzed using a BioPlex 200 machine (Bio-Rad) in the Blood-Based Biomarkers Laboratory (part of the Heymach's laboratory) at M. D. Anderson Cancer Center. Commercially available, validate, pre-made mixtures of beads will be used. Currently the profile consists of: 1) Bio-Plex 27-plex cytokine panel (BioRad, Cat# M50-0KCAF0Y); 2) Bio-Plex 23-plex cytokine panel (BioRad, Cat# M50-005KMII); and 3) smaller bead sets for EGF, TGFalpha, MMP-9, and E-Selectin (Lincoplex, HCYTO-60K-02 and HCVD1-67AK-02). Note that the final profile may be modified as new assays are developed. We have worked extensively with each of these assays in the past. [At this time, MBAs for osteopontin (OPN), IGF family members, Placental growth factor (PlGF), and several members of the VEGF family are in development and these factors would need to be assayed by ELISA (R&D Systems), volume permitting, if the MBAs are not available at the time of analysis. Because of sample volume constraints, a maximum of 3-5 ELISA assays can be conducted in addition to the MBAs.] Samples will be assessed in duplicate on the same plate. Plasma samples will be processed as per manufacturer's instructions. The combined MBA analyses, therefore, require less than 200 microliters of plasma. ELISA assays will be conducted as per manufacturer's instructions using a MicroQuant plate reader in the laboratory. For each plate, the standard curves will be assessed to ensure that the expected assay range is achieved (typically 0.2 or 2 pg/ml to 3,200 or 32,000 pg/ml depending on the marker)

The following assays will be performed and others will be added as appropriate.

Multiplex bead arrays
Bio-Plex 27-Plex Panel (BioRad) Cat# M50-0KCAF0Y
Bio-Plex 23-Plex Panel (BioRad) Cat# M50-005KMII

3-plex for Luminex: Human CVD Biomarker Panel 1, Catalog # HCVD1-67AK (MMP-9, sICAM-1, and sE-Selectin)

ELISA
Human Osteopontin (OPN) Quantikine ELISA Kit (R&D Systems) Cat#DOST00
Human Soluble Carbonic Anhydrase IX ELISA Kit (R&D Systems) Cat#DCA900
Human sVEGF R2/KDR Quantikine ELISA Kit (R&D Systems) Cat# DVR200
Human Collagen IV EIA kit (Argutus Medical) Cat#BIO82

Pro-angiogenic factors
VEGF
bFGF
EGF
TNFα
IL-6
IL-8
IL-1b
MMP-9
HGF
MCP-1
PDGF-bb
PIGF

Anti-angiogenic factors
IL-12p40/70
IFN-A2
IFN-G
MIG
IP-10

Inflammatory
ICAM-1

Markers of hypoxia
Osteopontin
sCA9
SDF-1α

Endothelial function/damage
E-selectin
sVEGFR-2
Collagen IV

Other cytokines/chemokines
RANTES
MIP-1α
MIP-1β
Eotaxin
CTACK
GRO-A
MCP-3
MIF
MIG
TRAIL

Other interleukins
IL-1ra
IL-2
sIL-2RA
IL-3
IL-4
IL-5
IL-7
IL-9
IL-10
IL-13
IL-16
IL-17
IL-18

Growth factors
GM-CSF
G-CSF
M-CSF
SCF
NGF-B

Statistical Analysis:
We have investigated potential blood-based biomarkers in a randomized phase II trial of sorafenib vs. sorafenib and interferon. Using multiplexed bead assays (MBAs) and ELISAs to broadly assess a profile of cytokines and angiogenic factor (CAFs), we have identified plasma markers that predicted improved progression-free survival (PFS) in patients in each arm. A CAF signature, derived by combining individual markers, was more predictive than individual markers alone. *In vitro* studies and patient data suggest that CAFs may be regulated by tumor hypoxia, Akt/mTOR signaling, and other pathways. Based on this and additional studies in other cancer types, w*e hypothesize that broad profiling of CAFs in plasma of RCC patients can be used to identify groups of patients that receive different degrees of benefit from different therapeutic regimen.* We also hypothesize that CAF profiling can identify markers of therapeutic resistance and tumor pathway activation. Our primary goal in this project is to develop predictive biomarkers of benefit (prolongation in PFS and overall survival, OS) using plasma specimens from this randomized phase II trial.

For the multiplexed bead arrays, the data is assessed in the following manner. For each plate, the standard curves are assessed to ensure that the expected assay range was achieved. For each individual sample, the mean concentration is calculated for duplicate samples, and the coefficient of variance % (CV%) is calculated for all analytes. If the median CV% was greater than 25%, analysis of the sample is repeated. In the rare case that the repeat CV% was greater than 25%, one of the two analyses is selected based on lower CV% and consistency with prior values.

The multiplexed beads are assessed in a similar manner. For each plate, the standard curves are assessed to ensure that the expected assay range was achieved. For each individual sample, the mean concentration is calculated for duplicate samples, and the CV% is calculated. If the CV% for an individual sample is greater than 50%, the value is rejected.

Two important issues impacting the potential utility of the CAF profiling are baseline variability and stability during storage and freeze-thaw cycles. To investigate these issues, we assessed two baseline plasma specimens (taken ~1 week apart) from 163 patients and 65 patients in two lung cancer trials, and two additional baseline serum samples from 144 patients in a separate trial. We found a high degree of correlation between the two baseline values. As expected, serum levels of VEGF were higher than plasma. We also assessed the effect of 1-4 freeze-thaw cycles or of storage at 4 °C for 48 hours compared to first thaw levels. Levels of all but one CAF (IL-5) were relatively stable (<20% change under these conditions), suggesting that CAF profiles should be relatively stable over 1-2 thaw cycles.

We are interested in changes in CAF levels from baseline (BL) that are associated with either tumor progression or are predictive of PFS. It is expected that approximately 80% of the patients will complete cycle 2. To identify potential markers of therapeutic resistance, we will fit linear mixed-effects models for each marker that is measured. These models will incorporate random effects that allow each individual patient to have his or her own natural level as well as a fixed binary effect for "progressed" versus "not progressed." The significance of the fixed effect of progression is measured by an F-test. We will also explore more elaborate models that allow for a treatment effect that may distinguish changes on treatment from BL. To correlate changes in individual CAFs with clinical benefit from MK2206 vs. Everolimus, we will use Cox proportional hazards models. Primary analyses will use the differences in marker levels as continuous predictors. We will also explore the use of derived binary markers ("changed" or "unchanged"), where the thresholds for change will be set using mixed-effects linear models that incorporate repeated measures on the same individual patient. For the evaluation of markers to predict clinical benefit, we will take individual predictive markers and will combine them with the goal of identifying groups of patients with greater PFS and/or benefit. We will apply two different methods of analysis. First, we will fit multivariate Cox proportional hazards models that incorporate all individual markers that exhibit some predictive ability, using the Akaike Information Criterion (AIC) to eliminate markers that do not contribute significantly to the multivariate model. Second, we will apply robust clustering methods to identify subgroups of samples that exhibit similar CAF expression profiles, and test whether the resulting subgroups have different outcomes.

APPENDIX J MSKCC RISK STRATIFICATION

MSKCC Risk Stratification	
Karnofsky Performance Status	< 80
Corrected Calcium	> 10.0 mg/dL
Hemoglobin	< Lower Limit of Lab Reference Range

Risk Groups	
Favorable	0 Risk Factors
Intermediate	1 Risk Factor
Poor	2 or 3 Risk Factors

APPENDIX K MULTI-CENTER STUDY MANAGEMENT PLAN

Multi-Center Study Management Plan

For

National Cancer Institute (NCI) /
Cancer Therapy Evaluation Program (CTEP)Phase I/II & Phase II Studies
Version 4/10

Table of Contents

1.0 INTRODUCTION

This Study Management Plan (SMP) outlines the procedures and requirements for institutions collaborating with MD Anderson Cancer Center (MDACC) in the conduct of a National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) sponsored research protocol.

2.0 PURPOSE

To establish standards that will ensure compliance with Federal Regulations, Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multicenter Guidelines.

3.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multicenter Guidelines, the MDACC Principal Investigator, MDACC NCI Support Services (MDACC NCISS), and the participating institution will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the SMP):

3.1 MDACC Principal Investigator (MDACC PI)

The MDACC PI will accept responsibility for all aspects of the Study Management Plan to include:

Protocol Development

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments by the NCI and the MDACC IRB.
- List each participating investigator and institution on the protocol title page including address, phone number, and email and designate the lead institution on the title page.
- Assure all participating institutions are using the correct version of the protocol.

Study Oversight

- Monitor progress and overall conduct of study at all participating institutions.
- Ensure all CTEP reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- **Research Team Teleconferences:** The MDACC PI & research team, MDACC NCISS, and participating institution PI and research staff will participate in a teleconference every 2 – 4 weeks, as needed, and will discuss the following information

- Patients enrolled at participating sites including
  - Brief history
  - Eligibility for trial
  - Status of treatment
  - Adverse Events
  - Response evaluation

- Review of safety data
  - Unexpected toxicities
  - Serious Adverse Events
  - IND safety reports

3.2 MDACC NCI Support Services (MDACC NCISS)

To assist the MDACC PI in meeting his/her responsibilities MDACC NCISS will assume the following general responsibilities:

Administrative Support

- Act as the central liaison between the MDACC PI, participating institution, and NCI CTEP/PIO Office.

- Maintain a contact list of all study participants at MDACC and the participating institution.

Regulatory Management

- Distribute approved protocols to participating institutions, notify them of amendments, and provide them with copies of approved amended protocols.

- Ensure that each participating institution has the appropriate assurance on file with the Office of Human Research Protection (OHRP form 310) and this has been submitted to the CTEP PIO.

Regulatory Document Collection: Refer to Section 3.3 for a list of documents that must be submitted to MDACC NCISS prior to protocol activation and submitted on an ongoing basis for the duration of the study.

Study Management Support

- Conduct study initiation meetings with MDACC PI and provide support to the participating institution research staff, as required.

- Distribute external Serious Adverse Event safety reports to participating sites.

- Notify participating institutions of protocol hold or closure.

Data Management Support

- Provide participating sites with access, training, and support for electronic data entry.

- Notify participating institution research teams of data locks prior to quarterly data transmission due dates

- Monitor data quality and issue data queries / error log findings.

Quality Assurance

- Coordinate and participate in regularly scheduled teleconferences with the MDACC PI, the participating institution PI and their respective research teams to review study conduct.

- Audit participating institutions by on-site inspection of selected patient records and / or by requesting source documents and research records as requested.

3.3 Participating Institution Principal Investigator

The general responsibilities for each participating institution are as follows:

Regulatory Compliance

- **Study Contact List:** Provide a list of key study personnel and update MDACC NCISS with research staff changes on a timely basis.

- **NCI Investigator Registration:** Maintain an active NCI Investigator Registration number for any physician who will be consenting / treating patients to the study and provide confirmation of annual renewal.

- **IRB Approval**: Submit protocol and amendments to local IRB prior to initiating any protocol activity / changes.

  Note: If IRB approval for amendments is not obtained within the timeframe specified at time of amendment distribution accrual will be suspended until IRB approval is obtained.

- **Regulatory Documents:** Provide copy of required regulatory documents to MDACC NCISS prior to activation.

  1. Federal Wide Assurance (FWA) number
  2. Laboratory certifications (CLIA / CAP)
  3. Normal laboratory values
  4. NCI Investigator Registration Number/expiration dates for all physicians
  5. Delegation of authority log
  6. Copy of initial IRB approval documents

The following regulatory documents must be submitted on an ongoing basis for the duration of the study:

1. Copy of IRB annual approval documents. Note: If IRB annual approval is not received prior to the anniversary of the previous approval, accrual will be suspended until the annual approval is received.
2. Copy of IRB approval documents for any protocol or informed consent revisions. Note: If IRB approvals for amendments are not received within the timeframe indicated at the time of distribution, accrual will be suspended until IRB approval is obtained.
3. Confirmation of renewal of NCI Investigator Registration Number
4. Copy of CTEP-AERS reports for Serious Adverse Events
5. Evidence of IRB review of external safety reports
6. Protocol violations and deviations submitted to the participating institution IRB.
7. Copy of all signed informed consents for patients enrolled on the trial, if requested by the MDACC PI.
8. Copy of IRB approval documents for any protocol status changes: activation, study closed to new patient enrollment, study closure, study termination. Note: If IRB annual review is not provided on or before the anniversary of the previous approval, accrual will be suspended until the annual re-approval is received.

- **IND Safety Reports:** MDACC NCISS will distribute IND safety reports and appropriate guidance regarding IRB submissions and patient notification to the participating institutions.

Study Management

- **Eligibility:** Ensure patients meet all eligibility criteria prior to registering the patient on study.

- **Adverse Events:** Submit Expedited Adverse Event reports directly to CTEP (via CTEP-AERS) as required per protocol and provide copies to the MDACC PI and NCISS. Submit Routine Adverse Events via Clinical Oncology Research System (CORe.)

- **Protocol Compliance:** Adhere to the MDACC IRB definition of protocol deviation and protocol violation and requirements for reporting.

  Protocol Deviation: Noncompliance with the protocol that does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data. Deviations may be caused by the action of the subject, the investigator, the research staff, or natural events.

  Protocol Violation: Changes to protocol procedures without prior approval of

the IRB/Sponsor. These changes may have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the data, and may cause an unanticipated problem to the subject or others. Violations may also significantly alter the clinical effectiveness of the treatment or the evaluation of its toxicity.

Procedures for Reporting Protocol Violations/Deviations

Participating Institutions: Protocol violations/deviations occurring at a participating institution will be submitted to that site's own IRB. A copy of the participating institution's IRB violation/deviation report will be forwarded to the MDACC NCISS **within 7 calendar days after the original submission.**

Coordinating Center: Upon receipt of the violation/deviation report from the participating institution, MDACC NCISS will submit the report to the MDACC PI for review.

Data Collection

The Clinical Oncology Research System (CORe) is a web based database that is used for patient registration (for Phase I, Phase I/II and Phase II trials) and data entry (for Phase I/II, II trials). CORe can be accessed at www.oncologyresearch.org . Study staff at participating institutions will be provided with a username and password for CORe at the time of study activation.

- **Patient Registration:** All patients, regardless of the phase of the trial, will be registered in CORe prior to beginning treatment.

  *At the time of registration portions of a patient's protected health information will need to be entered. In order for the site to enter this information the patient must have signed an informed consent document, which includes an authorization for the release of protected personal health information (IC/A). The authorization that each institution obtains to use and disclose protected health information **must** include MD Anderson Cancer Center as an entity that they will share data with. This consent and authorization (IC/A) document authorizes MD Anderson Cancer Center to collect and retain documents, reports, and/or information which relate to the patient's participation on the protocol. This document also authorizes MD Anderson Cancer Center to send data and/or composite data for the entire study to each site participating in the trial.*

- **Data Entry:** Enter data in CORe according to the following data schedule

At time of registration (Phase I/II and II trials)	• Assign patient number • Name & demographics • Eligibility checklist
Within 1 week of registration (Phase I/II and II trials)	• Pre-study data including o Registering institution o Disease subgroup code (NCI CDU) o Disease code (NCI CDU) o Payment method (NCI) o Zubrods PS o Baseline abnormalities o Prior therapy o Number of prior chemo regimens
Within 3 weeks after the completion of each cycle. (Phase I/II and II trials)	• Treatment Course o Course Number o Cycle start date o Treatment code (NCI CDU) o Height (cm) o Weight (kg) o AE Experienced o Treating institution • Treatment Agent o Agent code (NCI CDU) o Total dose this course o Dose change • Adverse Events o Adverse event o Symptoms (required if AE other used) o Grade o Onset date o Resolved date o Relationship o AE report sent to CTEP
Within 1 week after the completion of the cycle required for response assessment (Phase I/II and II trials)	• Protocol Summary o Last dose date (date of last treatment) o Off treatment reason (if applicable) o Evaluability o Evaluable for response o Protocol response o Response date o Progression date (if applicable)
Within 1 week after	• Off Protocol

completing treatment or taken off study (Phase, I/II and II trials)	o Off date o Death date (if applicable) o Death date source o Death comment o Cause of death

Specifics Regarding Phase II Trials

- **Data Locks:** Data will be transmitted to NCI quarterly on January 31, April 30, July 31, and October 31. ***Approximately 3 weeks prior to the transmission date, the participating institution will be informed by MDACC NCISS that the data will be locked during data transmissions. During this period of data lock, no new patient data and/or changes to previously entered data should be made unless instructed by MDACC NCISS.***

- **Data Queries:** Following data transmission NCI will issue an error log to MDACC NCISS detailing any corrections that need to be made to data prior to protocol acceptance. MDACC NCISS will communicate the required changes to the participating institution. NCISS will periodically review the data for completeness. You may receive queries directly from NCISS prior to data submission to the NCI. ***Required data corrections must be completed as instructed by MDACC NCISS.***

4.0 PATIENT CONFIDENTIALITY AND AUTHORIZATION STATEMENT

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or ***disclosed in the course of treatment, payment or health care operations.*** The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of an MDACC Multicenter trial the participant in the trial must sign an authorization form. This Authorization may or may not be separate from the Informed Consent. The Authorization may require local IRB approval before presentation to a potential trial participant. The participating institution, with the approval from the NCI/CTEP and MDACC, will provide an Informed Consent template, which covered entities, must use.

MDACC and participating institutions will attempt to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why MDACC has chosen to use Authorizations, signed by the participant on the trial, rather than limited data sets with data use agreements.

5.0 ON-SITE AUDITING

Purpose of Audit

To ensure that the data analyzed to determine study results accurately reflect the primary source documents and that any clinical study was conducted in accordance with an Institutional Review Board (IRB)-approved protocol. The audit program reviews protocol management in the following categories: eligibility, informed consent, treatment, disease outcome/response, toxicity, and general data quality. Compliance with all federal, National Cancer Institute and institutional requirements for the protection of human subjects is also assessed.

In addition, the audit program provides education to the research staff regarding issues identified during the audit and assists research teams to develop appropriate ways to correct deficiencies identified by the audit.

Selection for Audit

Participating institutions can be selected for audit at any time. Audit will generally be performed on a random basis and may occur at 6 – 12 month intervals.

Audit Notification

The participating institution principal investigator (PI) and study coordinator shall be notified two to four weeks in advance of the audit start date. If the audit is initiated due to suspected deficiencies the advance notice may be shorter than 2 weeks. All audit notifications shall be delivered to the PI and study coordinator by e-mail. It is important that a person who is familiar with the research protocol and the study subjects enrolled on the trial be available (but not necessarily present) during the audit to assist the auditors in locating documentation that may be difficult to find in the primary medical record.

The notification will include:

- **The date of the audit**
- **A list of the patient records to be audited**
- **A list of documents required for the audit**

Responsibilities of Participants in the Audit

Clinical Trials Auditors: If more than one auditor visits the site a lead auditor will be designated to guide the audit process. It shall be the auditor's responsibility to print a copy of the protocol and be familiar with the study prior to the start of the audit.

Principal Investigator and Research Staff: The principal investigator is responsible for assuring that all requested audit materials are available at the time of the audit. These materials shall include the following:

- **One copy of an original signed and dated informed consent document (ICD) for each participant. For patients who have been re-consented while on study, an original signed and dated informed consent must be available for each IRB-approved version of the informed consent.**
- **All patient records: in-patient charts (if applicable), protocol-specific patient source documents (signed and dated pill diaries, symptom records), database printouts, and patient research files**
- **Correspondence and source documentation from outside institutions pertaining to patient research data**
- **Radiology films and other specified studies, if requested**
- **Any operative, pathology and radiotherapy reports required by protocol**
- **Regulatory Binder**

The research staff must have all patient research charts and the Regulatory Binder organized in a systematic and consistent fashion. The presence of organized study records reduces the potential for queries and helps prevent repeated questions to the study coordinator / PI requesting assistance in locating items during the audit.

Conducting the Audit

Medical Record Review: At the time of the medical record audit, source documentation shall be reviewed and used to independently verify study data. Data quality shall be assessed by measuring it against the standards for optimal data collection as defined in the research protocol. Data entered in CORE should match precisely with the corresponding information on the primary source document.

The research team shall also be evaluated on protocol compliance with the study schedule, regulatory requirements, and guidelines for Good Clinical Practice (GCP). Although the PI may delegate responsibilities for various aspects of the protocol management, the PI alone retains ultimate responsibility for the conduct of the clinical trial.

The following elements are reviewed during the audit:

Activation/Continuing Review Information: The auditor shall verify that:

- IRB approval has been obtained prior to study activation and patient enrollment;
- An annual continuing review has been completed within 365 days from initial date of approval;
- Confirmation that all consenting physicians have a current NCI Investigator Registration number

- Protocol amendment, informed consent, and IRB approval dates are appropriate;
- Patients were treated following CORe registration.
- All regulatory documents are in the regulatory binder(s)

Informed Consent Document: The ICD must:

- Be the appropriate IRB-approved version at the time the patient was enrolled. For NCI studies, the ICD must also have received NCI's approval before it is used in obtaining informed consent.
- Contain the patient's signature and date;
- Contain the signature and date of the person who is obtaining the informed consent;
- Contain the signature of the witness and date it was signed; if applicable
- Indicate selection of optional studies verified by patient initials
- List M. D. Anderson as an authorized reviewer on ICD's from outside institutions (where M. D. Anderson serves as the lead institution on a multicenter trial). On multicenter trials where M. D. Anderson is not the lead site, any institution that may request protected health information should be listed in the HIPAA section of the M. D. Anderson ICD.

The informed consent process must be documented in the on-study note located in each patient's medical record.

Eligibility: The eligibility checklist is compared against the primary medical record to confirm that all criteria were met prior to registration on the trial. If documentation cannot be located, eligibility is noted as "unable to confirm" due to insufficient data. The patient shall be considered ineligible if one or more of the eligibility requirements were not satisfied.

Protocol Compliance: Source documentation is used to verify that the performance status has been assessed and that the results of all required tests have been obtained within the protocol-specified time frame prior to the start of treatment. On-study visits, lab tests, and diagnostic studies shall be checked for adherence to the study schedule. If testing or visits were missed, the auditor shall verify that a protocol deviation/violation report was completed for each occurrence and submitted to the IRB, and a copy placed in the Regulatory Binder. A deviation log may be utilized as per institutional policy.

Treatment Administration: The audit team confirms that patients receive the correct dose, route, dosing interval, and timing of the treatment administered. Dose modifications shall also be checked and compared against the protocol. The auditor shall assure that the proper body surface area (BSA) was calculated. The auditor shall also check the medical record for correct and consistent recording of the study subject's weight and shall look for dose adjustments based on body weight changes as defined in the protocol.

Disease Outcome / Response: The auditor shall verify baseline and on-study disease status by reviewing tumor measurements analyses in the medical record/research file. Solid tumor measurements shall be compared to imaging reports and/or original radiology films to confirm tumor response. For hematologic tumors, documented response shall be verified using

appropriate analyses as stated in the protocol. If the auditor cannot verify the outcome response, a physician auditor shall be consulted for a final decision.

Toxicity: All toxicities shall be documented in the medical record or recorded on patient data forms. These shall include the appropriate Common Toxicity Criteria term to describe the toxicity, the grade of toxicity, the attribution, date of onset, and date of resolution. The auditor shall confirm that all patients have been followed for toxicities for thirty days from the last date of protocol therapy. When a SAE occurs, the auditor shall verify that initial and follow-up reporting is appropriate as required in the Code of Federal Regulations and in accordance to NCI / CTEP's policy.

General Data Quality: This category concerns the quality and completeness of source documentation as well as the accuracy of data transcription from the source document to the case report form. Emphasis shall be placed on clear and complete reporting of the findings and correct matching of all data elements. Any inconsistent, incomplete, illegible, or hard to follow records shall be noted. Comments shall be made regarding repeated discrepancies that appear to affect the validity of the data or indicate that the management of the protocol needs more oversight.

Audit Findings

- Following completion of the audit, a preliminary audit findings report will be completed and be presented at the Audit Findings meeting or the "Exit Interview meeting".
- The purpose of the exit interview is to provide an opportunity for education, clarification, immediate dialogue, and feedback. It is not intended as a time to resolve all of the issues noted in the audit findings.
- The principal investigator and the study coordinator responsible for the study being audited are required to attend. Additional research staff associated with the study is encouraged to attend as well.
- As time allows, the lead auditor shall educate the research team in interpretation of the various regulatory requirements / institutional policies and shall provide guidance on the development of a corrective action plan to address issues involving major deficiencies.
- At the conclusion of the exit interview, the lead auditor may also discuss best practice guidelines and offer suggestions for improvement on data collection and protocol management.
- Following the exit interview the lead auditor shall amend the audit findings to include any corrections/clarifications noted during the exit interview.
- Once the audit findings have been modified, the lead auditor shall send a return receipt e-mail containing a copy of the audit findings to the PI and study coordinator.
- Upon receipt of the e-mail, the research team shall have two weeks to respond and return the audit findings to the lead auditor.
- The PI/study coordinator shall be responsible for providing a written response to each of the findings cited during the audit.

- To properly respond to the audit findings, the research team must enter a response immediately below each query. All research team responses shall be entered in red directly onto the audit findings document.
- When appropriate, a corrective action plan shall be included to complete the response.
- In situations where the lead auditor must review a source document to verify a research team response, the study coordinator shall provide a photocopy of this source document. All photocopies must be provided to the lead auditor by the deadline for audit response noted in the e-mail.
- **Once all of the queries have been addressed and the response is complete, both the individual preparing the document and the PI for the study must print out and sign one copy of the audit findings report. An electronic copy of the same document shall be e-mailed to the lead auditor.**
- Once the lead auditor receives the electronic copy of the response to the audit findings, he or she shall review the explanations/corrective action plans and shall create a summary report of outstanding audit findings, PI responses and any other audit activities.
- **The final audit report will be forwarded to the Lead PI, the MD Anderson IRB and the Quality Improvement Oversight Committee (QIOC) for review.**
- **The QIOC is a multi-disciplinary committee at MD Anderson that examines the findings of protocol audits to evaluate for the presence of system issues that may require further action.**