DF/HCC Protocol #: *20-284*

TITLE: A phase I/IB trial of abemaciclib alone or in combination with MK-6482 in advanced renal cell carcinoma

Coordinating Center: *Dana Farber Cancer Institute*
450 Brookline Avenue, Boston, MA 02215

Principal Investigator (PI): *Toni Choueiri, M.D*
Dana-Farber Cancer Institute
450 Brookline Avenue, Boston, MA 02215
Phone - 617-632-5456
Fax - 617-632-2165
E-mail - toni_choueiri@dfci.harvard.edu

Other Investigators: *Bradley A McGregor, M.D*
Dana-Farber Cancer Institute
E-mail – bradley_mcgregor@dfci.harvard.edu

David McDermott, MD
Beth Israel Deaconess Medical Center
dmcdermo@bidmc.harvard.edu

Ramaprasad Srinivasan, M.D., Ph.D.
National Cancer Institute
Bethesda, MD 20892
E-mail - ramasrin@mail.nih.gov

Statistician:
Wanling Xie
Dana Farber Cancer Institute
450 Brookline Avenue, Boston, MA 02215
Phone - 617-582-7928
Fax - 617-632-2444
E-mail - wxie@jimmy.harvard.edu

Study Coordinator:
TBD

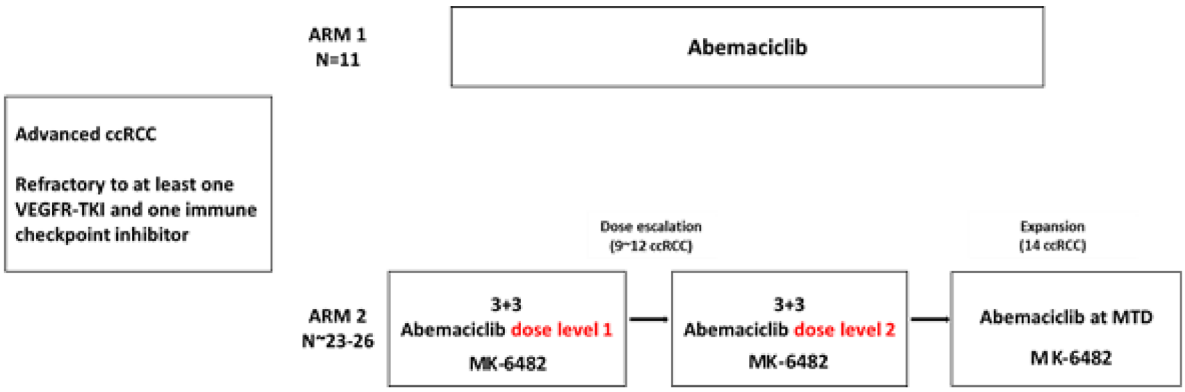
Responsible Research Nurse:
TBD

Other Agent(s): MK-6482, provided by Merck
Abemaciclib, provided by Eli Lilly and Company

IND #: *147776*
IND Sponsor: Toni Choueiri, MD

Protocol Type / Version # / Version Date : *Version #3 07/19/2021*

SCHEMA



1. Cycle length is 28 days
2. Follow up - Participants will be followed for survival and next line of systemic treatments every 6 months, until death or 2 years after treatment discontinuation.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This a two-arm, non-randomized phase 1/1B trial aiming at assessing the safety and activity of abemaciclib alone (arm 1), and abemaciclib plus MK-6482 (arm 2) in patients with advanced refractory clear-cell renal cell carcinoma (rccrcc). Imaging assessments will be performed every 8 weeks during the first six months of the study, then every 12 weeks, in both arms. Patients will undergo mandatory biopsies before therapy and at progression if initial response, in the absence of contra-indication.

In arm 1, abemaciclib monotherapy will be given at the recommended starting dose as monotherapy, until radiographic progression, unacceptable toxicity or withdrawal. A total of 11 patients are expected to be enrolled in arm 1 at a rate of 3 patients per month.

Initially, patients will only be enrolled to arm 1, abemaciclib monotherapy to establish a single arm benchmark activity. Once arm 1 is enrolled with ORR data, we will start enrolling on Arm 2 (combination arm).

Arm 2 will follow a standard dose escalation and dose expansion design (3+3). The dose escalation phase will evaluate the MTD of abemaciclib when administered in combination with MK-6482, using two predefined dose levels. The dose expansion phase will treat patients with abemaciclib at the MTD in combination with MK-6482. Patients will be treated until radiographic progression, unacceptable toxicity or withdrawal. A total of 23-26 patients are expected to be enrolled in arm 2 at a rate of 3 patients per month, including a total of 20 patients treated at the MTD of abemaciclib in combination with MK-6482.

1.2 Primary Objectives

<u>Arm 1 – abemaciclib single agent:</u>
To determine the response rate of abemaciclib in patients with advanced ccRCC

<u>Arm 2 – combination therapy of abemaciclib and MK-6482</u>
To determine the MTD of abemaciclib and MK-6482 in combination.
To determine the response rate of abemaciclib and MK-6482 in patients with advanced ccRCC.

1.3 Secondary Objectives

To determine additional toxicity and safety information from the combination of abemaciclib and MK-6482 in the expanded cohort of participants treated at the MTD.

To determine the duration of response (DOR), progression-free survival (PFS), and overall survival (OS) of abemaciclib alone and in combination with MK-6482.

To assess the 77 profiles (PK) of MK-6482 and abemaciclib.

1.4 Exploratory objectives

To evaluate pharmacodynamic (PD) markers of MK-6482 and abemaciclib.

To determine clinical and biological correlates of response and survival to abemaciclib alone and in combination with MK-6482 at the MTD.

2. BACKGROUND

2.1 Clear-cell renal cell carcinoma

Kidney cancer affects more than 400,000 patients each year[1], among whom one third present with metastatic disease[2]. Clear-cell renal cell carcinoma (ccRCC) represent the most common histological subtype of renal cell carcinoma, as it is found in approximately 70% of patients diagnosed with kidney cancer[2]. While 5-year survival is above 90% in a context of localized disease, prognosis of metastatic patients remain poor with a 5-year survival of 12%[3].

The main oncogenic event identified as a driver in ccRCC was the loss of tumor suppressor VHL and the subsequent activation of the Hypoxia-Inducible Factor (HIF) pathway. HIF-1α and HIF-2α are transcription factors that promote the activation of pro-oncogenic transcriptional programs, including notably angiogenesis, cell proliferation and survival, anaerobic metabolism, and invasion. In normoxic conditions, the protein VHL binds to hydroxylated HIF proteins, leading to VHL-dependent ubiquitinylation and proteosomal degradation. In hypoxic conditions or in a context of VHL loss, HIF will accumulate and enter the nucleus to promote the transcription of its pro-oncogenic targets[4]. Genetic or epigenetic inactivation of VHL has been reported in more than 90% of ccRCCs[5].

Since the discovery of VHL and the HIF pathway, other pathways have been identified as essential in the promotion of ccRCC. Pathways frequently altered include the mTOR pathway, as well as chromatin remodeling genes including *BAP1*, *PBRM1* and *SETD2*[2]. More recently, cell cycle genes alterations have been reported as a potential driver of aggressiveness in advanced ccRCC. In the Cancer Genome Atlas cohort, alterations of *CDKN2A,* encoding cell cycle inhibitor proteins p16(INK4A) and p14(ARF), have been reported in 16% of all RCCs and were associated with poor prognosis[6]. In addition, *CDKN2A/B* alterations are reported to be more frequent in metastatic sites of ccRCC, and suspected to drive aggressive phenotypes[7,8].

Prognosis of metastatic ccRCC, in the era of antiangiogenic therapies, can be inferred by the International Metastatic renal cell carcinoma Database Consortium (IMDC) classification, based on 6 clinical and biological factors: Karnofsky performance-status score of less than 80, time from initial diagnosis to treatment initiation of less than 1 year, hemoglobin level below the lower limit of the normal range, corrected serum calcium level above the upper limit of the normal range, absolute neutrophil count above the upper limit of the normal range, and platelet count above the upper limit of the normal range. Patients with ccRCC and good (0 criteria), intermediate (1-2 criteria), and poor prognosis (>2 criteria) harbor a 2-year overall survival of 75%, 53%, and 7%, respectively.

Principles of treatment in ccRCC rely on antiangiogenics directed against VEGFR, and immune checkpoint inhibitors targeting PD-1/PD-L1 and/or CTLA-4. The combination of nivolumab plus ipilimumab has been approved upfront in patients with IMDC intermediate and poor-risk disease in 2018, while the combination of pembrolizumab plus axitinib has been FDA-approved in the same setting for unselected patients in 2019. Both combinations improved response rates and survival compared to sunitinib and redefined the standard of care. However, up to 40% of patients still do not experience objective response with these new strategies[9]. Activity of second-line

agents, including nivolumab and cabozantinib monotherapy, is also limited with objective response rates that do not exceed 30%[10,11]. Legacy MTOR inhibitors, approved in refractory disease, harbor an objective response rate lower than 5%[12].

Overall, novel targets for RCC outside of immunotherapy and VEGFR inhibitors are lacking, with few options available for those patients who progress on standard therapy. It is thus essential to evaluate new therapeutic avenues in this hard-to-treat disease.

2.2 Abemaciclib

Abemaciclib is a selective, potent small molecule directed against CDK4 and CDK6, cyclin-dependent kinases involved notably in G1-S cell cycle progression. Cell cycle genes alterations are found across solid tumors and are suggested to be involved in tumor promotion and resistance to therapy[13].

2.2.1 Activity and safety of abemaciclib

Abemaciclib demonstrated antitumor activity in multiple *in vitro* and *in vivo* human cancer models, including notably breast cancer, colorectal cancer, glioblastoma multiforme, non-small cell lung cancer. The safety of abemaciclib (LY2835219) has been evaluated in a single-arm phase 1 study involving adult patients with metastatic breast cancer, colorectal cancer, glioblastoma, melanoma, non-small cell lung cancer[14]. The most common grade 3 adverse events (> 10% incidence) were leukopenia (10%), neutropenia (9%), thrombocytopenia (7%), diarrhea (5%). Based on pharmacokinetic data, the recommended phase 2 dose was 200 mg po bid. Tumor responses were reported with single agent abemaciclib in this phase 1 trial for patients with breast cancer, melanoma, and non-small cell lung cancer.

The MONARCH-1 phase 2 study evaluated abemaciclib in women with advanced, ER-positive breast cancer that had progressed after 1 or 2 lines of systemic chemotherapy and demonstrated a 19.5% response rate[15]. Most frequent adverse events (>20%) included diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (46%), abdominal pain (39%), vomiting (35%), headaches (21%), creatinine increased (99%), white blood cell decreased (91%), neutrophil count decreased (88%), anemia (69%), platelet count decreased (41%), ALT increased (30%), AST increased (26%), hypokalemia (26%), hyponatremia (21%). Grade 3 adverse events in > 5% of patients included diarrhea (20%), fatigue (13%), white blood cell decreased (28%), neutrophil count decreased (27%), hypokalemia (5%).

Abemaciclib has been also evaluated in combination with endocrine therapy. The MONARCH-2 phase 3 study evaluated abemaciclib plus fulvestrant in patients with advanced (HR+/HER2-) breast cancer who progressed on prior endocrine therapy, demonstrating a response rate of 48% in this setting[16]. Frequent adverse events of abemaciclib in combination with fulvestrant included diarrhea (86%) and neutropenia (46%). Rare cases of liver function tests abnormalities (13%) and deep vein thrombosis (5%) have been reported. The MONARCH-3 study evaluated first-line combination of abemaciclib plus non-steroidal aromatase inhibitor in advanced (HR+/HER2-) breast cancer, and demonstrated an objective response rate of 59%, with a similar toxicity profile[17].

Based on these trials, current approved dosing in breast cancer is 200mg in monotherapy and 150mg in combination with endocrine therapy based on the results of these two studies. Abemaciclib has not been studied in clinical models of kidney cancer as of 2019.

2.2.2 **Pharmacokinetics and pharmacodynamics of abemaciclib**

Abemaciclib can be taken with or without food. However, a concomitant high-fat high-calorie meal can increase abemaciclib exposure, as demonstrated in healthy subjects, with an AUC of abemaciclib plus metabolites increased by 9% and Cmax by 26%.

Half-life is 17-38 hours; metabolism is primarily hepatic and dependent on CYP3A4. Three major metabolites of abemaciclib, M2, M18 and M20, are found at a concentration > 10% of the parent drug. Those also exert inhibition of CDK4/6 and undergo hepatic metabolism.

Abemaciclib and its metabolites are bound to human plasma proteins: 96.3% for abemaciclib, 93.4% for M2, 96.8% for M18, and 97.8% for M20. Abemaciclib is also a substrate of P-gp and BCRP *in vitro*, but the effect of P-gp or BCRP inhibitors on abemaciclib are unknown. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV). Concentration of abemaciclib and metabolites M2 and M20 in cerebrospinal fluid are similar to unbound plasma concentration.

Abemaciclib, M2 and M20, do not induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations. Abemaciclib, M2 and M20, down regulate mRNA of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4. The mechanism and clinical relevance of this down regulation are not understood, but no time-dependent changes in abemaciclib concentration due to inhibition of CYP3A4 has been observed.

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (i.e., 20 ms) in the QTc interval.

2.3 MK-6482

MK-6482 is a selective, potent small molecule directed against HIF-2α, disrupting its hetero-dimerization with the aryl hydrocarbon receptor nuclear translocator, preventing its translocation to the nucleus and subsequent transcription of target genes.

2.3.1 **Activity and safety of MK-6482**

In vivo and *in vitro* models demonstrated antitumor activity of MK-6482 with dose-dependent reduction in HIF-2α expression. There were no significant off-target effects as measured by mouse studies and *in vitro* studies of receptors, ion channels, kinases and phosphatases panels. Toxicity in animal models consisted in reversible hematologic abnormalities, as well as irreversible effects on spermatogenesis reported in rats[18].

A phase 1 study of MK-6482 is currently ongoing. The dose-escalation phase included 30 patients with solid tumors, among which 9 had RCC, treated with MK-6482 doses ranging from 20mg to

160mg daily[19]. No DLT has been reported. The only grade 3 adverse event > 10% was anemia, which occurred in 33% of patients including 13% with grade 3. Other adverse events >30% included anemia (75%), fatigue (67%), dyspnea (47%), nausea (33%), and cough (31%). The recommended phase 2 dose (RP2D) was 120mg daily. Among 6 patients with ccRCC treated at RP2D, one patient had a partial response and 4 had stable disease.

2.3.2 **Pharmacokinetics and pharmacodynamics of MK-6482**

In the phase 1 trial of MK-6482, exposure increased with dose. At 120 mg, MK-6482 was absorbed with a mean Cmax of 1.8 μg/mL and a mean half-life of 20.9 hours[18].

In vivo models showed a high volume of distribution (> total body water) in all animal species, suggesting wide tissue distribution. In rat, brain to plasma concentration ratios range from 0.36 to 0.53.

In vitro models showed a low clearance of MK-6482 in human hepatocytes, and only one metabolite of MK-6482 was observed in human hepatocytes. Additional experiments revealed that MK-6482 oxidative metabolism was minimal in most species. No CYP450 enzyme reaction phenotyping has been performed. One glucosidic glucuronide metabolite detected in rats and dogs (PT3317) was found to be dependent on UGT2B17, mainly expressed in the small intestine.

In vitro models showed that MK-6482 did not inhibit any CYP enzymes by either competitive (7 CYP isoforms) or time-dependent (CYP3A4) mechanisms up to at least 50 μM. MK-6482 did however increase production of CYP3A4 mRNA in cultured human hepatocytes with a half-maximal effective concentration (EC_{50}) of 9.63 to 12.2 μM. The mean C_{max} value for the clinical dose of 120 mg is about 2-fold less than the concentrations at which CYP induction effects were observed.

2.4 Rationale to evaluate abemaciclib alone and in combination with MK-6482

There is an essential need to expand therapeutic options for patients with refractory ccRCC, as options remain limited outside of VEGFR-directed therapies and immune checkpoint inhibitors. In addition, optimal therapeutic strategies following combinations of immune checkpoint inhibitors are still to be defined.

Cell cycle is emerging as a key oncogenic pathway in ccRCC. In particular, *CDKN2A/B* loss or promoter methylation are reported in 10% to 60% of all RCC subsets. These alterations frequently appear in the context of 9p loss and are usually associated with poorer prognosis in RCC, independently of histological subtype[20]. Preclinical models confirmed the therapeutic potential of cell cycle inhibitors in RCC. Palbociclib provided potent antitumor activity in multiple RCC cell lines, and homozygous loss of p15 (*CDKN2B*) and p16 (*CDKN2A*) were predictors of response to palbociclib[21]. Abemaciclib combined with the anti-angiogenic sunitinib provided synergistic antitumor activity in CAKI-1 and 786-O xenograft models[22]. Thus, evaluation of abemaciclib alone and in combination with anti-angiogenics in ccRCC represents a promising therapeutic avenue.

MK-6482 is a novel HIF-2α inhibitor harboring anti-angiogenic properties. By its direct action on HIF-2α, it acts upstream of current VEGFR inhibitors. As such, it may provide additional activity by inhibiting a larger range of oncogenic processes regulated by HIF, including but not limited to survival, proliferation, metabolism, invasion. In addition, preclinical data from the Kaelin laboratory at Dana-Farber suggests that CDK4/6 inhibitors could rescue resistance to HIF-2α inhibition in murine models. Thus, MK-6482 is an ideal compound for combination strategies with abemaciclib.

Abemaciclib and abemaciclib plus MK-6482 represent new compounds that may offer additional therapeutic opportunities in ccRCC. Preclinical data suggest potential for activity in ccRCC, and both drugs are well tolerated. Herein we propose to evaluate abemaciclib alone or in combination with MK-6482 in patients with advanced refractory ccRCC, in a phase 1/1B trial.

2.5 Correlative Studies Background

Both abemaciclib and MK-6482 are first evaluated in a context of advanced, refractory ccRCC. These agents harbor a wide range of anti-oncogenic properties through cell cycle inhibition and downstream HIF effectors inhibition, providing the opportunity to investigate multiple potential predictive biomarkers of response to therapy.

Multiple potential biomarkers of response to CDK4/6 inhibitors have been described in solid tumors including RCC. First, preclinical models showed that RCCs with bi-allelic CDKN2A alterations might harbor increased sensitivity to CDK4/6 inhibitors. Multiple reports in other solid tumors pinpointed several alterations that may confer resistance (*Rb* loss, *CDK6* amplification or other Cyclin/CDK activation)[23,24] or sensitivity to CDK4/6 inhibitors (D-cyclin activating features)[24]. In addition, it has been shown that CDK4/6 inhibitors could provide enhanced antitumor immunity, notably through activation of specific T cells transcriptional programs[25,26]. Exploring alterations in the tumor and microenvironment at a genomic, transcriptomic, and proteomic level is thus important to uncover biomarkers that could improve patient selection in the future.

New data emerge regarding sensitivity of ccRCC to anti-angiogenics. In a study of 53 patients with advanced ccRCC treated with sunitinib, 4 unsupervized transcriptomic subgroups were identified, with distinct response rates to sunitinib[27]. Poor responders to sunitinib were patients who belonged to subgroups ccRCC1/4, while good responders belonged to ccRCC2/3 subgroups. The ccRCC4 subgroup was characterized by expression of genes involved in immune response and chemotaxis, as well as several copy number alterations. Both ccRCC1 and 4 had higher methylation than other subtypes, and both overexpressed MYC targets. A recent analysis of the phase 2 trial evaluating atezolizumab, atezolizumab plus bevacizumab or sunitinib reported on outcomes associated with gene expression signatures[28]. Patients who had a high expression of genes involved in angiogenesis had improved outcomes when treated by sunitinib. These data indicate that transcriptomic profiling is a new tool that can help establish relevant predictive markers of response to angiogenic therapies. Evaluating these classifications in the context of HIF-2α inhibition could help inform therapeutic strategies.

In this study, our goal is to explore potential biomarkers of response to abemaciclib alone or abemaciclib plus MK-6482. Correlative studies will be performed on tumor samples before treatment and at progression, including but not limited to immunostaining and molecular analyses. Blood samples will be collected before and on study to assess candidate circulating biomarkers.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologically or cytologically confirmed unresectable advanced or metastatic renal cell carcinoma with clear cell component. Patient with extensive sarcomatoid histology are accepted.

3.1.2 Participants must have failed or developed an intolerance to at least 1 prior anti-VEGFR systemic therapy and 1 immune checkpoint inhibitor for metastatic RCC. No limit on the number of prior lines of therapies.

3.1.3 Measurable disease as per RECIST 1.1. See section 12 for the evaluation of measurable disease.

3.1.4 Age ≥ 18 years

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see **Appendix A**)

3.1.6 Participants must undergo fresh tumor biopsy unless medically unsafe or not feasible.

3.1.7 Normal organ and marrow function as defined below:

- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥100,000/mcL
- Hemoglobin ≥10g/dL (transfusions allowed)
- Total bilirubin ≤2.0 x institutional upper limit of normal with the following exception: patients with known Gilbert disease should have a serum bilirubin ≤ 3 x ULN
- AST(SGOT)/ALT(SGPT)≤3.0 × institutional upper limit of normal with the following exception: patients with known liver metastases should have AST and ALT ≤ 5 x ULN
- Creatinine clearance ≥30 mL/min/1.73 m^2 according to the Cockcroft-Gault equation. (APPENDIX F)
- Urine protein/creatinine ratio (UPC ratio) ≤2

3.1.8 Women of child-bearing potential and men must agree to use adequate contraception (intrauterine device or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and 6 months after completion abemaciclib plus MK-6482 and at least 3 weeks after the completion of abemaciclib administration. If condoms are used as a barrier method, a spermicidal agent should be added as a double barrier protection. A negative pregnancy serum test should be obtained within 7 days of therapy initiation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she must discontinue treatment immediately. Data on fetal outcome and breast-feeding are to be collected for regulatory reporting and drug safety evaluation.. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 6 months after completion abemaciclib plus MK-6482 and at least 3 weeks after the completion of abemaciclib administration.

3.1.9 Ability to swallow oral medications

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

3.2 Exclusion Criteria

A patient will be excluded from the study if he or she meets any of the following criteria:

3.2.1 Patients receiving any other investigational agents.

3.2.2 Patients who received prior CDK4/6 inhibitors.

3.2.3 For Arm 2 only, patients who have received prior HIF-2α inhibitor.

3.2.4 Participants who have received any continuous or intermittent small molecule therapeutics (excluding monoclonal antibodies) ≤ 4 effective half-lives prior to starting study drug or who have not recovered from side effects of such therapy to grade 1 or less (except for non-clinically significant laboratory abnormalities).

3.2.5 Patients must have discontinued all biologic therapy including therapeutic antibodies at least 28 days before C1D1.

3.2.6 Participants who have received wide field radiotherapy ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy to at least grade 1.

3.2.7 Participants with untreated metastatic ccRCC to the brain may participate in this trial if clinically and radiographically stable per investigator's assessment and not on corticosteroid (equivalent to >/= 10 mg prednisone) or antiepileptic therapy.

3.2.8 O2 saturation <92% by arterial blood gas analysis or pulse oximetry on room air

3.2.9 Untreated deep vein thrombosis or pulmonary embolism, or event of deep vein thrombosis or pulmonary embolism within 2 weeks of treatment start. Patient should be on at least 1 week of anticoagulation before C1D1.

3.2.10 The patient has serious and/or uncontrolled preexisting medical condition(s) that, in the judgment of the investigator, would preclude participation in this study (for example, interstitial lung disease, severe dyspnea at rest or requiring oxygen therapy, severe renal impairment [e.g. estimated creatinine clearance <30ml/min], history of major surgical resection involving the stomach or small bowel, or preexisting Crohn's disease or ulcerative colitis or a preexisting chronic condition resulting in baseline Grade 2 or higher diarrhea)."

3.2.11 Patient with active systemic bacterial infection (requiring IV antibiotics at the time of initiating study treatment), fungal infection, or detectable viral infection. Patients with known viral infection (such as HIV) are excluded given the potential for interactions between antiretroviral agents and abemaciclib, and the potential for increased risk of life-threatening infection with therapy that is myelosuppressive. If you are not known to have HIV, a HIV test is required.

3.2.12 Patients with known Hepatitis B or Hepatitis C infection are excluded only if there is evidence of active infection (detectable Hepatitis B surface antigen, detectable Hepatitis C RNA).

3.2.13 Prior allogenic stem cell or solid organ transplant.

3.2.14 Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of oral drugs (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

3.2.15 Participants who have undergone major surgery ≤ 4 weeks (28 days) prior to starting study drug(s) or who have not recovered from side effects of such therapy.

3.2.16 Participants who are currently taking therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulant.

3.2.17 Other malignancy diagnosed within 2 years of first study treatment unless negligible risk of metastases or death according to the investigator (included but not limited to carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer, ductal carcinoma in situ of the breast, non-muscle invasive urothelial carcinoma, or other malignancy not deemed to impact patients 5-year life expectancy).

3.2.18 Has a personal history of any of the following conditions: syncope of cardiovascular etiology, ventricular arrhythmia of pathological origin (including, but not limited to, ventricular tachycardia and ventricular fibrillation), sudden cardiac arrest.

3.2.19 Has had any major cardiovascular event within 6 months prior to study drug administration iincluding but not limited to: myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic event or New York Heart Association Class III or IV heart failure. Patients with history of DVT or PE are eligible provided DVT or PE occurred at least 2 weeks prior to C1D1 and anticoagulation has been initiated at least 1 week before C1D1.

3.2.20 History of symptomatic respiratory condition considered clinically significant by the investigator. History of asymptomatic radiation pneumonitis within a previous radiation field is permitted.

3.2.21 Participants with a known hypersensitivity to the study compounds or to its excipients.

3.2.22 Participant is unable or unwilling to abide by the study protocol or cooperate fully with the investigator

3.2.21 Females that are pregnant or lactating

3.2.23 Participants who have taken herbal medications and certain fruits within 7 days prior to starting study drug. Herbal medications include, but are not limited to St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Fruits include the CYP3A inhibitors Seville oranges, grapefruit, pommelos.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention within 7 calendar days. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.1 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.2 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana Farber Cancer Institute by the Study Coordinator. All sites should call the Study Coordinator 617-582-8313 to verify availabilities. The required forms will be provided to all external sites by the DFCI study coordination.

Following registration, participants should begin protocol therapy within 7 calendar days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered. The Study Coordinator should be notified of cancellations as soon as possible.

4.3 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and emailed/faxed to the DFCI Project Manager:

- Signed and dated DFCI eligibility checklist (signed by MD)
- Current IRB approved consent form signed by participant and Investigator (MD only)
- HIPAA authorization form

- External site subject registration form
- The following source documentation is typically required:
  - Documentation of prior treatments/procedures performed to treat RCC
  - Reports documenting disease status
    - MRI or CT Brain
    - Chest CT
    - CT or MRI Abdomen and Pelvis
    - Bone Scan if applicable
  - Pathology Report
  - Concomitant medication list
  - Progress note or equivalent documentation of consenting visit
  - Progress note documenting medical history and oncologic history
  - Screening Labs
    - Complete blood count with differential
    - Electrolytes
    - Liver Function Tests
    - Urinalysis
    - Coagulation factors
    - Pregnancy test
    - Viral serologies (HBV, HCV, HIV)
  - Screening visit note with vital signs, weight, height, ECOG performance status, physical examination
  - Screening ECG, ECHO

The participating site will then call 617-582-8313 or e-mail the Study Coordinator to verify eligibility. The Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration

5. TREATMENT PLAN

5.1 Treatment Regimen

For patients enrolled in arm 1, abemaciclib single-agent will be administered orally, twice daily, at a starting dose of 200mg bid, on days 1 to 28 of a 28-day cycle as described in **Table 1**. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

Arm 2 consist in a standard 3+3 dose escalation scheme with two planed dose levels of abemaciclib, 100mg bid and 150mg bid, in association with MK-6482 at the dose of 120mg qd, as described in **Table 2** and **Table 3**. MTD is defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in cycle 1. If only three patients are treated at the MTD, an additional three patients will be added for a total of six patients at the MTD. The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved.

Participants will be continued on therapy until radiographic progression or withdrawal for other reason as detailed in section 5.6.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Table 1. Regimen description in Arm 1.

Arm 1: Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Abemaciclib	*None*	*200mg*	*PO*	*Every 12 hours*	*28 days (4 weeks)*

Table 2. Dose escalation schedule in Arm 2.

Dose Escalation Schedule		
Dose Level	**Dose**	
	Abemaciclib	***MK-6482***
Level 1- Starting Dose	100mg bid	120mg daily
Level 2	150mg bid	120mg daily

Table 3. Regimen Description in Arm 2.

Arm 2: Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Abemaciclib	*None*	*See dose escalation schedule*	*PO*	*Every 12 hours*	*28 days (4 weeks)*
MK-6482	*Fasting(1)*	*120mg*	*PO*	*Every 24 hours*	

(1) MK-6482 should be taken in the morning at least 2 hours after the last meal and patients should refrain from eating for at least 1 hour after taking each dose. Should be taken in the morning and can take with abemaciclib.

The participant 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 cycle.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Patients should meet the clinical requirements for eligibility criteria at cycle 1 day 1. The following laboratory parameters should be met:

- ANC ≥ 1,500 mcL
- platelet count ≥ 100,000/uL
- hemoglobin ≥ 10 g/dL (transfusions allowed)
- total bilirubin ≤ 2.0 x institutional upper limit of normal with the following exception: patients with known Gilbert disease should have a serum bilirubin ≤ 3 x ULN
- AST(SGOT)/ALT(SGPT) ≤3 × institutional upper limit of normal with the following exception: patients with known liver metastases should have AST and ALT ≤ 5 x ULN
- creatinine clearance ≥30 mL/min/1.73 m^2 according to the Cockcroft-Gault formula

5.2.2 Subsequent Cycles

Labs should be reviewed and toxicities should be assessed prior to therapy.

5.3 Agent Administration

5.3.1 Abemaciclib

Abemaciclib will be supplied as tablets for oral administration. The tablets should be stored at room temperature according to the range provided on the product label and not crushed, chewed or dissolved. Investigators should instruct patients to store the tablets in the original package and in a location inaccessible to children.

Abemaciclib will be taken orally every 12 (± 2) hours on Days 1 through 28 of a 28-day cycle, for a total of 56 doses per cycle. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted.

5.3.2 MK-6482

MK-6482 will be supplied as tablets for oral administration. MK-6482 should not be crushed, chewed or dissolved in water. MK-6482 must be stored in a secure location in accordance with the study drug label.

MK-6482 will be taken orally every approximately 24 hours on Days 1 through 28 of a 28-day cycle, for a total of 28 doses per cycle. Patients should not consume food beginning 2 hours before and ending 1 hour after taking MK-6482. During all cycles, MK-6482 should be taken at approximately the same times each day. Missed doses of MK-6482 may be made up if taken within 12 hours after the scheduled administration time. Patients who vomit after study drug administration should not retake that study drug dose but should resume taking study drug at the next scheduled administration time.

5.4 Definition of Dose-limiting Toxicity

For patients treated in arm 2, DLT will be defined as any abemaciclib or MK-6482 related toxicity resulting in discontinuation or dose reduction per the guidelines in the Section 6.2 to 6.87 within the first 28 days of treatment, for which there is no clear alternative explanation (i.e. disease related).

DLTs will be defined as any of the following events not clearly due to the underlying disease or extraneous causes:

- Any death
- Non-hematologic toxicity:
    - Grade 3 or higher
    - Hy's law cases
- Hematologic toxicity (for non-acute leukemia indications):
    - Grade 4 neutropenia for more than 7 days
    - Grade 3 or higher thrombocytopenia with clinically significant bleeding
    - Neutropenic fever

The DLT definition may exclude:

- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care
- Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis

Patients within arm 2 who do not receive at least 80% of the intended abemaciclib plus MK-6482 doses during the first 28 days for reasons other than toxicity, will not be evaluable for DLTs and will be replaced. Once a tolerable dose combination has been determined in arm 2, patients will no longer be replaced in the study.

Dose escalation will proceed within each cohort according to **Table 4**. Dose-limiting toxicity (DLT) is defined above.

Table 4. Dose-escalation scheme

Number of Participants with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 participants at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
1 out of 3	Enter at least 3 more participants at this dose level. • If 0 of these 3 participants experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional participants will be entered at the next lowest dose level if only 3 participants were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 participants must be entered at the recommended phase 2 dose.

5.5 General Concomitant Medication and Supportive Care Guidelines

Concomitant medication is defined any medication, over-the-counter preparation, or alternative therapies used within 7 days prior to the screening evaluation and prior to the last study visit. All concomitant medications administered within 14 days prior to Cycle 1, Day 1 and during the study until last study visit will be collected on study-specific electronic Case-Report Forms (eCRFs). The reason(s) for treatment and dates of treatment should be reported to the investigator and recorded as instructed on the study-specific eCRFs.

The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. **Appendix B** presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

5.5.1 **Allowed therapy**

Patients should receive adequate supportive care if appropriate, including but not limited to:

- Antiemetic and anti-diarrheal medication
- Blood derived-products
- Bone resorption inhibitors after appropriate oral examination and counseling for oral hygiene.
- Local corticosteroids, including inhaled, intranasal, topical or intra-articular compounds.
- Systemic corticosteroids at a dose ≤ 20 mg prednisone equivalent.
- Anticoagulation with LMWH, or subcutaneous or oral Factor Xa inhibitor for prophylactic or therapeutic uses.
- Non-live vaccines are allowed including toxoid and recombinant vaccines.
- Hormonal therapy

5.5.2 **Prohibited therapy**

Any other therapy administered for the treatment of kidney cancer, either approved or experimental, is prohibited. This includes but is not limited to chemotherapy, immunotherapy, herbal therapy, or other alternative systemic therapy targeting kidney cancer. Any investigational medical device is prohibited.

Therapeutic oral vitamin K inhibitors are prohibited. The platelet anti-aggregatory compound clopidogrel is also prohibited.

Live vaccines are prohibited during the course of study.

Immunosuppressive agents are prohibited during the course of study participation. Systemic steroids, at doses greater than the equivalent of 20 mg prednisone daily, may not be used.

5.5.3 **Restricted therapy**

Local anticancer therapies can be considered in case of progression or clinical indication. Those include radiation therapy, thermal ablation, surgery. Limited data are available with abemaciclib and radiotherapy. Thus, caution should be exercised with coadministering abemaciclib with radiotherapy. Sponsor must be contacted in these situations to ensure adequate risks related to the procedure and concomitant study treatment. In this situation where a target lesion is treated by such procedure, the participant may continue the study but may not be evaluable for response. However, the patient might remain evaluable for progression after discussion with the study sponsor.

Abemaciclib is predominantly cleared by oxidative metabolism via CYP3A4. Clinical drug interaction studies with a CYP3A inhibitor and CYP3A inducer significantly altered the PK of abemaciclib and its circulating major metabolites.

CYP3A inducers:
Avoid concomitant use of CYP3A inducers (**Appendix B**) and consider alternative agents.

CYP3A inhibitors:
Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a strong CYP3A inhibitor is unavoidable, reduce the abemaciclib dose by one dose level (**Table 5**) or, in the case of ketoconazole, reduce the abemaciclib dose by two dose levels. In patients who have had a dose reduction by one dose level due to adverse reactions, further reduce the abemaciclib dose to dose level -2 (**Table 5**). Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.

In vitro studies in primary cultures of human hepatocytes indicate that abemaciclib might inhibit the metabolism of CYP2B6 substrate drugs in vivo. Based on this finding, sensitive substrates of CYP2B6 such as bupropion and efavirenz should be substituted or avoided if possible.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy
- Pregnancy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

The overall PI must be notified in case of unusual or life-threatening adverse events.

5.7 Duration of Follow Up

After removal from protocol therapy, participants will be followed for safety for 90 days, or until initiation of new cancer-directed treatment, or until death, whichever occurs first.

Participants removed from protocol therapy with ongoing treatment-related adverse event(s) will be followed until resolution or stabilization of the adverse event(s), initiation of new cancer-directed treatment, or death.

Participants removed from protocol who did not experience disease progression will be followed as per protocol until progression, initiation of new cancer-directed treatment, or death.
Participants will be followed for survival and next line of systemic treatments every 6 months, until death or 2 years after treatment discontinuation. Follow-up will be performed by phone calls and review of health records.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-OP-1.

5.9 Replacement

Participants that would be taking off study before receiving any dose of the study drugs will not be part of the analysis, such participant will be replaced. Participants who are enrolled on study but do not reach time of first imaging assessment (8 weeks) will not be evaluable and may be replaced.

5.10 Study and site discontinuation

The overall PI has the ability to discontinue the study, at his discretion, if enrollment is unsatisfactory or if the incidence and severity of adverse events put participants' health at risk. In case of study discontinuation, the PI would notify the investigators in the participating centers.

The overall PI may close any study center in case of incomplete or inaccurate data regarding, poor adherence to protocol, or non-compliance with International Conference on Harmonization guideline for Good Clinical Practice.

6. DOSING DELAYS/DOSE MODIFICATIONS

Stringent inclusion and exclusion criteria as well as close monitoring of both serious and non-serious adverse events aim at ensuring the safety of the participants in this study. All AEs will be defined and graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Safety monitoring includes physical examination, laboratory assessments, as well as serial interval histories. All serious adverse events and protocol-defined events of interest will be specifically reported. Investigators and the overall PI will review adverse events on a regular basis during the study.

Dose delays and modifications will be made as indicated in the following tables. The descriptions and grading scales found in the revised NCI-CTCAE version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Regarding treatment-related side effects, abemaciclib and MK-6482 have different adverse event profiles related to their therapeutic class. Some of these adverse events overlap. Management of adverse events potentially attributed to all study compounds, guidelines for dose delays or dose modifications should apply to all study drugs. If an adverse event is attributed to a specific compound, management of dose delays or modifications should be done independently.

Examples of events of particular interest, by frequency or severity, related to abemaciclib include neutropenia, diarrhea, elevated liver function tests. Examples of events of particular interest, by frequency or severity, related to MK-6482 include anemia, edema, fatigue, diarrhea, nausea.

In general, adverse events should be managed with appropriate supportive care. Dose modifications or delays have to be considered in case of unacceptable toxicity and ineffective symptomatic treatment, in order to prevent aggravation of toxicities. Decision of dose delays or reduction may occur at any time, at the discretion of the investigator. Interruption of all study compounds during a period longer than 12 weeks should lead to study discontinuation, unless specific approval by the overall PI.

6.1 Dose levels of abemaciclib and MK-6482

Dose adaptations of abemaciclib and/or MK-6482 are permitted following guidelines provided in **Table 5** and **Table 6**. If a patient who, in the judgment of the investigator, is receiving clinical benefit from study therapy requires further dose reduction than is outlined in **Table 5** and **Table 6**, then the investigator must discuss with the PI prior to any further dose reduction. For patients requiring dose reduction(s), re-escalation to a prior dose level is permitted only after consultation with the overall PI.

Table 5. Dose adjustments of abemaciclib (arm 1 and 2)

Dose Level	Abemaciclib Dose (Arm 1)	Abemaciclib Dose (Arm 2, starting dose 150mg)	Abemaciclib Dose (Arm 2, starting dose 100mg)
0	200mg bid	150mg bid	100mg bid

- 1	150mg bid	100mg bid	50mg bid
- 2	100mg bid	50mg bid	-
- 3	50mg bid	-	-

Table 6. dose adjustments of MK-6482 (arm 2)

Dose Level	MK-6482 Dose
0	120mg qd
-1	80mg qd
-2	40mg qd

6.2 General guidelines for dose delays and dose modifications

General guidelines for dose reductions and delays according to non-laboratory and laboratory adverse events are summarized in **Table 7** and **Table 8**, respectively. Hematologic adverse events, thrombotic adverse events, diarrhea, nausea, vomiting, liver function tests and serum creatinine abnormalities are subject to specific guidelines described in the following sections.

In the situation where an adverse event is thought to be related to both study drugs (abemaciclib, MK-6482) in arm 2, recommendation for the management of toxicities related to all study drugs should apply. In the situation where an adverse event requiring is considered related only to abemaciclib or MK-6482 in arm 2, recommendation for the management of toxicities related only to abemaciclib or MK-6482 may apply. If a patient requires omission of more than 25% of doses for one or both study drugs during a cycle for tolerability, then treatment may continue if the investigator determines the patient is receiving clinical benefit.

A cycle is defined as the planned treatment interval of 28 days plus any subsequent delay prior to start of the next cycle. A delay in the start of a cycle due to holidays, weekends, bad weather, or other unforeseen circumstances will be permitted up to 7 days and not counted as a protocol deviation. Dose omissions are allowed within a cycle. Imaging evaluations should continue on schedule regardless of treatment delays or interruptions.

Table 7. General guidelines for dose adjustments and delays related to non-laboratory toxicities in patients treated with abemaciclib and abemaciclib plus MK-6482. These guidelines do not apply to the management of thrombotic adverse events, diarrhea, nausea, and vomiting, interstitial lung disease/pneumonitis which are subject to specific guidelines reported within following sections.

Treatment Related Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**
Grade 2 toxicity > 7 days not resolving despite appropriate symptomatic treatment	Hold abemaciclib until resolution of toxicity to baseline or grade 1.	Hold abemaciclib and/or MK-6482 until resolution of toxicity to baseline or grade 1.
Grade 3 toxicity	Hold abemaciclib until resolution of toxicity to baseline or grade 1.	Hold abemaciclib and/or MK-6482 until resolution of toxicity to baseline

	Resume abemaciclib at lower dose level.	or grade 1. Resume abemaciclib and/or MK-6482 at lower dose level.
Grade 4 toxicity	Hold abemaciclib until resolution of toxicity to baseline or grade 1. Resume with lower abemaciclib dose level.	Discontinue MK-6482. Hold abemaciclib until resolution of toxicity to baseline or grade 1. Resume with lower abemaciclib dose level.

Table 8. General guidelines for dose adjustments and delays related to laboratory toxicities in patients treated with abemaciclib and abemaciclib plus MK-6482. These guidelines do not apply to the management of hematologic, liver function tests, and serum creatinine abnormalities, which are subject to specific guidelines reported within following sections.

Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**
Any drug-related grade 3 or 4 laboratory toxicity that does not resolve within 48 hours and considered clinically significant by the investigator	Hold abemaciclib until resolution of toxicity to baseline or grade 1. Resume with lower abemaciclib dose level.	Discontinue MK-6482. Hold abemaciclib until resolution of toxicity to baseline or grade 1. Resume with lower abemaciclib dose level.

6.3 Hematologic adverse events

Hematologic toxicities including neutropenia, leukopenia, anemia, and thrombocytopenia have been observed in patients treated with abemaciclib, and causality has been established. Hematologic toxicities including anemia (on-target effect of MK-6482), lymphopenia, thrombocytopenia have been observed in patients treated with MK-6482.

Complete blood counts should be monitored prior to the start of therapy, at least every 2 weeks for the first 2 months then monthly. These tests may be ordered locally, and performed within 3 business days for each timepoint.

Patients should be monitored closely for signs of infection, anemia, and bleeding. Dose adjustment may be considered for hematological toxicity ≥ Grade 3. Hematological toxicities must resolve to baseline or at least Grade 2 prior to the start of each cycle.

Blood cell growth factors are only to be used in a manner consistent with American Society of

Clinical Oncology (ASCO) guidelines. Dosing of abemaciclib must be suspended if the administration of growth factors is required and must not be restarted within 48 hours of the last dose of growth factors having been administered. When restarted, the dose of abemaciclib must be reduced by 1 dose level if a dose reduction for the specific event necessitating the use of the growth factors has not already occurred.

Fever or infection in the presence of severe neutropenia should be managed promptly with broad-spectrum antibacterial therapy, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. Anemia and thrombocytopenia should be treated supportively and if necessary with red cell or platelet transfusions.

Table 9a. General guidelines for dose adjustments and delays related to non-anemia hematologic toxicities in patients treated with abemaciclib and abemaciclib plus MK-6482.

Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**
Grade 3	Hold abemaciclib until resolution of toxicity or grade 2. Abemaciclib dose may be reduced by one dose level, at investigator discretion	Hold abemaciclib and/or MK-6482 until resolution of toxicity to grade 2. Abemaciclib dose may be reduced by one dose level, at investigator discretion Resume MK-6482 at lower dose level.
Recurrent grade 3 Grade 3 thrombocytopenia with bleeding Grade 3 neutropenia with body temperature ≥ 38.5°C Grade 4	Hold abemaciclib until resolution of toxicity or grade 2. Abemaciclib dose must be reduced by one dose level.	Hold abemaciclib and/or MK-6482 until resolution of toxicity to grade 2. Abemaciclib dose must be reduced by one dose level. Resume MK-6482 at lower dose level.

Table 9b General guidelines for dose adjustments and delays related to anemia in patients treated with abemaciclib and abemaciclib plus MK-6482.

Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**

Grade 3	Hold abemaciclib until resolution of toxicity to grade 2.	Hold abemaciclib and/or MK-6482 until resolution of toxicity to grade 2.
Grade 4	Hold abemaciclib until resolution of toxicity to grade 2. Transfusion and/or ESA support Abemaciclib dose must be reduced by one dose level.	Hold abemaciclib and/or MK-6482 until resolution of toxicity to grade 2. Transfusion and/or ESA support Abemaciclib dose must be reduced by one dose level. Resume MK-6482 at lower dose level.

6.4 Diarrhea, nausea, vomiting

Diarrhea, nausea and vomiting have been described with both study drugs. Guidelines for dose adjustments and delays related to diarrhea, nausea and vomiting are described in **Table 10**.

At enrollment, patients should receive instructions on the management of diarrhea. In the event of diarrhea, supportive measures should be initiated as early as possible. These include the following:

- At the first sign of loose stools, patients should initiate anti-diarrheal therapy (for example, loperamide) and notify the investigator/site for further instructions and appropriate follow-up.
- Participants should be encouraged to drink fluids (for example, 8 to 10 glasses of clear liquids per day)
- Site personnel should assess response within 24 hours
- If diarrhea does not resolve with anti-diarrheal therapy within 24 hours to either baseline or Grade 1, study drug should be held until diarrhea is resolved to baseline or grade 1.
- If diarrhea resolves to baseline or grade 1, participants should resume dosing as outlined in **Table 10**.

In severe cases of diarrhea, measuring neutrophil counts and body temperature and proactively managing diarrhea with antidiarrheal agents is recommended (page 16). In addition, patients with ≥ grade 3 diarrhea should be reviewed by a treating physician once per week until the diarrhea has resolved to ≤ grade 1.

If diarrhea is severe (requiring IV rehydration) and/or associated with fever or severe neutropenia, broad-spectrum antibacterial therapy, including coverage for enteric (gram-negative and anaerobic) bacteria. If neutropenic fever persists for 5 days despite broad-spectrum antibacterial therapy, empiric antifungal therapy should be initiated. If diarrhea persists after antibiotic treatment, testing for Clostridium difficile is indicated as antibiotic therapy might precipitate C. difficile infection.

Patients with severe diarrhea or any grade of diarrhea associated with severe nausea or vomiting should be carefully monitored and given IV fluid (IV hydration) and electrolyte replacement. In these patients, electrolytes and renal function should be monitored regularly during the period of IV hydration.

Table 10. General guidelines for dose adjustments and delays related to diarrhea, nausea and vomiting in patients treated with abemaciclib and abemaciclib plus MK-6482.

Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**
Grade 2 > 24 hours despite appropriate supportive measures	Hold abemaciclib until resolution of toxicity or grade 1. Abemaciclib dose may be reduced by one dose level, at investigator discretion	Hold abemaciclib and MK-6482 until resolution of toxicity to grade 1. Abemaciclib dose may be reduced by one dose level, at investigator discretion Resume MK-6482 at lower dose level.
Any grade requiring hospitalization and/or IV fluids. Recurrent grade 2 despite appropriate supportive measures. Grade 3 or 4.	Hold abemaciclib until resolution of toxicity or grade 1. Abemaciclib dose must be reduced by one dose level.	Hold abemaciclib and MK-6482 until resolution of toxicity to grade 1. Abemaciclib dose must be reduced by one dose level. Resume MK-6482 at lower dose level.

6.5 Liver function tests abnormalities

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation have been described with the use of abemaciclib. Hepatic monitoring should depend on the severity and persistence of the observed laboratory test abnormalities.

Liver function tests including ALT should be monitored prior to the start of therapy, at least every 2 weeks for the first 2 months, then monthly. These tests may be ordered locally, and performed within 3 business days for each timepoint.

Management of hepatic adverse events is summarized in **Table 12**.

Table 11. General guidelines for dose adjustments and delays related to elevated liver functions tests in patients treated with abemaciclib and abemaciclib plus MK-6482.

Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**
Grade 2 AST/ALT elevation > 7 days, or recurrent grade 2AST/ALT elevation, despite maximal supportive measures	Hold abemaciclib until resolution of toxicity or grade 1. Resume abemaciclib at lower dose level.	Hold abemaciclib and MK-6482 until resolution of toxicity to grade 1. Resume abemaciclib at lower dose level. Resume MK-6482 at lower dose level.
Grade 3 ASL/ALT elevation > 48 hours	Hold abemaciclib until resolution of toxicity or grade 1. Resume abemaciclib at lower dose level.	Discontinue MK-6482. Hold abemaciclib until resolution of toxicity to grade 1. Resume abemaciclib at lower dose level.
Grade 3 ASL/ALT elevation and serum bilirubin > 2xULN without evidence of cholestasis. Grade 4 ASL/ALT elevation	Discontinue abemaciclib.	Discontinue abemaciclib and MK-6482.

Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. If a study patient experiences elevated ALT 5×ULN and elevated total bilirubin 2×ULN, or ALT 8×ULN, liver tests, including ALT, AST, total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine phosphokinase (CPK), should be repeated within 48 hours to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator, based on the hepatic monitoring tests below.

Table 12. Hepatic Monitoring Tests for a Hepatic Treatment Emergent Abnormality.

Hepatic Hematology	**Haptoglobin**
Hemoglobin	
Hematocrit	**Hepatic Coagulation**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented and bands	
Lymphocytes	**Hepatic Serologies[a]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody**
AST	**Anti-actin antibody**
GGT	**Anti-smooth muscle antibody**
CPK	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

a Reflex/confirmation dependent on regulatory requirements and/or testing availability.

6.6 Thrombotic adverse events

Thrombotic adverse events have been reported with abemaciclib. Any study drug-related grade 3 cardiovascular, vascular or thrombotic event should lead to discontinuation of both abemaciclib and MK-6482, and initiation of appropriate supportive therapy.

6.7 Serum creatinine elevation

Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular transporters without affecting glomerular function (as measured by iohexol clearance). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

Patient can continue with grade 2 creatinine elevation as long as lab value is not deemed clinically significant by investigator, and as long as creatinine remains stable upon repeat testing performed within 7 days. If creatinine is deemed clinically significant, or trends upward on

repeat testing in clinically significant manner, follow dose modification table (table 8) for management of grade 3/4 lab abnormalities.

6.8 Interstitial lung disease (ILD)/Pneumonitis

General Guidance for Interstitial lung disease (ILD)/Pneumonitis events

Interstitial lung disease (ILD) / pneumonitis has been identified as an adverse drug reaction for abemaciclib. Adverse events reported included events such as interstitial lung disease, pneumonitis, obliterative bronchiolitis, organizing pneumonia, pulmonary fibrosis. The majority of events were Grade 1 or Grade 2 with serious cases and fatal events reported.

Monitor for clinical symptoms or radiological changes indicative of ILD/pneumonitis and please ask patients to report any new or worsening pulmonary symptoms. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams.; these symptoms should be investigated and treated as per local clinical practice and/or guidelines (including corticosteroids as appropriate). Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations. Investigations may include imaging such as high resolution computer tomography (HRCT), bronchoalveolar lavage (BAL), and biopsy as clinically indicated (see also Table 13: *refer to dose adjustment table for interstitial lung disease/pneumonitis*).

Table 13: Dose Modification and Management — Interstitial Lung Disease/Pneumonitis

Toxicity	**Arm 1 – abemaciclib alone**	**Arm 2 – Abemaciclib plus MK-6482**
Grade 1 or 2	No dose modification is required.	No dose modification is required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or Grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.	Hold abemaciclib and MK-6482 until resolution of toxicity to baseline or grade 1. Resume abemaciclib at lower dose level. Resume MK-6482 at lower dose level.
Grade 3 or 4	Discontinue abemaciclib.	Discontinue abemaciclib and MK-6482.

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 reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse events list for abemaciclib

Frequent adverse events reported in >20% of patients treated with abemaciclib single-agent include diarrhea (90%), fatigue (65%), nausea (64%), decreased appetite (46%), abdominal pain (39%), vomiting (35%), headaches (21%), creatinine increased (99%), white blood cell decreased (91%), neutrophil count decreased (88%), anemia (69%), platelet count decreased (41%), ALT increased (30%), AST increased (26%), hypokalemia (26%), hyponatremia (21%).

Grade 3 adverse events reported in >5% of patients treated with abemaciclib single-agent include diarrhea (20%), fatigue (13%), white blood cell decreased (28%), neutrophil count decreased (27%), hypokalemia (5%).

7.1.2 Adverse events list for MK-6482

Based on preliminary phase I data, frequent adverse events with MK-6482 include anemia (75%), fatigue (67%), dyspnea (47%), nausea (33%), and cough (31%).

The only frequent grade 3 adverse event reported in > 10% of patients treated with MK-6482 single-agent is anemia (13%).

7.2 Adverse Event Characteristics

7.2.1 Adverse event

An AE is any unfavorable and unintended sign, symptom, or disease associated with the use of an investigational product or other protocol-imposed intervention, regardless of attribution. Those include:

- AEs not previously observed that emerge during the protocol-specified AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, treatment run-in, or other protocol-mandated intervention

− Pre-existing medical conditions other than the condition being studied, being judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

7.2.2 **CTCAE** term (AE description) and grade.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. 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.

7.2.3 **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.

Attributing the AE to the study treatments (s) means that there is a plausible temporal relationship between the onset of the AE and administration of the study drugs, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the study drug(s); and/or the AE abates or resolves upon discontinuation of the study drug(s) or dose reduction and, if applicable, reappears upon re-challenge.

7.2.4 **Serious adverse event**

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

− It results in death

− It is life threatening. It does not include an AE that, had it occurred in a more severe form, might have caused death.

− It requires or prolongs inpatient hospitalization

− It results in persistent or significant disability/incapacity

− It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational drug

− It is considered a significant medical event by the investigator based on medical judgment, notably by jeopardizing the patient or leading to require medical/surgical intervention to prevent one of the outcomes listed above.

7.2.5 **Diagnosis, signs and symptoms**

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.2.6 **Death**

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death."

7.2.7 **Pre-existing condition**

A pre-existing medical condition is one that is present at the start of the study. Such condition should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre existing condition has changed by including applicable descriptors

7.2.8 **Hospitalizations**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

7.2.9 **Pregnancy**

If a female subject becomes pregnant while on study, she will be taken off study treatment. Pregnancy occurring on study or within 3 months after the last study drug should be reported

expeditiously to the sponsor. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drugs should be reported as an SAE.

7.2.10 **Post-Study Adverse Events**

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior study drugs exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

7.3 Adverse Event Reporting

7.3.1 **Reporting to DFCI**

Investigators must report to the Overall PI any adverse event that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

In the event of an unanticipated problem or life-threatening complications **treating investigators** must immediately notify the Overall PI.

SAEs, whether related or unrelated to the study drugs, should be transmitted to the sponsor within 24 hours of the awareness date.

7.3.2 **For Multi-Center Trials where a DF/HCC investigator is serving as the Sponsor, each external site must abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.**

DF/HCC Adverse Event Reporting Guidelines are as follows:

- Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.
- Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the **Table 14**.

Table 14. Guidelines for adverse events reporting.

Attribution	DF/HCC Reportable Adverse Events(AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	10 calendar days#	10 calendar days	24 hours*
Possible Probable Definite	Not required	10 calendar days	10 calendar days#	10 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

- The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.3.3 Reporting to Eli Lilly

- To comply with applicable laws, regulations and standards regarding Investigator's and Institution's obligations, as the sponsor of the Study, to collect and report adverse events to regulatory authorities, IRBs, Ethics Committees or other third parties. In addition to the obligations set forth below, Investigator and Institution agree to provide Lilly with a copy of all information Investigator and/or Institution submit to regulators related to any adverse events for the Study Drug that occur during the Study that Investigator and/or Institution have not otherwise provided Lilly;

- To notify Lilly, sub-investigators, and the IRB of any problems involving risk to Study patients and report new safety information to IRBs in accordance with applicable requirements;

- Notify Lilly within fifteen (15) business days of Investigator and/or Institution receiving notification of any "serious" adverse event experienced by a patient participating in the Study and receiving Study Drug. For purposes of this requirement, "serious" means: (1) death; (2) in-patient hospitalization or prolonged hospitalization; (3) life-threatening; (4) persistent or significant disability or incapacity; (5) congenital anomaly or birth defect; or (6) other serious events that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other five listed outcomes. Serious adverse events should be reported to Lilly using a CIOMS Form or other form acceptable to Lilly. Investigator and Institution further agree to make available promptly to Lilly such records as may be necessary and pertinent for Lilly to further investigate an adverse event in the Study that is possibly associated with the Study Drug.

- **SAE Reporting Email Address:** mailindata_gsmtindy@lilly.com
  - The Mandatory MedWatch Form 3500A can be used for SAE reporting

7.3.4 **Reporting to Merck**

Any serious adverse event, or follow up to a serious adverse event, deemed related to study procedures from the time of consent up to study drug initiation, must be reported within 24 hours to the Sponsor (DFCI) and within 2 working days to Merck Global Safety. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, that occurs to any subject from the time of study drug initiation through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor (DFCI) and within 2 working days to Merck Global Safety.
Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: 215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

7.3.5 **Reporting to the Food and Drug Administration (FDA)**

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

For expedited reporting, AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided. should AEs that vary in nature, intensity or frequency from the expected toxicity information provided in the protocol and the investigator brochure.

7.3.6 **Reporting to Hospital Risk Management**

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional

policy.

7.3.7 **Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1 Abemaciclib

8.1.1 Description

Abemaciclib, (IUPAC: N-[5-[(4-ethylpiperazin-1-yl)methyl]pyridin-2-yl]-5-fluoro-4-(7-fluoro-2-methyl-3-propan-2-ylbenzimidazol-5-yl)pyrimidin-2-amine), or LY2835219, is a potent and selective inhibitor of CDK4 and CDK6 with IC50 of 2 nM and 10 nM, respectively. It has a molecular weight of 602.7 and it chemical formula is C28H36F2N8O3S.

The half-life is 17-38 hours. Metabolism is primarily hepatic and dependent on CYP3A4. Three major metabolites of abemaciclib, M2, M18 and M20, are found at a concentration > 10% of the parent drug. Those also exert inhibition of CDK4/6 and undergo hepatic metabolism.

Abemaciclib and its metabolites are bound to human plasma proteins: 96.3% for abemaciclib, 93.4% for M2, 96.8% for M18, and 97.8% for M20. Abemaciclib is also a substrate of P-gp and BCRP in vitro, but the effect of P-gp or BCRP inhibitors on abemaciclib are unknown. The geometric mean systemic volume of distribution is approximately 690.3 L (49% CV). Concentration of abemaciclib and metabolites M2 and M20 in cerebrospinal fluid are similar to unbound plasma concentration.

Abemaciclib, M2 and M20, do not induce CYP1A2, CYP2B6, or CYP3A4 at clinically relevant concentrations. Abemaciclib, M2 and M20, down regulate mRNA of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4. The mechanism and clinical relevance of this down regulation are not understood, but no time-dependent changes in abemaciclib concentration due to inhibition of CYP3A4 has been observed.

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (i.e., 20 ms) in the QTc interval.

8.1.2 Form

Abemaciclib, manufactured by Eli Lilly and Company, will be provided in the form of 50mg tablets in a bottle.

Inactive ingredients are as follows:
- Excipients: microcrystalline cellulose 102, microcrystalline cellulose 101, lactose monohydrate, croscarmellose sodium, sodium stearyl fumarate, silicon dioxide.
- Color mixture ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, and iron oxide red.

8.1.3 Storage and Stability

Abemaciclib needs to be stored in the original package. Abemaciclib needs to be kept at room temperature.

8.1.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.5 **Availability**

Abemaciclib will be provided for clinical trial use as 50mg tablets by Eli Lilly and Company. Storage conditions are described in the medication label.

8.1.6 **Administration**

Abemaciclib will be taken orally every 12 (± 2) hours with or without food. Tablets should not be crushed, chewed or dissolved. During all cycles, abemaciclib should be taken at approximately the same times each day. If a patient misses or vomits a dose, that dose should be omitted.

8.1.7 **Ordering**

Eli Lilly and Company will supply abemaciclib and ordering will take place through Eli Lilly and Company. The study team will complete the Drug Request Form, which is kept as a separate document.

8.1.8 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.9 **Destruction and Return**

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Eli Lilly and Company. Destruction will be documented in the Drug Accountability Record Form.

8.2 MK-6482

8.2.1 **Description**

MK-6482 is a potent selective inhibitor of HIF-2α. Mean half-life of MK-6482 is 22.5 hours. MK-6482 oxidative metabolism is minimal in most species. No CYP450 enzyme reaction phenotyping has been performed. One glucosidic glucuronide metabolite detected in rats and dogs (PT3317) was found to be dependent on UGT2B17, mainly expressed in the small intestine.

MK-6482 do not inhibit any CYP enzymes by either competitive (7 CYP isoforms) or time-dependent (CYP3A4) mechanisms up to at least 50 μM. MK-6482 however increase production of CYP3A4 mRNA in cultured human hepatocytes with a half-maximal effective concentration (EC_{50}) of 9.63 to 12.2 μM. The mean C_{max} value for the clinical dose of 120 mg is about 2-fold less than the concentrations at which CYP induction effects are observed.

8.2.2 **Form**

MK-6482, manufactured by Merck, will be provided in the form of 40mg oblong tablets for oral administration.

Each MK-6482 Tablet contains MK-6482 formulated as a spray-dried dispersion with hydroxypropyl methylcellulose acetate succinate, microcrystalline cellulose, mannitol, croscarmellose sodium, and magnesium stearate.

8.2.3 **Storage and Stability**

MK-6482 must be stored in a secure location in accordance with the study drug label.

8.2.4 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.5 **Availability**

MK-6482 will be provided for clinical trial use as 40mg tablets by Merck Storage conditions are described in the medication label.

8.2.6 **Administration**

MK-6482 will be taken orally every approximately 24 hours. Patients should not consume food beginning 2 hour before and ending 1 hour after taking MK-6482. MK-6482 tablets should not be crushed, chewed or dissolved in water. Missed doses of MK-6482 may be made up if taken within 12 hours after the scheduled administration time. Patients who vomit after study drug administration should not retake that study drug dose but should resume taking study drug at the next scheduled administration time.

8.2.7 **Ordering**

Merck will supply MK-6482 and ordering will take place through Merck. The study team will complete the Drug Request Form, which is kept as a separate document.

8.2.8 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.9 **Destruction and Return**

Drug should be destroyed at the site, after the investigator approves the drug destruction policy at the site. Drug will not be returned to Merck. Destruction will be documented in the Drug Accountability Record Form.

9. BIOMARKER STUDIES

Exploratory correlative studies will be performed to assess potential predictors of response to abemaciclib and abemaciclib plus MK-6482. Tissue samples, and whole blood for germline DNA, will be analyzed by investigators at DFCI and collaborating institutions, such as the Broad Institute (Harvard/MIT, Boston), for all patients enrolled on this trial.

Rapid progress in understanding and treating cancer will occur when some of the genetic information derived from tissues and blood can be shared with other researchers. In particular, the National Institutes of Health (NIH) and other organizations have developed special data (information) repositories that analyze data and collect the results of certain types of genetic studies. These central banks will store genetic information, and provide them to qualified researchers to do more research. Therefore, we may share results with these public databases. Some of this information may be made available over the internet and will be freely available to anyone who is interested (an open access database). Other, more detailed information may only be accessed by scientists at other research centers who have received special permission to review study participants' de-identified data (a controlled access database).

Study participant's information will be sent only with a code number attached. Name or other directly identifiable information will not be shared with these repositories or with other investigators. There are many safeguards in place to protect participant's information while they are stored in these repositories and used for research. There is a slight risk of loss of privacy when sharing this information with these banks but we have established procedures to encode study participant information and to protect participant data. The repositories also have robust procedures in place to protect the confidentiality of the stored data. We will do everything we can to protect study participant's data but we cannot absolutely guarantee its privacy or predict how genetic information will be used in the future.

9.1 Blood studies

9.1.1 Blood collection

Blood will be collected at baseline, Cycle 1 Day 1 and Cycle 1 Day 15. For DF/HCC participating sites, 30 mL of blood will be collected as per the Laboratory Manual and couriered within 6 hours of collection to The Gelb Center for Translational Research. For non-DF/HCC participating sites, 30 mL of blood will be collected at baseline and stored as per the Laboratory Manual and batch shipped at the end of study to The Gelb Center for Translational Research.

9.1.2 Procedures

Germline DNA
Germline DNA from whole blood will be used as control for molecular studies. It will also be used to evaluate clonal hematopoiesis of indeterminate potential and correlate this parameter with outcomes.

Circulating biomarkers

Serum plasma will be collected. Plasma will be collected to analyze candidate circulating biomarkers including cytokines and chemokines and their evolution on treatment.

Cell-free circulating DNA
Quantitative detection of cell-free circulating tumor DNA will be evaluated during the course of the study, and correlated with outcomes.

9.2 Tissue studies

9.2.1 Tissue collection

Archival tissue will be retrieved if available. Patients will undergo mandatory baseline tumor biopsy (unless medically unsafe), and post-treatment tumor biopsy after progression, in case of initial response (unless medically unsafe).

Archived tumor tissue collected pre-study as per the Laboratory Manual will be stored at ambient temperature and shipped quarterly to the Signoretti Laboratory, Brigham and Women's Hospital, Boston.

Frozen specimens from tumor biopsies will be stored at -80°C, and specimens fixed in formalin will be stored at 4°C until shipping. The tumor specimens will be shipped to the Signoretti Laboratory quarterly.

Fresh tissue from biopsy specimens will be collected as stated in this protocol and according to institutional guidelines, and put on ice to be transported to the processing laboratory or cryopreserved. A portion of fresh tissue will be dissociated into a single cell suspension and frozen for future studies, including but not limited to single cell transcriptomic, epigenetic, and proteomic studies, and cell line creation.

9.2.2 Procedures

Molecular profiling
Mutation profiling will be performed using massively parallel sequencing technology and a targeted gene panel (Oncopanel) and/or whole exome and/or whole genome sequencing. Gene expression signatures will be explored with whole transcriptome sequencing. The sequencing data will be analyzed for somatic mutations, copy number alterations, overexpressed genes, and chimeric transcripts and a complete set of potential driver alterations will be compiled in archival tissue, in baseline biopsies, and in biopsies performed at progression.

Immunostaining
Immunohistochemistry, immunofluorescence, and/or other advanced imaging techniques will be used to determine the expression of cell cycle genes in tumor cells. Other candidate biomarkers of response to therapy may be explored.

10. PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES

10.1 Pharmacokinetic Assessments

Blood samples for the determination of plasma abemaciclib, abemaciclib metabolites, MK-6482, and MK-6482 metabolites will be collected at multiple time points throughout the study as noted in **section 11**. The date and time of collection of all PK blood samples should be recorded. Validated liquid chromatography/mass spectrometry (LC-MS/MS) methods will be used to assay the samples for plasma concentrations of abemaciclib, abemaciclib metabolites, MK-6482, and MK-6482 metabolites. Additional metabolites, if detected, may be assessed using non-validated methods. Details for the collection, processing, storage, and shipment of samples can be found in the study laboratory manual.

10.2 Pharmacodynamic Assessments

Blood samples collected for serum soluble factors will be assessed for erythropoietin concentration. Whole blood samples will be subjected to DNA isolation to determine genomic status of drug metabolizing enzymes and other hypoxia pathway components that may influence drug exposure and/or response to drug treatment.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 4 weeks prior to the start of therapy, at the exception of pregnancy test that should be performed within 7 days of therapy start. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Study calendar is described in **Table 15**.

Table 15. Study calendar.

	Pre-treatment[1]	Cycle 1[2]		Cycle 2[2]		Cycle 3+[2]	Every 8 weeks[3]	Treatment discontinuation visit (within 30 days of last treatment)[4]	Follo w-up[5]	EDC Timepoints
		D1	D15	D1	D15	D1				
Informed Consent	X									Baseline
Demographics	X									Baseline
History and Physical[6]	X	X	X	X	X	X		X		Baseline, every cycle and EOT
ECOG Performance Status	X	X	X	X	X	X		X		Baseline, every cycle and EOT
Vital Signs[7]	X	X	X	X	X	X		X		Baseline, every cycle and EOT
Weight	X	X	X	X	X	X		X		Baseline, every cycle and EOT
Height	X									
Hematology[8]	X	X	X	X	X	X		X		Baseline, every cycle and EOT
Serum Chemistry[9]	X	X	X	X	X	X		X		Baseline, every cycle and EOT
Liver Function Tests[10]	X	X	X	X	X	X		X		Baseline, every cycle and EOT
Urine protein/creatinine ratio	X									Baseline
Coagulation Factors[11]	X									Baseline
Pregnancy Test[12]	X			X		X				Baseline, Cycle 2 D1 and every cycle day 1 after
Viral Serologies[13]	X									Baseline
C-Reactive Protein	X									Baseline
EKG	X									Baseline
ECHO	X									Baseline
MRI or CT Brain[14]	X						X[15]			Baseline and every 8 weeks
Imaging[16]	X						X			Baseline and every 8 weeks
FKSI-19	X						X	X		Baseline, every 8 weeks and EOT
BFI	X						X			Baseline and

										every 8 weeks
Concomitant Medications	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**Baseline, every cycle and EOT**
Adverse Events	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**Baseline, every cycle and EOT**
Abemaciclib[17]		**X**								**Every cycle**
Germline DNA[18]		**X**								**C1D1**
Archival Tumor Tissue[19]	**X**									**Baseline**
Tumor Biopsy[20]	**X**							**X**		**Baseline and EOT**
Pharmacokinetic samples[21]		**X**								**Cycle 1 Day 1**
Pharmacodynamic samples [22]		**X**	**X**							**Cycle 1 Day 1 and Cycle 1 Day 15**
Survival Follow-Up									**X**	**Follow Up**
Arm 2 only										
MK-6482[23, 24]		**X**								**Arm 2 every cycle**

1: Baseline evaluations are to be conducted within 28 days prior to the start of therapy, at the exception of the serum pregnancy test that must be performed within 7 days of therapy start. Scans must be done within 28 days prior to the start of therapy. All baseline screening should be done prior to registration.

2: A cycle will be defined as 28 days.

3: Imaging assessments, quality of life assessments will take place:
- every 8 weeks (+/- 7 days) for the first 6 months.
- After 6 months, imaging assessments and quality of life assessments can take place every 12 weeks (+/- 10 days)

4: Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit.

5: After progression/treatment discontinuation, participants will be followed for survival and receipt of next line therapies every 6 months until death or 2 years after treatment discontinuation. Participants removed from protocol therapy with ongoing treatment-related adverse event(s) will be followed until resolution or stabilization of the adverse event(s), initiation of new cancer-directed treatment, or death. Participants removed from protocol who did not experience disease progression will be followed as per protocol until progression, initiation of new cancer-directed treatment, or death.

6: Physical examination should include general description of participant, head, eyes, ears, nose, and throat, chest, abdominal, extremities, neurologic, skin, and lymph node examination. Any other evaluation is up to the discretion of the practitioner. It will not be considered a violation if the exam is not described as outlined here.

7: Vital signs include blood pressure, heart rate, respiratory rate, body temperature and pulse oximetry.

8: Hematology testing to include full CBC with WBC, ANC, hemoglobin, and platelet count and differential.

9: Serum chemistry to include full comprehensive metabolic panel with sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, albumin, magnesium, and LDH.

10: Liver function tests to include AST, ALT, total bilirubin, and direct bilirubin

11: Coagulation factors to include PT, aPTT, and INR.

12: Pregnancy test only needs to be obtained in women of childbearing potential, within 7 days of therapy start.

13: Hepatitis B virus (HBV) serology (HBsAg, hepatitis B core antibody), and HCV serology (anti-HCV). HBV DNA test is required for patients who have known positive serology for hepatitis B core antibody. HCV RNA test is required for patients who have known positive serology for anti HCV. HIV testing is also required if you are not known to have HIV.

14: MRI of the brain with and without contrast is preferred. If a patient is not able to obtain an MRI, CT imaging with contrast is acceptable. If a patient is no able to receive contrast, CT head without contrast is acceptable.

15: Brain imaging should be performed along with other imaging assessments during the study in case the participant has previously treated brain metastases at baseline. Brain metastases at baseline that are untreated, symptomatic, or that require corticosteroids constitute an exclusion criteria.

16: Diagnostic CT chest and CT or MRI of the abdomen and pelvis should be obtained at baseline and at every planned assessment. All baseline scans used to determine disease burden should be continued during restaging scans. In instances when providers would like to follow with bone scans they can be followed at 8 or 12 weeks by provider discretion. Actual images and imaging reports at all time points including baseline, on study, and at treatment discontinuation must be sent to DFCI for central review once a patient has discontinued treatment.

17: Abemaciclib given twice daily as directed by the principal investigator.

18: Blood for germline DNA analysis will be collected once at Cycle 1 Day 1.

19: Archival tissue should be requested prior to therapy initiation if available. A note from the study team should be provided documenting availability of tissue.

20: Baseline fresh tumor biopsies are not optional, and must occur at least 7 days prior to the first dose of therapy if medically feasible and safe. Progression tumor biopsies are mandatory if medically safe. The progression tumor biopsy must be at least 2 weeks after the participants' last dose of the study drugs.

21: At the Cycle 1 Day 1 Visit, patients will have 4mL of blood drawn for PK assessments before and 3 (± 15 minutes) hours after study drug administration.

22: One blood sample for analysis of PD effects (e.g., EPO) will be collected before study drug administration on Cycle 1 Day 1 and Cycle 1 Day 15. One whole blood RNA sample for RNA expression analysis will be collected before study drug administration on Cycle 1 Day 1 and Cycle 1 Day 15. Two whole blood DNA samples will be collected at the Week 1 Day 1 visit only for sequencing of genes encoding proteins that may be involved in regulating MK-6482 metabolism or in response to the combination treatment.

23: MK-6482 given once daily as directed by the principal investigator.

24: Patients should hold morning doses of abemaciclib and MK-6482 tablets on clinic visit days on Cycle 1 Day 1 and Cycle 1 Day 15 until after completion of the first blood collection. The time of ingestion of abemaciclib and MK-6482 tablets should be recorded and subsequent time dependent procedures should be performed relative to the MK-6482 dose ingestion time.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks during the first six months of the study, then every 12 weeks, in both arms. Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). 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.

12.1.1 **Definitions**

Evaluable for Target Disease response. Only those participants 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 target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants 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.

12.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥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 not be considered measurable.

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, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered 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 participant, 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. If a target lesion is biopsied at screening, this lesion must be followed as non-target lesions after the biopsy unless it is the patients only target lesion. If there is only one target lesion, it should be followed as a target lesion regardless.

12.1.3 **Methods for Evaluation of Disease**

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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 in 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.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of 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.

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 data 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 from CT, MRI may be used instead of CT in selected instances.

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.

12.1.4 **Response Criteria**

12.1.4.1 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.

12.1.4.2 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).

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).

12.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

12.1.4.4 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. Evaluation of best overall response should be performed according to **Table 16** and **Table 17** guidelines.

Table 16. Evaluation of best overall response in patients with measurable disease (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 weeks 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: Participants 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.

Table 17. Evaluation of best overall response in patients with non-measurable disease (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

12.1.4.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

12.1.5 **Response Review**

Tumors will be assessed for response and progression by RECIST version 1.1 by central radiology review.

12.1.6 **Progression-Free Survival**

Overall Survival: Overall Survival (OS) is defined as the time from trial treatment start to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from trial treatment start to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from trial treatment start to progression, or censored at date of last disease evaluation for those without progression reported.

13. 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).

13.1 Data Reporting

13.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

13.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

13.1.3 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13.2 Multi-Center Guidelines

This protocol will adhere to DF/HCC Policy MULTI-100 and the requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and External Sites and the procedures for auditing are presented in Appendix C.

14. STATISTICAL CONSIDERATIONS

This is a multi-center, open-label, phase I/IB study of abemaciclib (arm 1) or abemaciclib plus MK-6482 (arm 2) in patients with advanced refractory ccRCC.

The primary objective of arm 1 is to evaluate the objective response rate of abemaciclib in this population.

The co-primary objectives in arm 2 are to determine the MTD of abemaciclib plus MK-6482, and to determine the objective response rate of abemaciclib plus MK-6482 at the MTD in this population.

Arm 2 will be opened after enrollment of arm 1 is completed.

14.1 Endpoints

14.1.1 Primary Endpoint

Arm 1

Objective response rate (ORR) defined as the percentage of patients with partial (PR) or complete response (CR) as best overall response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by central review.

Arm 2

MTD of abemaciclib plus MK-6482, defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in cycle 1.

Objective response rate (ORR) defined as the percentage of patients with partial (PR) or complete response (CR) as best overall response according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 by central review.

14.1.2 Secondary endpoints

Duration of response (DOR) as defined in section 12.1.4.5.

Progression-free survival (PFS) defined as the time from trial treatment start to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Overall survival (OS) defined as the time from trial treatment start to death due to any cause, or censored at date last known alive.

Safety and tolerability according to NCI CTCAE v5.0.

Quality of life using FKSI-19 and BFI. The FKSI-19 is a 19 item questionnaire with each item scored on a scale of 0-4 for a total score of 0-76 with higher scores indicating fewer symptoms (Appendix D)[29]. The BFI is a 9 item questionnaire with each item scored on a scale of 0-10. Scores are categorized as mild (1-3), moderate (4-6), or severe (7-10). A global fatigue score can be found by averaging the score obtained on each test item completed (**Appendix E**)[30].

Pharmacokinetics of abemaciclib and MK-6482.

14.1.3 **Exploratory endpoints**

Pharmacodynamics of abemaciclib and MK-6482.

Correlates of response and survival: clinical and biological data, study of archival tissue, fresh tumor tissue and blood samples collected before and on therapy.

14.2 Sample Size and Accrual

There is limited data regarding clinical activity of abemaciclib and MK-6482 in ccRCC. Activity of abemaciclib has been described in a phase 1 trial in solid tumors that did not involve ccRCC patients[14]. Response rates in advanced refractory breast cancer patients treated with abemaciclib single agent was 19.5%[15].

MK-6482 is has been evaluated in a phase I/II trial involving patients with refractory ccRCC. Preliminary data showed that among 55 patients treated at the MTD, objective response rate was 22%. Toxicities involved mainly anemia, hypoxia and edema. Drug discontinuations due to adverse events were less than 10%.

Therefore, in arm 1, planned sample size is 11 patients, allowing a 0.80 probability to observe 2 or more responses if the true ORR is 25% or higher.

Arm 2 will evaluate two dose levels and follow a standard 3+3 dose escalation scheme. Once the MTD is determined and 6 patients have been treated at the MTD, 14 additional patients will be enrolled for a total of 20 patients treated at the MTD. As ORR is 20-25% for ccRCC patients treated with MK-6482 single-agent, we target an ORR of 50% for the combination of abemaciclib plus MK-6482. With a planned sample size of 20 patients treated at the MTD, there is 94% power to distinguish an ORR of 50% from an ORR of 20% under one-stage design (one-sided alpha=0.09). The combination is considered effective if 7 or more responses are observed out of 20.

The total enrollment will be up to 37 patients (11 in arm 1 and 23~26 patients in arm 2). The accrual is expected to be 3-4 patients per month for a duration of 12 months to complete enrollment.

14.3 Statistical Analysis

14.3.1 Analysis Datasets

The following Analysis datasets are planned for this study:

Full Analysis Set (FAS): The FAS will include all eligible patients who receive at least one dose of protocol therapy. All efficacy endpoints will be analyzed using the FAS Population.

Safety Analysis Set: Safety analysis will be conducted using the Safety Analysis Set defined as any participant receiving one dose of study treatment.

14.3.2 Efficacy Analysis (arm 1 and 2)

Number and percent of patients who achieve overall response (CR or PR) by RECIST 1.1 will be summarized with 80% two-sided exact binomial confidence intervals (CI) in the FAS cohort. Subjects who have non-evaluable response, withdraw or die prior to the first response evaluation will be conservatively counted as non-responders in the primary analysis of ORR.

14.3.3 Determination of the MTD (arm 2)

Three to six patients will initially be treated for 28 days (1 cycle) and a safety evaluation will be done by the overall PI before any further patients are enrolled. MTD is defined as the highest dose studied at which no more than 1 of 6 subjects has experienced a DLT in cycle 1. If only three patients are treated at the MTD, an additional three patients will be added for a total of six patients at the MTD. The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved.

14.3.4 Secondary Endpoints Analysis

Time to event endpoints (PFS, DOR and OS, as defined in section 12.1.4.5, 12.1.6 and 14.1.2) will be estimated using the method of Kaplan-Meier, for each treatment arm. Median and event-free rate at selected timepoints along with 95% confidence intervals will be provided.

For toxicity reporting, all adverse events will be graded and analyzed using CTCAE version 5. Type of adverse events, intensity (grading), and attribution will be provided in a listing. The worst grade will be used if any toxicity event is reported multiple times on the same participant. All adverse events resulting in discontinuation, dose modification, and/or dosing interruption, and/or treatment delay of drug will also be summarized. All laboratory test results will be classified according to the CTCAE version 5.

14.3.5 Quality of Life (QOL) Endpoints Analysis

The QOL will be measured by the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI)-19 and the Brief Fatigue Inventory (BFI). The questionnaires will be administered per schedule defined in section 11 (study calendar).

The FKSI-19 comprises of 19 items (each score ranging from 0-4) with a possible maximum total score of 76. The BFI is a 9 items questionnaire (each score ranging from 0-10) with a possible maximum score of 90. The calculated total scores at each timepoint and changes from baseline will be summarized with mean and standard deviation. Changes from baseline will be graphically presented. For FKSI-19, the proportion of patients with "clinically significant" symptoms (those scoring 3 or 4) will also be descriptively summarized over times across all items or by sub-domains. Missing assessments may be due to stopping treatment, not completing the FKSI or BFI assessments, and other reasons. Information on reasons why the patient did not complete the FKSI-19 or BFI Form will be collected.

14.3.6 **Pharmacokinetic analyses**

All PK concentration data (MK-6482, MK-6482 metabolites, abemaciclib, abemaciclib metabolites) will be listed in each arm and by dose cohort.

Blood samples for the determination of concentration of MK-6482, MK-6482 metabolite, abemaciclib, abemaciclib metabolites will be obtained before (pre-dose), 3 hours (± 15 minutes) post-dose at Cycle 1 Day 1 visit. The plasma concentrations of MK-6482, MK-6482 metabolites, abemaciclib, abemaciclib metabolites at each collection time will be summarized descriptively (n, arithmetic mean, standard deviation, minimum, median, maximum, and coefficient of variation) by arm and dose cohort. Figures displaying individual and mean plasma concentrations will be provided.

14.3.7 **Pharmacodynamic analyses**

Summary statistics (n, arithmetic mean, standard deviation, median, minimum, and maximum) for the observed data and percentage change from baseline will be presented for PD blood sample parameters by arm and dose cohort.

Blood samples for assessment of pharmacodynamic parameters such as EPO will be obtained as per schedule of events. Whole blood RNA and DNA samples will be used to determine genomic status of drug metabolizing enzymes and other hypoxia pathway components that may influence drug exposure and/or response to drug treatment.

The value, change from baseline, and percent change from baseline will be listed and summarized for each scheduled time-point during the study for each of the pharmacodynamic parameters.

14.3.8 **Correlative Endpoints Analysis**

The planned correlative analyses include (but are not limited to):

- molecular profiling using Oncopanel, whole exome sequencing and whole transcriptome sequencing.
- immunohistochemistry, immunofluorescence and other advanced imaging techniques to assess expression of oncogenic proteins on tumor cells
- candidate circulating immune markers before and during therapy

- circulating cell-free DNA (cfDNA) values during the course of therapy
- germline DNA from whole blood

Gene mutation frequencies and mean ± SD of quantitative transcriptome will be summarized in overall population. It is anticipated that we will have tissue samples assayed in about 60% of participants (N=22) at baseline and in 40% (N=15) at progression.

Candidate circulating biomarkers and their changes from baseline will be summarized during the course of therapy. Normality will be assessed and appropriate transformation will be made at time of analysis. Paired T-test or Wilcoxon signed rank test will be conducted for any paired comparison between timepoints. Two-sample t-test or Wilcoxon rank sum test will be used to compare quantitative circulating biomarkers between responders and non-responders (by RECISTcriteria) as exploratory analyses.

14.4 Safety monitoring

No formal stopping rule regarding the primary efficacy endpoints is planned. Adverse event reports are to be submitted within 28 days of each clinic visit. All relevant adverse events will be reviewed by the DSMC for up to 4 times each year. The DSMC will make recommendation to the study management team if it notes any concerns regarding patient safety or if further action needs to be taken based on the safety monitoring review results. Formal assessment of (targeted) adverse events will also be included in statistical analysis for secondary objectives as detailed in section 14.3.4.

15. ETHICAL CONSIDERATIONS

15.1 Compliance with Laws and Regulations

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive abemaciclib or abemaciclib plus MK-6482 treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in **Section 5.5**.

15.2 Informed Consent

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

15.3 Institutional Review Board or Ethics Committee Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug(s) by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Exelixis or Bristol Myers Squibb (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

15.4 Confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health

information) signed by the patient or unless permitted or required by law. Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Exelixis representatives and collaborators, Bristol Myers Squibb and representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

15.5 Study Medical Monitoring Requirements

This clinical research study will be monitored both internally by the PI and externally by the IRB. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed.

15.6 Study Medication Accountability

The recipient will acknowledge receipt of the drugs provided by Exelixis and Bristol Myers Squibb, indicating shipment content and condition. Damaged supplies
will be replaced.

Accurate records of all study drugs dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Genentech.

15.7 Data Collection

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA and the DFCI IRB.

16. PUBLICATION PLAN

The data will be collected by the Principal Investigator and analyzed by the Principal Investigator and the statistical team at DFCI. It is anticipated that the results would be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors.

17. REFERENCES

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394–424.

2 Hsieh JJ, Purdue MP, Signoretti S, *et al.* Renal cell carcinoma. *Nat Rev Dis Primer* 2017; **3**: 17009.

3 Cancer of the Kidney and Renal Pelvis - Cancer Stat Facts. SEER. https://seer.cancer.gov/statfacts/html/kidrp.html (accessed May 12, 2019).

4 Shen C, Kaelin WG. The VHL/HIF Axis in Clear Cell Renal Carcinoma. *Semin Cancer Biol* 2013; **23**: 18–25.

5 Sato Y, Yoshizato T, Shiraishi Y, *et al.* Integrated molecular analysis of clear-cell renal cell carcinoma. *Nat Genet* 2013; **45**: 860–7.

6 Ricketts CJ, Morris MR, Gentle D, *et al.* Genome-wide CpG island methylation analysis implicates novel genes in the pathogenesis of renal cell carcinoma. *Epigenetics Off J DNA Methylation Soc* 2012; **7**: 278–90.

7 Brastianos PK, Carter SL, Santagata S, *et al.* Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. *Cancer Discov* 2015; **5**: 1164–77.

8 Turajlic S, Xu H, Litchfield K, *et al.* Tracking Cancer Evolution Reveals Constrained Routes to Metastases: TRACERx Renal. *Cell* 2018; **173**: 581-594.e12.

9 Rini BI, Plimack ER, Stus V, *et al.* Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. *N Engl J Med* 2019; **0**: null.

10 Motzer RJ, Escudier B, McDermott DF, *et al.* Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015; **373**: 1803–13.

11 Choueiri TK, Escudier B, Powles T, *et al.* Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med* 2015; **373**: 1814–23.

12 Knox JJ, Barrios CH, Kim TM, *et al.* Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC. *Ann Oncol Off J Eur Soc Med Oncol* 2017; **28**: 1339–45.

13 Sanchez-Vega F, Mina M, Armenia J, *et al.* Oncogenic Signaling Pathways in The Cancer Genome Atlas. *Cell* 2018; **173**: 321-337.e10.

14 Patnaik A, Rosen LS, Tolaney SM, *et al.* Efficacy and Safety of Abemaciclib, an Inhibitor of CDK4 and CDK6, for Patients with Breast Cancer, Non-Small Cell Lung Cancer, and Other

Solid Tumors. *Cancer Discov* 2016; **6**: 740–53.

15 Dickler MN, Tolaney SM, Rugo HS, *et al.* MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. *Clin Cancer Res Off J Am Assoc Cancer Res* 2017; **23**: 5218–24.

16 Sledge GW, Toi M, Neven P, *et al.* MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol Off J Am Soc Clin Oncol* 2017; **35**: 2875–84.

17 Goetz MP, Toi M, Campone M, *et al.* MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer. *J Clin Oncol Off J Am Soc Clin Oncol* 2017; **35**: 3638–46.

18 Xu R, Wang K, Rizzi JP, *et al.* 3-[(1S,2S,3R)-2,3-Difluoro-1-hydroxy-7-methylsulfonylindan-4-yl]oxy-5-fluorobenzonitrile (MK-6482), a Hypoxia-Inducible Factor 2α (HIF-2α) Inhibitor for the Treatment of Clear Cell Renal Cell Carcinoma. *J Med Chem* 2019; **62**: 6876–93.

19 Papadopoulos KP, Jonasch E, Zojwalla NJ, Wang K, Bauer TM. A first-in-human phase 1 dose-escalation trial of the oral HIF-2a inhibitor MK-6482 in patients with advanced solid tumors. *J Clin Oncol* 2018; **36**: 2508–2508.

20 Ricketts CJ, De Cubas AA, Fan H, *et al.* The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. *Cell Rep* 2018; **23**: 3698.

21 Logan JE, Mostofizadeh N, Desai AJ, *et al.* PD-0332991, a Potent and Selective Inhibitor of Cyclin-dependent Kinase 4/6, Demonstrates Inhibition of Proliferation in Renal Cell Carcinoma at Nanomolar Concentrations and Molecular Markers Predict for Sensitivity. *Anticancer Res* 2013; **33**: 2997–3004.

22 Small J, Washburn E, Millington K, Zhu J, Holder SL. The addition of abemaciclib to sunitinib induces regression of renal cell carcinoma xenograft tumors. *Oncotarget* 2017; **8**: 95116–34.

23 Cornell L, Wander SA, Visal T, Wagle N, Shapiro GI. MicroRNA-Mediated Suppression of the TGF-β Pathway Confers Transmissible and Reversible CDK4/6 Inhibitor Resistance. *Cell Rep* 2019; **26**: 2667-2680.e7.

24 Gong X, Litchfield LM, Webster Y, *et al.* Genomic Aberrations that Activate D-type Cyclins Are Associated with Enhanced Sensitivity to the CDK4 and CDK6 Inhibitor Abemaciclib. *Cancer Cell* 2017; **32**: 761-776.e6.

25 Deng J, Wang ES, Jenkins RW, *et al.* CDK4/6 Inhibition Augments Anti-Tumor Immunity by Enhancing T Cell Activation. *Cancer Discov* 2017; : CD-17-0915.

26 Schaer DA, Beckmann RP, Dempsey JA, *et al.* The CDK4/6 Inhibitor Abemaciclib Induces a T Cell Inflamed Tumor Microenvironment and Enhances the Efficacy of PD-L1 Checkpoint Blockade. *Cell Rep* 2018; **22**: 2978–94.

27 Beuselinck B, Job S, Becht E, *et al.* Molecular subtypes of clear cell renal cell carcinoma are associated with sunitinib response in the metastatic setting. *Clin Cancer Res Off J Am Assoc Cancer Res* 2015; **21**: 1329–39.

28 McDermott DF, Huseni MA, Atkins MB, *et al.* Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nat Med* 2018; **24**: 749–57.

29 Rao D, Butt Z, Rosenbloom S, *et al.* A Comparison of the Renal Cell Carcinoma Symptom Index (RCC-SI) and the Functional Assessment of Cancer Therapy –Kidney Symptom Index (FKSI). *J Pain Symptom Manage* 2009; **38**: 291–8.

30 Mendoza TR, Wang XS, Cleeland CS, *et al.* The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999; **85**: 1186–96.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

Abemaciclib interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Abemaciclib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is CYP3A4. Abemaciclib is broken down by this enzyme in order to be cleared from your system.
- Abemaciclib must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme. Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of CYP3A4.
- Your prescribers should look at the web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.
- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: You should not take St. John's wort while you are taking Abemaciclib

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is

_____

and he or she can be contacted at

_____

INFORMATION ON POSSIBLE DRUG INTERACTIONS

You are enrolled on a clinical trial using the experimental agent _____. This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicine or if you start taking a new medicine.
- Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, and pharmacist) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

_____ interacts with a specific liver enzyme called **CYP**_____, and must be used very carefully with other medicines that interact with this enzyme.

- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP**_____."
- Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

Strong Inhibitors of CYP3A4	Strong Inducers of CYPA4
Antivirals Boceprevir Cobicistat Conivaptan Danoprevir Dasabuvir Elvitegravir Indinavir Lopinavir Nelfinavir Ombitasvir Paritaprevir Ritonavir Saquinavir Telaprevir Tipranavir **Anti-Fungals** Itraconazole Ketoconazole Posaconazole Voriconazole **Antibiotics** Clarithromycin Telithromycin Troleandomycin Conivaptan Diltiazem Verapamil Grapefruit juice/star fruit/Seville oranges Idelalisib Nefazodone	Carbamazepine Efavirenz Enzalutamide Erythromycin Mitotane Modafinil Nevirapine Oxcarbazepine Phenytoin Rifampin St. John's Wort

APPENDIX C MULTI-CENTER GUIDELINES

DFCI IRB Protocol #XX-XXX

APPENDIX C

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Polices and Operations .

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from External Sites in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to External Sites as needed.
- Oversee the data collection process from External Sites.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all External Site.
- Provide External Site with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor External Site either by on-site or remote monitoring.
- Maintain Regulatory documents of all External Sites which includes but is not limited to the following: local IRB approvals/notifications from all External Sites, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all External Sites (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 External Site

An External Site is an institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC investigator. The External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Externals may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
  Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
  Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. The following section will clarify DF/HCC requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and

implemented within a timely manner from receipt of the notification

- **Protocol closures and temporary holds:** External Sites will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Site. The External Site consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, the approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.3 IRB Re-Approval

Verification of IRB re-approval for the External Sites is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the External Site on or before the anniversary of the previous approval date.

3.4 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5 Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and faxed or e-mailed to the Coordinating Center:

- Current IRB approved informed consent document informed consent document signed by participant and investigator. Participant name and MRN must be redacted. Please ensure the participant's initials are written on each page of the informed consent document.
- HIPAA authorization form (if separate from the informed consent document)
- Signed and dated Eligibility Checklist.
- External site subject registration form
- The following source documentation is typically required:
    - Documentation of prior treatments/procedures performed to treat RCC
    - Reports documenting disease status
        MRI or CT Brain
        Chest CT
        CT or MRI Abdomen and Pelvis
        Bone Scan if applicable
    - Pathology Report
    - Concomitant medication list
    - Progress note or equivalent documentation of consenting visit
    - Progress note documenting medical history and oncologic history
    - Screening Labs
    - Screening visit note with vital signs, weight, height, ECOG performance status, physical examination
    - Screening ECG, ECHO

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).
- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.6 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the External Site receives confirmation of the participant's registration from the

Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without IRB approval will be permitted. All External Sites are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 Data Management

DF/HCC develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC provides a web based training for all eCRF users.

3.8.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

If study forms are not submitted on schedule, the External Sites will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

3.9 Protocol Reporting Requirements

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

3.9.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g.enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.9.2 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor and to the IRB of record.

3.9.3 Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.9.4 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

External Sites must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all External Site Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. External Sites will review and submit to their IRB according to their institutional policies and procedures

3.9.5 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.1 Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management

Site visits will generally occur once a year for sites that are actively enrolling participants and have participants in treatment. Additional monitoring activities may occur if incidences of non-compliance are discovered or at the request of the DF/HCC Sponsor. Virtual monitoring (source documents are sent to DFCI for review) may be performed in lieu of a site visit if the study staff and PI determine that virtual monitoring is appropriate for the site. The decision to perform virtual monitoring in lieu of a site visit will be based upon the site's enrollment, study compliance history, history collaborating with DFCI on other multi-center studies, and number of participants in active treatment.

Monitoring will occur before the clinical phase of the protocol begins and will continue during protocol performance through study completion.

Teleconferences between DFCI and the participating sites will be conducted on approximately a monthly basis. Meeting minutes for teleconferences will be issued to all participating sites. Site initiation visits will be conducted via teleconference. Ongoing training will also be conducted via teleconference as needed. The Coordinating Center, Dana Farber Cancer Institute will be available to all participating sites for resolving questions, concerns and facilitating compliance.

4.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each external site. Accrual will be monitored for each external site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The following **minimum** accrual requirements are recommended:

1) Phase I: 2 per site/annually
2) Phase II-III: 3 per site/annually. However, given the additional regulatory burden and cost of overseeing each site, a consideration of 5 per site/annually should be a minimum target for each site.
3) Note: Diseases that are extremely rare may have accrual expectations of 0-1 accruals/year.]

5. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Policies, and the Code of Federal Regulations (CFR).

5.1 DF/HCC Internal Audits

All External Sites are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety, or the integrity of the study are found, more participant records may be audited.

5.2 Audit Notifications

It is the External Site's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

5.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

5.4 External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be put on hold or closed.

APPENDIX D FKSI-19

STUDY ID_____ STUDY NUMBER_____
DATE_____
Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to <u>the past 7 days.</u>**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
RCC 2	I have had blood in my urine	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GF1	I am able to work (include work at home)	0	1	2	3	4

GF3	I am able to enjoy life	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

DRS-P = Disease-related symptoms subscale – Physical
DRS-E = Disease-related symptoms subscale – Emotional
TSE = Treatment side effects subscale
FWB = Function and well-being subscale

APPENDIX E BRIEF FATIGUE INVENTORY

Brief Fatigue Inventory

STUDY ID# _____ HOSPITAL # _____

Date: ____/____/____ Time: _____

Name _____ _____ _____
Last First Middle Initial

Throughout our lives, most of us have times when we feel very tired or fatigued. Have you felt unusually tired or fatigued in the last week? Yes ☐ No ☐

1. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

2. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

3. Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Fatigue — As bad as you can imagine

4. Circle the one number that describes how, during the past 24 hours, fatigue has interfered with your:

A. General activity
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

B. Mood
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

C. Walking ability
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

D. Normal work (includes both work outside the home and daily chores)
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

E. Relations with other people
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

F. Enjoyment of life
0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely Interferes

APPENDIX F COCKCROFT-GAULT CALCULATION

Female: $C_{Cr}=\{((140-age) \times weight)/(72 \times S_{Cr})\} \times 0.85$

Male: $C_{Cr} = ((140-age) \times weight)/(72 \times S_{Cr})$

Abbreviations/ Units

C_{Cr} (creatinine clearance) = mL/minute

Age = years

Weight = kg

S_{Cr} (serum creatinine) = mg/dL