A Phase II Clinical Trial Examining The Impact Of Neoadjuvant Axitinib On Primary Tumor Response In Patients With Locally Advanced Clear Cell Renal Cell Carcinoma

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SYNOPSIS

Primary Objective:

Assess objective response rate following the administration of axitinib for 12 weeks in patients with locally advanced biopsy-proven clear cell renal cell carcinoma prior to undergoing radical nephrectomy.

Secondary Objectives:

- Study the safety, tolerability, and feasibility of the administration of axitinib in patients with locally advanced biopsy-proven clear cell renal cell carcinoma prior to undergoing radical nephrectomy.
- Assess disease-free survival and overall survival in patients with locally advanced biopsy proven clear cell renal cell carcinoma treated with 12 weeks of neoadjuvant axitinib followed by radical nephrectomy.
- Collect renal tissue, blood (serum, plasma, DNA, and PBMC), and urine for future correlative biomarker studies.

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1. Background and Rationale

The American Cancer Society estimated an incidence of ~54,000 cases of renal cancer in 2009, with ~13,000 dying of their disease [1]. Seventy-five percent of renal tumors are of the clear-cell renal cell carcinomas (ccRCC). Angiogenesis plays an important role in the pathogenesis of ccRCC with production of VEGF [2]. The recent FDA approval of receptor tyrosine kinase inhibitors such as Sunitinib, Sorafenib, Everolimus, and Temsirolimus has dramatically changed the therapeutic paradigm of ccRCC, and has resulted in increased response rates in patients with metastatic ccRCC [3-6].

Axitinib, a novel oral tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 has been recently investigated in 52 patients with metastatic ccRCC who failed prior systemic therapy with Interferon-α or Interleukin-2 [7]. Responses were seen in 23 patients (44.2%), with two patients achieving complete response and one patient without prior nephrectomy having partial shrinkage of the primary renal tumor. Axitinib has also been investigated in 62 patients with metastatic ccRCC refractory to sorafenib [8], and partial response was observed in 22.6% of patients, with 80% experiencing some degree of tumor shrinkage. As such, axitinib appears to be a promising agent in the treatment of metastatic ccRCC.

We will be using the tyrosine kinase inhibitor axitinib up to 36 hours prior to radical nephrectomy in order to maximize the exposure time and potential benefit from this drug. This approach has been shown to be safe. Recently, Hellenthal et al [9] reported on a prospective trial of 3 months of the tyrosine kinase inhibitor sunitinib in 20 patients with renal cell carcinoma prior to radical nephrectomy. In 15 patients, sunitinib was stopped 1 day prior to surgery, and no surgical complications were attributable to sunitinib treatment. This is consistent with our experience [10], as we have not found a significant difference in surgical complications when comparing patients who received targeted therapy prior to radical nephrectomy with those who have not received any preoperative therapy.

Neoadjuvant therapy in the non-metastatic setting has the potential of improving overall survival, as seen from trials in non-metastatic bladder cancer [11]. To date, there are no published prospective trials of neoadjuvant targeted therapy prior to radical nephrectomy in patients without metastases. The use of axitinib in patients with ccRCC prior to radical nephrectomy has the potential of decreasing tumor size (which might allow us to perform a partial nephrectomy rather than a radical nephrectomy-thereby preserving renal function), regression of invasion into adjacent organs, regression of tumor venous thrombi, therefore improving surgical margins and treatment outcomes. In addition, collection of blood and tissue for molecular and genetic analysis is possible using this neoadjuvant approach, which will provide valuable information about molecular correlates of tumor response to

targeted therapy. Finding molecular correlates of activity or resistance to axitinib will allow us in future trials to select the appropriate patients to receive neoadjuvant therapy.

2. Protocol Drug

2.1. Axitinib

2.1.1. Dosage

Axitinib is given orally at a starting dose of 5mg twice daily (BID) with food. Dosage modifications will be discussed below.

2.1.2. Pharmacokinetics and Pharmacodynamics

Axitinib administered in the fed state is absorbed rapidly, with peak plasma concentrations occurring within 2 to 6 hours. Plasma concentrations declined with a terminal plasma half-life between 2 and 5 hours. Axitinib plasma PK reached steady state within 15 days. At the phase II dose of 5 mg BID given in the fasted state, the between-patient coefficient of variation for $AUC_{0\text{-}24}$ on cycle 1, day 15 was 90%; the corresponding coefficient of variation for C_{max} was 63%. Both the rate and extent of absorption were higher in the fasted state. Peak concentrations occurred 1 to 2 hours after dosing in the fasted state, and there was a median 49% increase in plasma exposures compared with the fed state. Plasma half-life was not changed appreciably in fed and fasted states.

In the presence of the potent proton-pump inhibitor rabeprazole, the rate of absorption of axitinib was decreased, but the extent of absorption was unaffected. Because of the minimal change in plasma exposure in the presence of rabeprazole, the effect of antacids on axitinib absorption was not considered to be clinically significant.

Twelve-hour urinary collections obtained on days 1 and 29 (cycle 2, day 1) demonstrated that < 1% of the administered dose appeared as unchanged drug in the urine regardless of dose, which indicates that the majority of drug elimination was through systemic metabolism.

Soluble plasma proteins (VEGF, fibroblast growth factor, tumor necrosis factor-alpha, and matrix metalloproteinases 2 and 9) evaluated as exploratory markers related to VEGFR signal transduction pathways did not show any variation with treatment.

2.1.3. Side Effects Profile

The most common side effects (all grades) are hypertension, diarrhea, fatigue, nausea, hoarseness, anorexia, dry skin, and weight loss.

3. Inclusion and Exclusion Criteria

3.1. Study Population

A total of 24 patients with clear cell renal cell carcinoma clinical stage T2-T3bN0M0 will be treated in this study with an estimated accrual of 3 patients per month. Please see section 6 for statistical considerations. We will enroll additional patients to allow for screen failures after biopsy results, or patient withdrawal.

3.2. Inclusion Criteria

3.2.1. Locally advanced renal cell carcinoma without evidence of metastatic disease with absence of adjacent organ invasion or retroperitoneal adenopathy (cT2-T3b, N0, M0). Patients with retroperitoneal lymph nodes ≤ 2 cm in size each are considered N0.

3.2.2. Predominant clear cell histology on pre-treatment biopsy of the primary tumor.

3.2.3. Patient should be candidate for curative radical nephrectomy.

3.2.4. ECOG Performance Status 0-1.

3.2.5. Patient must provide signed informed consent.

3.2.6. Male or female, age≥ 18 years.

3.2.7. Adequate renal function: serum creatinine level ≤ 1.5 x ULN or calculated creatinine clearance (as estimated by GFR using the MDRD formula) is ≥ 60 ml/min.

3.2.8. Adequate hepatic function: alkaline phosphatase ≤ 1.5 x ULN; total bilirubin, AST, and ALT ≤ 1.5 x ULN; INR <1.3 (or <3 if on anticoagulant therapy).

3.2.9. Adequate bone marrow function: ANC ≥ 1.5 x 10^9/L; Platelets ≥ 100 x 10^9/L; Hb >9 g/dL.

3.2.10. Urinary protein <100 on urinalysis (equivalent to <2+ by urine dipstick). If urinalysis protein ≥ 100 (equivalent to dipstick is ≥2+) then a 24-hour urine collection can be done and the patient may enter only if urinary protein is <2 g per 24 hours.

3.2.11. No hormonal therapy, chemotherapy, immunotherapy, or any other systemic therapy for a malignancy in the 5 years prior to current study enrollment.

3.2.12. Women of childbearing potential (defined as a female subject who is not surgically sterilized, not at least 1 year postmenopausal) must have negative urine or serum

pregnancy test within 4 weeks of enrollment and again on the day of starting therapy and she and/or her partner must utilize birth control while on therapy.

3.2.13. Male (defined as a male subject who has not been surgically sterilized) or female patients of child-producing potential must agree to use adequate contraception (e.g. IUD, condom plus spermicide, diaphragm, or cervical cap plus spermicide) or medical contraception as of date of study enrollment and for 1 month after last dose of axitinib. Subjects who are not currently sexually active must agree and consent to use one of the above-mentioned methods should they become sexually active while participating in the study.

3.3. Exclusion Criteria

3.3.1. Evidence of metastatic disease, adjacent organ invasion, retroperitoneal adenopathy on pre-treatment imaging. In addition, patients with inferior vena cava thrombi extending to the atrium or with evidence of Budd-Chiari Syndrome (hepatic dysfunction) will not be eligible for the protocol.

3.3.2. Patients who undergo embolization of their primary tumor

3.3.3. Previous treatment for their primary renal tumor, including prior chemotherapy, immunotherapy, targeted therapy, radiation therapy, cryotherapy, radiofrequency ablation or embolization.

3.3.4. Active malignancies other than renal cell carcinoma and/or history of other malignancy within the last 5 years, except for adequately treated cone-biopsied in situ carcinoma of the cervix or basal or squamous cell carcinoma of the skin.

3.3.5. Uncontrolled hypertension (BP>140/90 on medications) as documented by 2 baseline blood pressure readings taken at least 1 hour apart. The baseline systolic blood pressure readings must be ≤140 mm Hg, and the baseline diastolic blood pressure readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.

3.3.6. Current use or anticipated need for treatment with drugs that are known potent CYP3A4 inhibitors (ie, grapefruit juice, verapamil, ketoconazole, miconazole, itraconazole, erythromycin, telithromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, nefazodine, lopinavir, atazanavir, amprenavir, fosamprenavir and delavirdine).

3.3.7. Current use or anticipated need for treatment with drugs that are known potent CYP3A4 or CYP1A2 inducers (ie, carbamazepine, dexamethasone, felbamate, omeprazole, phenobarbital, phenytoin, amobarbital, nevirapine, primidone, rifabutin, rifampin, and St. John's wort).

3.3.8. Active gastrointestinal bleeding.

3.3.9. Malabsorption syndromes such as celiac disease, cystic fibrosis, inflammatory bowel disease, systemic sclerosis, and carcinoid syndrome.

3.3.10. Known HIV or Hepatitis C status.

3.3.11. Requirement of anticoagulant therapy with oral vitamin K antagonists. Low-dose anticoagulants for maintenance of patency of central venous access devise or prevention of deep venous thrombosis is allowed. Therapeutic use of low molecular weight heparin is allowed.

3.3.12. Active seizure disorder or evidence of brain metastases, spinal cord compression, or carcinomatous meningitis.

3.3.13. A serious uncontrolled medical disorder or active infection that would impair their ability to receive study treatment.

3.3.14. Any of the following within the 12 months prior to study drug administration: myocardial infarction, uncontrolled angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack and 6 months for deep vein thrombosis or pulmonary embolism

3.3.15. Withdrawal of consent.

3.3.16. Unwillingness or inability to comply with mandated pre-treatment biopsy or therapeutic regimen.

4. Trial Objectives

4.1. Primary Objective

Assess objective response rate following the administration of axitinib for 12 weeks in patients with locally advanced biopsy-proven clear cell renal cell carcinoma prior to undergoing radical nephrectomy.

4.2. Secondary Objectives

4.2.1. Study the safety, tolerability, and feasibility of Axitinib in patients with locally advanced biopsy-proven clear cell renal cell carcinoma prior to undergoing radical nephrectomy.

4.2.2. Assess disease-free survival and overall survival in patients with locally advanced biopsy proven clear cell renal cell carcinoma treated with 12 weeks of neoadjuvant Axitinib followed by radical nephrectomy.

4.2.3. Collect renal tissue, blood (serum, plasma, DNA, and PBMC), and urine for future correlative biomarker studies.

5. Assessment of Response

CT scans of the chest and abdomen will be evaluated by a urologist and an expert genitourinary radiologist. The urologist (investigator assessment) and the radiologist (independent assessment) will perform the tumor measurements. Response will be determined by the radiologist assessment. Tumor measurements will be documented in the tumor measurement form (one of the CRFs) and medical record. GURU will be used as electronic case report forms (CRF). RECIST version 1.0 criteria will be used as follows to quantify response to therapy:

- Complete Response (CR): Complete disappearance of renal mass.
- Partial Response (PR): At least a 30% decrease in the largest diameter (LD) of the renal mass taking as reference the baseline largest diameter.
- Progressive disease (PD): At least a 20% increase in the LD of the renal mass taking as reference the LD of the renal mass recorded since the treatment started. PD will also include development of any biopsy-proven metastatic disease.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the LD since the treatment started.
- Objective response rate (ORR) is defined as CR+PR.
- ORR will be evaluated when CT abdomen is done after 12 weeks of treatment (see Table 4).
- PD will be evaluated when CT abdomen is done after 7 weeks and 12 weeks of treatment (see Table 4).

6. Statistical Considerations

6.1. Statistical Considerations for Primary Objective

The primary objective of this study is to assess objective response rate (ORR) following the administration of axitinib for 12 weeks in patients with locally advanced biopsy-proven clear cell renal cell carcinoma prior to undergoing radical nephrectomy.

Twenty-four patients will be treated in this study. We plan to abort recruitment should we have reason to believe that axitinib does not provide minimal efficacy, defined as Pr[ORR ≥ 20% | data] < 5%. We also plan to stop recruitment should we have reason to believe that it may be harmful, defined as Pr[PD > 20% | data] > 80%, where PD is progressive disease. We will monitor study patients using the Bayesian approach of Thall [12]. ORR will be evaluated at week 12 following initiation of treatment and PD will be evaluated at week 7 and week 12 following initiation of treatment.

For calculating our stopping criteria and operating characteristics for futility and disease progression, we assume that ORR ~ Beta(0.4, 1.6) and PD ~ Beta(0.4, 1.6). The prior for both ORR and PD has a mean of 20% and a standard deviation of 23%.

We will continually evaluate patients for excessive PD as they are being enrolled. We will begin evaluating for minimal ORR after the first 18 patients have been treated and evaluated for responses. Given that those patients who have PD will be immediately terminated from the study treatment to have a nephrectomy, we do not feel that delaying evaluation for futility until 18 patients are treated will jeopardize patient wellbeing. Once the minimum number of patients has been treated and assessed for ORR and PD, we will continue to assess both outcomes after each additional patient has been evaluated.

The trial will be stopped for futility (low ORR) if

[# of patients with ORR / # of patients evaluated at Week 12] ≤ 1/18.

Likewise, the trial will be stopped for excessive PD if

[# of patients with PD / # of patients evaluated at Week 7 and 12] ≥ 3/6, 4/9, 5/13, 6/17, 7/21.

To illustrate the use of these stopping rules, suppose 18 patients are treated in this study and evaluated for response and only 1 had ORR. We would close the study for lack of efficacy. If 2 patients out of the first 18 respond, then an additional 6 patients will be treated for a total of 24 patients. Likewise, if 6 out of 17 patients had PD, we would close the study for excessive PD.

The operating characteristics for the futility monitoring rule are shown in Table 1 and for the PD monitoring rule are shown in Table 2. The operating characteristics in Table 1 do not

account for early stopping due to excessive PD; likewise, the operating characteristics in Table 2 do not account for early stopping due to futility.

We plan to stop recruitment if we observe 2 treatment-related deaths. Treatment-related deaths are defined as deaths directly caused by study drug while the patients are taking the study drug, or intraoperatively, or within 30 days after nephrectomy, and the decision to classify the deaths as directly caused by study drug will be made by the study Principal Investigator. Perioperative mortality for patients undergoing radical nephrectomy is estimated to be between 1% and 4% [13-15]. The operating characteristics associated with this decision criterion are shown in Table 3. These probabilities were derived by running 1,000 simulations.

We also plan to stop recruitment if two or more patients a) cannot undergo radical nephrectomy as a result of participating in the study, or b) experience a delay in time to radical nephrectomy of more than 6 weeks from last axitinib dose, or c) experience inadequate healing post-operatively defined as fascial dehiscence requiring reoperation, or d) experience severe bleeding post-operatively defined as bleeding requiring reoperation.

Table 1. Operating Characteristics of the ORR Futility Monitoring Rule

Success Rate	Probability of Stopping Early	Sample Size		
		P_{25}	P_{50}	P_{75}
0.05	0.775	18	18	18
0.10	0.455	18	24	24
0.15	0.221	24	24	24
0.20	0.106	24	24	24
0.25	0.039	24	24	24

Table 2. Operating Characteristics of the Excessive PD Monitoring Rule

Success Rate	Probability of Stopping Early	Sample Size		
		P_{25}	P_{50}	P_{75}
0.10	0.056	24	24	24
0.15	0.165	24	24	24
0.20	0.346	12	24	24
0.25	0.537	8	19	24
0.30	0.724	6	11	24

Table 3. Operating Characteristics of the Treatment-Related Mortality Stopping Rule

$\pi_{\text{treatment-related mortality}}$	Probability of Stopping Early	Sample Size		
		P_{25}	P_{50}	P_{75}

0.005	0.012	24	24	24
0.01	0.033	24	24	24
0.02	0.083	24	24	24
0.04	0.268	23	24	24
0.07	0.505	14	24	24
0.1	0.708	10	17	24
0.2	0.976	5	8	13

Based on operating characteristics of the ORR futility monitoring rule (Table 1), we have a 10.6% chance of closing the study early if the ORR truly is only 20%.

Once we have completed the study we will estimate the objective response rate for axitinib with a 90% credible interval. We will also report the posterior probability that the objective response rate is more than 20%. If this posterior probability is greater than 80%, we will conclude that axitinib was successful and therefore merits further study as a neoadjuvant therapy in this patient population. This would mean that axitinib would be considered successful if 7 or more patients had ORR.

6.2. Statistical Considerations for Secondary Objectives

6.2.1. To examine the safety of axitinib, we will tabulate reported adverse events (adverse events will be recorded per CTCAE v4.0).

6.2.2. To examine the tolerability of axitinib, we will use the FKSI-15 (Functional Assessment of Cancer Therapy-Kidney Specific Index-15, Appendix E) questionnaire and compare changes in response between different time points.

6.2.3. We will evaluate disease-free survival by plotting Kaplan-Meier curves and estimating median recurrence-free survival. Time to death or recurrence will be defined as the time from treatment start until death, recurrence or progressive disease, whichever comes first. Patients who did not die, recur or have progressive disease will be censored at date of last follow-up. These will be compared to contemporary, matched (2:1 matching, for age group, stage and grade), historical controls. Although small differences in recurrence-free and overall survival might not be detected in this current trial, this information will help us when designing future large trials with this particular agent.

7. Treatment Plan (Table 4)

7.1. Pre-treatment screening

7.1.1. Patients will undergo routine staging evaluation to include CT chest and abdomen with renal protocol, to evaluate extent of local disease and rule out the presence of metastatic disease. If the patient had these CT scans done at an outside facility within 4 weeks of enrollment in the trial, then these CT scans may not need to be repeated at MD Anderson, as long as the actual CD or DVD of the films are available (and not just the report) and as long as the protocols used for the CT scans were similar to those at MD Anderson (i.e. renal protocol with intravenous contrast needs to be used). If the CD or DVD is from an outside facility, it has to be reviewed by our urologist and/or radiologist here to check the quality of the images (for example, if the CT scan was done within 4 weeks of screening, but was done without intravenous contrast, the investigators might decide to repeat the CT scan prior to starting study treatment). If only a report is available, the CT scans will need to be repeated at MD Anderson to be eligible for the study. Bone scan and CNS imaging will be done at the discretion of the attending physician for patients with indications to do so (elevated alkaline phosphatase, bone pain for bone scan, and CNS symptoms for CNS imaging). An EKG will be done.

7.1.2. CBC, CMP (sodium, potassium, chloride, carbon dioxide, calcium, glucose, BUN, creatinine, magnesium, phosphorus, lactate dehydrogenase, AST, ALT, alkaline phosphatase, total and direct bilirubin, albumin, total protein), PT, PTT, TSH, free T3, free T4, and urinalysis will be obtained within 4 weeks of study enrollment. A pregnancy test will be done for women of childbearing potential within 4 weeks of enrollment and again on the day of starting therapy as explained in Section 3.2.

7.1.3. A history, physical examination, medication list (Appendix J), ECOG Performance Status, Adverse Events, and EKG will be performed and recorded in the medical record within 4 weeks of study enrollment as noted in Table 4.

7.1.4. Patients that meet eligibility criteria will undergo image-guided biopsy (18G core needle biopsy x 4 cores and touch prep-1 core for pathologic diagnosis, 3 optional cores for tissue banking) of their primary tumor to establish the presence of clear cell histology.

7.1.5. If a prospective patient has untreated hypertension at presentation, the patient will be placed on a medical regimen to control the hypertension, prior to enrollment (Enrollment

means when the patient meets all the study eligibility criteria and is ready to be registered in CORe step 2).

7.2. Treatment Phase

7.2.1. Eligible patients will provide written informed consent.

7.2.2. Prior to the initiation of therapy, a surgical date will be established.

7.2.3. Treatment Assignment: Each patient will receive a total of 12 weeks of axitinib. Patients will take the last dose of axitinib 1.5 days prior to surgery.

7.2.4. Adverse events monitoring and reporting:

7.2.4.1. Adverse events:

7.2.4.1.1. The investigator is responsible for determining the attribution of adverse events to study drug.

7.2.4.1.2. Adverse events will be documented in the medical record and entered into the case report form according to the Recommended Adverse Event Recording Guidelines for Phase II protocol (see table below).

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.2.4.1.3. Adverse events will be assessed at each patient visit, documented in the medical record, and entered into the CRFs. Adverse events should be treated appropriately. Such treatment may include changes in axitinib treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at

each visit of any changes in severity, the suspected relationship to the axitinib, the interventions required to treat it, and the outcome. In addition, Pfizer requires reporting of serious adverse events on the M.D. Anderson SAE forms. Reporting of adverse events will be done according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The following items will be recorded at least:

-Event description

-Date of onset of AE

-CTCAE grade/severity (1,2,3,4,5)

-Relationship to treatment with axitinib (unrelated, unlikely, possible, probable, highly probable/definite)

-Action taken (none, temporarily discontinued agent, drug treatment given/specify, permanently discontinued agent, non-drug treatment given/specify, hospitalization)

-Date of AE stop

-Outcome (recovered without sequelae, recovered with sequelae, ongoing, worsened, death)

-Serious AE (yes, no)

7.2.4.2. Serious Adverse events (SAE):

7.2.4.2.1. SAE reporting-SAEs will be recorded on a SAE form (Appendices G and H), in addition to the CRF AE documents. SAEs will be reported within 24 hours to Pfizer (Please see Pfizer SAE reporting guidelines in the appendix section)

7.2.4.2.2. SERIOUS ADVERSE EVENT REPORTING – M. D. Anderson Cancer Center: The following SAE Reporting Requirements, since this is an MDACC sponsored IND study, and all SAEs must be reported to IND Sponsor representative – the IND Office - according to the following:

7.2.4.2.2.1. A serious adverse event is – any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse

experience that, had it occurred in a more severe form, might have caused death

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity – a substantial disruption of a person's ability to conduct normal life functions
- A congenital anomaly/birth defect

7.2.4.2.2.2. In this protocol, we will not report those hospitalizations resulting from routine treatment not associated with any deterioration in condition, treatment for a pre-existing condition that is unrelated to axitinib and has not worsened since the start of axitinib; or for treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission.

7.2.4.2.2.3. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32):

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Office .
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in

"University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Serious Adverse Events". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, expected or unexpected, and regardless of attribution to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the IND office
- The MDACC "Internal SAE Report Form for Prompt Reporting" will be used for reporting to the IND office.
- Serious adverse events will be captured from the time the patient signs consent until 30 days after the last dose of drug. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND office. This may include the development of a secondary malignancy.

7.2.4.2.2.4. Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Office, according to 21 CFR 312.32.

7.2.4.2.2.5. It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2.5. Axitinib Starting Dose: Patients will receive up to 12 weeks of axitinib orally. Axitinib is started at a dose of 5mg BID (twice each day) taken orally with food. Dose adjustments, including dose increase or dose reduction should be based on adverse events experienced

by the individual patient. Axitinib should be taken beginning on day 1 of the study. Doses should be taken approximately 12 hours apart. Patients should be instructed to take their doses at approximately the same times each day. Patients should be instructed that if they vomit anytime after taking a dose, that they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken late up to 3 hours before the next scheduled dose, otherwise, it should be skipped. If doses are missed or vomited, this must be indicated in the source documents and CRFs. A pill diary (Appendix J) will be provided where the patient will record the date, time (AM or PM), and dose of axitinib taken, as well as the blood pressure measurement prior to axitinib intake (Appendix J). Available axitinib dose levels are listed below.

Dose Level	Dose	Dispensed As
+2	10 mg BID	2 X 5 mg Tablets BID
+1	7 mg BID	1 X 5 mg Tablet BID + 2 X 1mg Tablets BID
0 (Starting Dose)	**5 mg BID**	**1 X 5 mg Tablet BID**
-1	3 mg BID	3 X 1mg Tablets BID
-2	2 mg BID	2 X 1mg Tablets BID

7.2.6. Axitinib dose modifications during trial: Patients will receive axitinib at a starting dose of 5 mg orally twice daily until disease progression, unmanageable toxicity, withdrawal of consent occurs, or until 1.5 days prior to surgery.

7.2.6.1. Axitinib dose increase: Because previous studies indicated variable drug levels in patients, the axitinib dose will be increased in a step-wise fashion from 5 mg twice daily to 7 mg twice daily, then to 10 mg twice daily, in the absence of axitinib-related toxicity greater than or equal to grade 2 for a continuous 2-week period and in the absence of hypertension (defined as two blood pressure [BP] measurements of > 150/90 mmHg taken in the clinic > 1 hour apart) at any point during study. The clinical judgment of the treating physician should be exercised in up-titrating the axitinib dose.

7.2.6.2. Axitinib dose modifications for adverse events (other than hypertension and proteinuria):

7.2.6.2.1. Patients developing axitinib-related CTCAE Grade 1 adverse events may have their dose increased to next dose level.

7.2.6.2.2. Patients developing axitinib-related CTCAE Grade 2 adverse events should have their dose continued at the same dose level.

7.2.6.2.3. Patients developing axitinib-related CTCAE Grade ≥ 3 adverse events should have their dose reduced as indicated in section 7.2.6.2.6

7.2.6.2.4. If patients need to have their axitinib treatment interrupted for 2 or more continued-week period due to unmanageable toxicities or any other reason, their axitinib treatment will be permanently discontinued and considered treatment failures. Patients will then proceed to surgery to have their kidney tumors removed.

7.2.6.2.5. Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments (every 4 months for 1 year, every 6 months for the next 2 years and every 12 months for one more year) until disease progression or start of new treatment, and for survival thereafter until study completion.

7.2.6.2.6. The criteria for dose modification for study-drug-related adverse events are summarized in the table below:

CRITERIA FOR DOSE MODIFICATION FOR AXITINIB-RELATED ADVERSE EVENTS OTHER THAN HYPERTENSION OR PROTEINURIA	
Related Adverse Events	**INTERVENTION**
Grade 1	Increase to next dose level, or maintain if already at the maximum dose
Grade 2	Continue at same dose level
Grade 3 nonhematologic treatment-related toxicity* or Grade 3 hematologic toxicity	Decrease dose to one lower dose level
Grade 4 hematologic treatment-related toxicity**	Interrupt dosing; re-start at one lower dose level as soon as improvement to CTCAE Grade ≤2 occurs within 2 weeks. If a patient requires dose reduction below 2 mg BID when above fails, consideration should be given to stop axitinib if this recurs.
Grade 4 nonhematologic treatment-related toxicity	Stop Axitinib

* Patients who develop Grade 3 nonhematologic toxicities that are controlled with symptomatic medications or Grade 3 asymptomatic biochemistry laboratory abnormalities may be continued at the same dose level at the discretion of the investigator.

** Patients who develop Grade 4 lymphopenia or Grade 4 asymptomatic biochemistry laboratory abnormality may continue study treatment without interruption.

7.2.6.3. Axitinib dose-reduction for hypertension:

7.2.6.3.1. Electronic BP monitors will be provided to each patient for home use. Instructions to use them will be provided (Appendix F) and demonstration of their use will be done in the visit

prior to starting axitinib intake. Patients will self-monitor BP at home twice daily (before each axitinib dose). All BP measurements will be recorded in a diary (Appendix J) and brought to the clinic at each clinic visit. Patients will be instructed to inform their physicians in the event of systolic BP greater than 150 mmHg or diastolic BP greater than 100 mmHg, or if they develop symptoms related to elevated BP (e.g. headache or visual disturbance). During normal business hours the patient will call the urology research nurse for instructions. Outside of normal business hours, the patient will call the urologist on call through the page operator, and inform the urologist that they are enrolled in the axitinib trial. The urologist on call will then contact one of the axitinib study members (Dr. Wood, Dr. Matin, Dr. Tannir or Dr. Jonasch) for further instructions. Written contact information will be provided to each patient prior to initiation of axitinib (Appendix I)

7.2.6.3.2. New or additional antihypertensive therapy should be started if 2 BP readings, preferably taken in the clinic and separated by at least 1 hour, show the following: 2 systolic BP readings greater than 150 or 2 diastolic BP readings greater than 100 mm Hg. Alternately, the dose of existing antihypertensive medication(s) may be increased. If the patient is already on maximal antihypertensive treatment, the axitinib dose should be reduced by 1 dose level.

7.2.6.3.3. Patients who have 2 systolic BP readings, separated by at least 1 hour, greater than 160 mm Hg, or 2 diastolic BP readings, separated by at least 1 hour, greater than 105 mm Hg, should have treatment with axitinib held. (Note: if axitinib is held, patients receiving antihypertensive medications should monitor closely for hypotension and restart axitinib at one lower dose level as soon as BP is <150/100 mm Hg. Plasma half-life of axitinib is 2 – 6 hours and BP usually decreases within 1-2 days following dose interruption.) Treatment with axitinib should be restarted at 1 lower dose level as soon as the systolic blood pressure reduces to less than 150 mm Hg and the diastolic BP reduces to less than 100 mm Hg.

7.2.6.3.4. Patients who develop recurrent systolic hypertension (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg) or recurrent diastolic BP >100 mm Hg following previous axitinib dose reduction should undergo another dose reduction by one dose level.

7.2.6.3.5. Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments (every 4 months for 1 year, every 6 months for the next 2 years and every 12 months for one more year) until disease progression or start of new treatment, and for survival thereafter until study completion. Guidance on dose interruption and reduction for hypertension is summarized in the table below.

7.2.6.3.6. The antihypertensive medications (if the patient is taking any) will be tapered after axitinib is stopped, in order to maintain a blood pressure level that is less or equal to 140/90. Once the patient is at this blood pressure level, his blood pressure/blood pressure medications will be managed by his primary care physician.

HYPERTENSION MANAGEMENT PLAN FOR AXITINIB			
Degree of Blood Pressure Elevation			**Management**
Systolic Pressure		Diastolic Pressure	
2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >100 mm Hg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication and maintain dose of axitinib. If on maximal antihypertensive treatment, reduce axitinib to one lower dose level.
2 BP readings separated by at least 1 hour show systolic pressure >160 mm Hg	OR	2 BP readings separated by at least 1 hour show diastolic pressure >105 mm Hg	Interrupt dosing*; adjust antihypertensive medication; as soon as BP is less than 150/100 mm Hg, restart axitinib at one lower dose level.
Recurrent hypertension following previous dose reduction (2 BP readings separated by at least 1 hour show systolic pressure >150 mm Hg)	OR	Recurrent diastolic BP >100 mm Hg (2 BP readings separated by at least 1 hour) following previous dose reduction	Repeat axitinib dose reduction by one lower dose level. If a patient requires dose reduction below 2 mg BID, interrupt dosing adjust antihypertensive medication; as soon as BP is less than 150/100 mm Hg, restart axitinib. Consideration should be given to stop axitinib if this recurs.

* If axitinib is held, patients receiving antihypertensive medications should monitor closely for hypotension. Plasma half-life of axitinib is 2 – 6 hours and BP usually decreases within 1-2 days following dose interruption.

7.2.6.4. Axitinib dose-reduction for proteinuria:

7.2.6.4.1. If urinalysis shows protein qualitative level ≥ 100 (equivalent to ≥ 2+ proteinuria on dipstick), perform 24-hour urine collection. Dosing may continue while waiting for test results. [Equivalence of protein qualitative levels on urine dipstick and urinalysis are as follows: 1+ on dipstick is equivalent to 30 on urinalysis, 2+ on dipstick is equivalent to 100 on urinalysis, 3+ on dipstick is equivalent to 300 on urinalysis, and 4+ on dipstick is equivalent to >2000 on urinalysis]

7.2.6.4.2. If < 2 g proteinuria/24 hour is reported, continue dosing at the same dose level.

7.2.6.4.3. If ≥ 2 g proteinuria/24 hours is reported, hold dosing and repeat 24 hour urine collection for proteinuria and creatinine clearance (interval at investigator discretion) until proteinuria is < 2 g/24 hours. Restart axitinib at the same dose or one lower dose level at discretion of the investigator.

7.2.6.4.4. Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments (every 4 months for 1 year, every 6 months for the next 2 years and every 12 months for one more year) until disease progression or start of new treatment, and for survival thereafter until study completion.

7.2.7. Concomitant therapy

7.2.7.1. The patient will provide a list of medications taken within 4 weeks prior to enrollment, and will provide a new list during each clinic visit while being treated with axitinib. The name, dose, date of start, date of stop (if use for short term), indication of the medication will be listed. (Appendix J)

7.2.7.2. The patient should not start a new prescription medication or over-the-counter medication before consulting with the study investigator, except in the case of a medical emergency.

7.2.7.3. No other cancer/investigational therapies should be started during the current study without consulting with the study investigator.

7.2.8. Treatment intake monitoring

7.2.8.1. The patient will be provided with a pill diary to record date of treatment, day of treatment, time of treatment, dose. Missed doses will be recorded as well. (Appendix J)

7.2.8.2. Pill counting. The patient will bring the axitinib bottle(s) when coming for a clinical visit. Pills will be counted by nurse/provider and recorded on a CRF and medical records.

7.2.8.3. Unused or expired axitinib pills will be disposed per MDACC institutional policy.

7.2.9. Treatment Start-Eligible patients will start treatment within 4 weeks of enrollment.

7.2.10. A history, physical examination, medication list (Appendix J), ECOG Performance Status, Adverse Events, FKSI-15 questionnaire (Appendix E) will be performed and recorded in the medical record and appropriate CRFs on weeks 3, 7, and 12. An EKG will be performed and the results recorded in the medical record and appropriate CRFs on weeks 3 and 12.

7.2.11. Laboratory studies that include CBC, CMP, PT, PTT, UA will be obtained prior to starting axitinib, then at week 3, week 7, and week 12 after starting axitinib. In addition, blood studies for TSH, free T3, and free T4 will be performed prior to starting axitinib, and then blood studies for TSH will be performed at week 3, week 7, and week 12 after starting axitinib. With each blood draw, 4 tubes of research blood will be drawn and processed for DNA, serum, plasma, and PBMC isolation for correlative studies, after the patient has provided informed consent.

7.2.12. Imaging: CT scans of the chest and abdomen (renal protocol) will be obtained on week 7 and week 12 of therapy. Patients with evidence of disease progression by RECIST version 1.0 at week 7 (primary or metastatic) will be considered treatment failures and their axitinib treatment will be permanently discontinued. Subsequently, their surgery will be performed earlier than initially planned. The urologist (investigator assessment) and the radiologist (independent assessment) will perform the tumor measurements. Response will be determined by the radiologist assessment. Tumor measurements will be documented in the tumor measurement form (one of the CRFs) and medical record.

7.2.13. Surgery: Following successful completion of presurgical therapy, patients will undergo radical nephrectomy (open or laparoscopic at the surgeon's discretion), with retroperitoneal lymph node dissection. Extent of lymph node dissection will be recorded in the operative record and should include the ipsilateral nodes from renal hilum to aortic bifurcation, as well as the interaortocaval nodes from renal hilum to aortic bifurcation. Primary tumor specimens will be immediately sent to pathology on ice for further processing and correlative study specimen harvest. Routine perioperative parameters will be recorded and will include operative approach, operative time, estimated blood loss, ease of surgical dissection, comment on tissue planes, intraoperative complications (with grade), post-operative complications (with grade), blood transfusions, length of ICU stay (if applicable), length of hospital stay, perioperative mortality (within 30 days of surgery). The operating urologist will make a decision based on their extensive surgical expertise if these adverse events are attributable to axitinib or not. These events will certainly be monitored and recorded by the operating urologist, and discussed with the IND if they arise.

7.3. Post-treatment follow-up

7.3.1. Patients will be seen at week 19 (+/- 1 week) and evaluated with CT chest and abdomen (renal protocol), full laboratory analysis (CBC, CMP), collection of blood and urine for research, and full history and physical examination. Evidence of disease recurrence [If a patient develops any evidence of biopsy-proven RCC after axitinib/surgery (in the form of local disease or distant disease), the patient will be labeled as having disease recurrence] or treatment related morbidity will be recorded. Pathology will be reviewed and will be assessed for histology, Fuhrman grade, percentage tumor viability, pathologic tumor size, presence of venous, extracapsular, sinus, or nodal involvement.

7.3.2. A history, physical examination, medication list (Appendix J), ECOG Performance Status, Adverse Events, FKSI-15 questionnaire (Appendix E) will be performed and recorded in the medical record and appropriate CRFs on week 19.

7.3.3. Patients will be followed with similar evaluations every 4 months (+/- 2 weeks) for the first year, then every 6 months (+/- 2 weeks) for the next 2 years, , then yearly (+/- 1 month) until year 5 postoperatively. Evidence of recurrence or treatment related morbidity will be recorded.

8. Tissue, Blood, and Urine Banking

8.1. Tissue-Kidney biopsy specimen and kidney surgical specimen will be collected

8.1.1. Kidney biopsy specimen. A total of 4 adequate biopsy cores are needed. Each core should undergo touch prep by cytopathologist to ensure biopsy quality (ie, malignant cell present with minimal necrosis/hemorrhage). More cores will be obtained if touch prep shows inadequate diagnosis (to obtain a total of 4 adequate cores).

8.1.1.1. One core will be fixed for pathologic evaluation and sent for pathology department for review prior to starting treatment.

8.1.1.2. Three cores will be immediately placed in 3 separate cryotubes, labeled appropriately, and stored at -70° to -80°C for future use.

8.1.1.3. All 4 touch prep slides will be labeled appropriately, and stored at room temperature for future use.

8.1.2. Kidney surgical specimen:

8.1.2.1. Tissues from final kidney surgical specimen (4 pieces of tumor, 5-10mm diameter each; and 4 pieces of normal appearing kidney cortex, 5-10mm diameter each) will

be collected in the pathology department. Each piece will be placed in a separate cryotube, labeled appropriately, and stored at -70° to -80°C for future use.

8.1.2.2. In accordance with pathology standards, several blocks of tissue will be fixed in formalin and embedded in paraffin, and stored at room temperature for future use.

8.2. Blood

8.2.1. Four different tubes will be collected at specified visits (Table 4), processed, labeled appropriately, and stored in aliquots at -70° to -80°C for future use.

8.2.1.1. Tube 1 (8cc): PAXgene Blood DNA tube to collect DNA

8.2.1.2. Tube 2 (8cc): BD Vacutainer CPT tube to collect plasma (Sodium Citrate) and PBMC

8.2.1.3. Tube 3 (10cc): BD Vacutainer EDTA tube to collect plasma (K2 EDTA) and PBMC

8.2.1.4. Tube 4 (10cc): BD Vacutainer Serum tube to collect serum

8.3. Urine

8.3.1. 30-50cc fresh voided urine obtained will be collected at specified visits (Table 4), processed, labeled appropriately, and stored in aliquots at -70° to -80°C for future use.

8.4. Blood and urine collection for research are optional but extremely valuable for the study. These samples will be used in the future to study predictors of response to therapy with axitinib.

9. Good Clinical Practice

9.1. Informed Consent:

The investigator/team will explain to the patient the nature of the clinical trial, its goal, potential benefits and risks. The patient will be informed that participation in the trial is voluntary, and that withdrawal is allowed at any time of the study, and that withdrawal will not affect subsequent medical treatment or relation with treating investigator/team. The informed consent is a document written in non-technical language. The patient will need to read the consent, ask pertinent questions, sign and date prior to starting study treatment. Separate consents will be obtained for required preoperative biopsy.

9.2. Institutional Review Board (IRB):

Prior to enrolling the first patient in this study, the protocol, related documents, and the informed consent forms will be reviewed by the Departmental Research Committee, the Clinical Research Committee, and the IRB. Pertinent amendments to the protocol will need to be approved by the IRB and the IND Sponsor – IND Office.

9.3. Ethical Conduct of Study

This study will be conducted according to GCP, US 21 Code of Federal Regulations (CFR) Part 50 (Protection of Human Subjects); US 21 CFR Part 56 (IRBs); US 21 CFR Part 54 (Financial Disclosure); International Conference on Harmonization (ICH) Guidance for Industry, E6 GCP: Consolidated Guidance; the Nuremberg Code; and, where applicable, the 1996 version of the Declaration of Helsinki (World Medical Association Declaration of Helsinki, 1996).

9.4. Patient Confidentiality:

All information collected during the study will be recorded in case report forms (CRF) and placed in a patient-specific folder. The information in the CRFs will then be put into a research database at M.D. Anderson Cancer Center. This database will identify the patient by a study number. The study number will be assigned by the research nurse, and all subsequent research records will contain the study number only. The link between the study number and patient identifiers will be kept in a limited access database with password protection. The informed consent will be kept in the medical record. The research records will be kept in the research nurse office at M.D. Anderson Cancer Center, and will be accessible to the Principal Investigator, the collaborators, and the research staff as designated by the Principal Investigator. Strict adherence to HIPAA regulations will be maintained at all times. The research subject will not be identified in any reports on this study. The results will be identified by the patient's study number. Only authorized personnel such as members of the University of Texas M.D. Anderson Cancer Center Institutional review board, Principal Investigator, Co-Investigators, collaborators, and research staff will be allowed to access the data. Data [abdominal CT scans, age, gender, race, height, weight, body mass index, serum albumin (both before and after treatment with axitinib), serum total protein (both before and after treatment with axitinib), current disease status, response to axitinib treatment, complications related to axitinib treatment or surgery, performance status, pathologic tumor stage, pathologic tumor grade, and tumor size] from this study may also be shared and used in protocol PA15-0949.

Table 4. Summary of protocol studies

Studies	Pre-treatment*	W1	W3	W5	W7	W9	W12	W13	W19 (±1w)	Q4M x 1Y (±2w)	Q6M x 2Y (±2w)	Q12M X 2Y (±1M)
History & Physical	X		X		X		X		X	X	X	X
Medication list	X	X	X		X		X		X	X	X	X
ECOG PS	X	X	X		X		X		X	X	X	X
FKSI-15[1]		X	X		X		X		X	X		
Adverse Events	X		X		X		X		X	X	X	X
Nurse phone call[2]				X		X						
Informed consent	X											
EKG	X		X				X					
Routine labs												
CBC	X		X		X		X		X	X	X	X
CMP[3]	X		X		X		X		X	X	X	X
PT, PTT	X		X		X		X					
TSH	X		X		X		X					
Free T3, free T4	X											
Urinalysis	X		X		X		X					
Pregnancy test (urine or serum)	X	X										
Study blood[#]												
PAXgene DNA	X[4]		X		X		X		X	X	X	X
Red top	X[4]		X		X		X		X	X	X	X
Purple top	X[4]		X		X		X		X	X	X	X
CPT	X[4]		X		X		X		X	X	X	X
Study urine[#]	X[4]		X		X		X		X	X	X	X
Imaging												
CT chest	X				X		X		X	X	X	X
CT abdomen	X				X		X		X	X	X	X
MRI brain[5]	X[5]											
Bone scan[6]	X[6]											
Pathology												
Percutaneous biopsy	X											
Final pathology								X				
Nephrectomy								X				
Axitinib		----------X----------										

*Evaluations need to be completed within 4 weeks of study enrollment

[#]Blood and urine collection for research are optional but extremely valuable for the study. These samples will be used in the future to study predictors of response to therapy with axitinib

[1] FKSI-15, Functional Assessment of Cancer Therapy-Kidney Specific Index-15 (Appendix E)

[2] Nurse phone call will mainly assess adverse events and BP measurements

[3] CMP includes sodium, potassium, chloride, carbon dioxide, calcium, glucose, BUN, creatinine, magnesium, phosphorus, lactate dehydrogenase, AST, ALT, alkaline phosphatase, total and direct bilirubin, albumin, total protein
[4] The blood samples for research can be drawn on W1-prior to first intake of axitinib-if it was not drawn at enrollment
[5] If CNS symptoms are noted
[6] If alkaline phosphatase is abnormal or if bone pain is present
W=week, M=month, Y=year, Q=every

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