Investigational Protocol

Proposed Title: "PADRES" (Prior Axitinib as a Determinant of Outcome of RENal Surgery)

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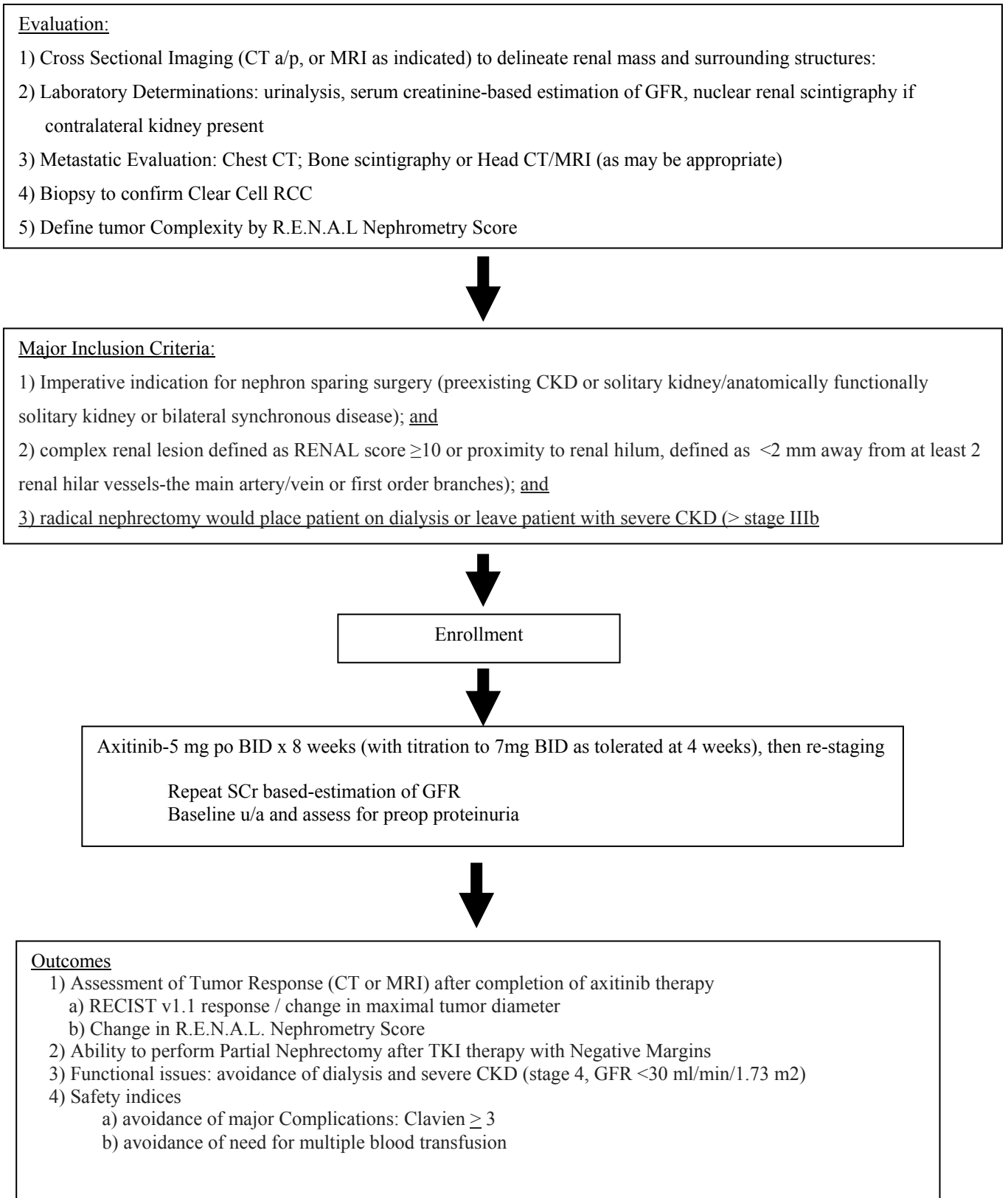
SCHEMA

A single arm phase II study of axitinib in patients with clear cell renal cell carcinoma (RCC) in patients with strong indications for partial nephrectomy (PN) for whom PN is not currently possible due to anatomic considerations and residual renal function concerns. Evaluation of tumor downsizing will be performed including changes of tumor complexity by nephrometry score (n=50 total).



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1. OBJECTIVES

We hypothesize that pretreatment with axitinib will be safe and improve the feasibility of complex nephron sparing surgery in select patients with localized clear cell RCC and imperative indications for partial nephrectomy.

1 Primary objective: <u>The primary objective of the study is to prospectively assess utility of axitinib in facilitation of partial nephrectomy where partial nephrectomy was not thought to be safe/possible in the setting of imperative indication for complex renal masses in renal cell cancer.</u>

2 Secondary objectives: To determine the safety, tumor diameter (per RECIST v1.1) volume change, surgical morbidity and renal functional outcomes following neoadjuvant axitinib for RCC.

Anatomical/morphometric:

a) tumor diameter/volume change,
b) conversion of hilar to non-hilar tumors,
c) reduction in RENAL morphometric score.

Functional Considerations:

a) Requirement of acute dialysis
b) Change in GFR
c) Whether or not GFR crosses 30 threshold, or decline by GFR to >50% of baseline.

Safety indices:

a) Incidence of Clavien >3 complications
b) Avoidance of need for multiple blood transfusions

2. BACKGROUND

Renal cell carcinoma is increasing at a rate of 2-3% in the industrialized world.[1] In 2014, there were approximately 63,920 newly diagnosed and 13,860 projected deaths attributed to kidney cancer in the United States.[2] Twenty to thirty-two percent of patients presenting with renal cortical neoplasia present with baseline chronic kidney disease,[3] and of these at least 50% present with higher stage disease.[4] While nephron sparing surgery is imperative for these patients, patients with higher stage disease are at increased likelihood of not being able to undergo nephron sparing surgery due to inability to safely preserve normal functioning parenchyma or the risks of the operation with a larger mass. Nonetheless, emerging data demonstrate oncological equivalence and potential renal functional benefit in these larger tumors when feasible by nephron sparing surgery.[5,6]

Data from series for partial nephrectomy for large renal masses (>7 cm), while demonstrating oncological equivalence to radical nephrectomy,[5-10] nonetheless demonstrate this to be a high-risk procedure even in centers of excellence, with 8-24% risk of blood transfusion, 20% risk of major complications, and a 10-18% risk of urinary fistulae with partial nephrectomy in the setting of larger tumors.[7-11] Furthermore, while partial nephrectomy may yield a renal functional benefit compared to radical nephrectomy,[8,12] benefits are incremental and dependent on tumor complexity and amount of preserved parenchyma.[12]

Thus, there exists a significant need in the RCC population to facilitate less morbid resection of complex renal masses by nephron sparing surgery and to increase the safety of these procedures, as well as to improve the long-term outcomes in this high-risk subgroup of patients.

Hypothesis: Pretreatment with axitinib will be safe and will facilitate complex nephron sparing surgery in select patients with localized clear cell RCC and imperative indications for partial nephrectomy, where partial nephrectomy was thought to be not feasible/efficacious in preserving renal parenchyma.

2.3 Background RCC Biology and Targeted Therapy

Important advances in the understanding of the molecular and genetic components of RCC have ushered in a new era of targeted molecular therapy. These treatments have primarily focused on blocking signaling pathways associated with the von Hippel–Lindau tumor suppressor gene. Inactivation of this gene leads to elevated levels of hypoxia inducible factor alpha (HIF-a) and overexpression of vascular endothelial growth factor (VEGF).Small molecule inhibitors of this pathway targeting the VEGF receptor tyrosine kinase and mammalian target of rapamycin (mTOR) pathways have proven efficacy. Landmark studies in the past decade helped pave the way for approval of sorafenib, sunitinib, temsirolimus, everolimus, and recently pazopanib and axitinib. Other studies identified a role for bevacizumab in combination with interferon-alpha for mRCC. These agents have demonstrated improved survival outcomes over traditional immunotherapeutic regimens with better tolerability.[13]

2.3.1 Rationale for Primary Targeted Therapy

Using these agents in the neoadjuvant setting for locally advanced renal cell carcinoma represents a new and promising treatment paradigm. Neoadjuvant targeted therapy offers the potential advantage of tumor downstaging which may make surgical interventions possible in some patients who would not otherwise be surgical candidates. Reduction of the primary tumor and metastatic disease may also make any surgical intervention less morbid, provided sufficient washout time is given to limit wound complications. Furthermore, as the biological understanding of RCC advances, tissue provided from initial biopsy may provide a genetic tumor fingerprint that would allow more individualized targeted therapy with a chance for better patient selection and efficacy.[13-15]

Emerging data from prospective Phase II Studies as well as retrospective analyses have demonstrated consistent primary tumor size reduction to facilitate surgical resection. The first report examining the effect of sunitinib on the primary tumor in metastatic RCC was by van der Veldt and colleagues from VU University Medical Center in the Netherlands, who retrospectively analyzed 22 patients, and using the RECIST criteria, noted that 4 patients had a partial response, 12 had stable disease, and 1 had progressive disease. Excluding the patient with progressive disease, the median volume reduction was 31% associated with a median increase in the volume of necrosis of 39%. In this cohort, three patients underwent nephrectomy and tumors showed extensive necrotic areas next to small fields of vital tumor cells.[14] Thomas and colleagues from the Cleveland Clinic were the first to report response of advanced primary renal tumors to treatment with neoadjuvant sunitinib. In their series, 19 patients with advanced renal cell carcinoma deemed unsuitable for initial nephrectomy due to locally advanced disease or extensive metastatic burden were treated with standard dosing sunitinib (50 mg daily for 4 weeks followed by 2 weeks off therapy). Primary tumor partial responses were noted in three patients (16%) while stable disease in seven (37%), and nine (47%) had disease progression in the primary tumor. With a median of two cycles of TKI therapy, primary tumor shrinkage was observed in eight patients (42%) with an average decrease in primary tumor size of 24% (range 2–46%).[15] At median follow-up of 6 months (range 1–15), four patients (21%) had undergone nephrectomy and five died of disease progression. No unexpected surgical morbidity was encountered. Cowey and colleagues from the University of North Carolina Group performed a phase II clinical trial with sorafenib in patients with stage II or higher RCC (17 localized, 13 metastatic), noting a primary reduction in 77% of patients with a mean diameter reduction of 9.6% in the primary tumor. Using RECIST criteria, two patients had a partial response and 26 had stable disease, with no patients progressing on therapy.[16]

These studies suggest that most primary clear cell RCC tumors experience a modest decrease in size, which can potentially facilitate tumor resection in the setting of complex tumor anatomy. However, further, prospective, multicenter investigation is necessary to provide more detailed outcomes data and to refine selection criteria.

2.3.2 Utilization of Primary Targeted Therapy Prior to Nephron Sparing Surgery

A potentially important and clinically promising indication for neoadjuvant targeted therapy is to downsize locally advanced and complex tumors and to enable nephron sparing

surgery when it may not have otherwise have been feasible, safe, or optimized.

Silberstein et al at UCSD reported on the efficacy of neoadjuvant TKI therapy prior nephron-sparing surgery in 12 patients with 14 tumors in the setting of locally advanced and/or metastatic disease and with imperative indication for nephron-sparing surgery; all patients had bulky local disease or central lesions. A mean tumor size reduction of 21.1% was observed, with a partial response in 4 of 14 (28.6%) tumors and stable disease in the remaining ten (71.4%) tumors. All attempted partial nephrectomies were successful with negative margins, and at a mean follow-up of 24 months, 10 of 12 patients are alive, with one dying from metastatic RCC. Three of the 14 renal units developed delayed urinary leaks which only occurred in those given postoperative sunitinib. These data provided proof of principle and suggested that in well selected patients with imperative indications for nephron-sparing surgery in the setting of locally advanced disease, primary TKI therapy results in tumor response and may facilitate or enable challenging partial nephrectomy.[17] Rini et al. conducted a Phase II trial evaluating utility of pazopanib to optimize renal parenchymal preservation in patients with high complexity kidney masses (R.E.N.A.L. score 10-12) with perihilar tumors and in whom surgery was likely to otherwise yield a glomerular filtration rate of less than 30 ml/minute/1.73 m^2. A total of 25 patients were enrolled, with 71% of tumors demonstrating a decrease in R.E.N.A.L. score and 92% of patients experienced a reduction in tumor volume. Six of 13 patients for whom partial nephrectomy was not possible at baseline were able to undergo partial nephrectomy after treatment. Furthermore, mean parenchymal volume that could be saved with surgery increased from an estimated 107 to 173 cc ($p = 0.0015$). [18]

Karam et al. from MD Anderson performed a single arm Phase II clinical trial examining the effect of axitinib in patients with locally advanced non-metastatic clear cell renal cell carcinoma. A total of 24 patients were treated. Median reduction of primary tumor diameter was 28.3%. By RECIST criteria, eleven patients experienced a partial response, 13 had stable disease, with no progression of disease while on axitinib.[19] Please see below for further details of toxicities and complications encountered with axitinib in the neoadjuvant setting.

Thus an emerging body of data suggest that neoadjuvant tyrosine kinase inhibitor therapy may facilitate complex partial nephrectomy, while optimizing renal parenchymal preservation. Nonetheless, the data collected in most series are small, with all but one study reporting 30 or less patients.[20] Further data are required to establish efficacy and provide longer term follow up on renal functional outcomes.

2.3.3 Primary Objective and Rationale for Study

The primary objective of the study is to assess utility of axitinib in facilitation of partial nephrectomy where partial nephrectomy was not thought to be safe/possible in the setting of imperative indication for complex renal masses in renal cell cancer.

This study is unique in that it will only assess feasibility of partial nephrectomy in patients with complex renal masses, determined by an objective morphometric measure, which are otherwise thought to be unsalvageable. To this data no other study has specifically looked at this question

2.4 Axitinib

Axitinib (Inlyta; Pfizer Inc., New York, NY, http://www.pfizer.com) is an indazole derivative obtained by chemical synthesis. Based on in vitro data, axitinib was a selective kinase inhibitor that appeared to be more potent on VEGF receptor (VEGFR) kinases and platelet-derived growth factor receptor kinases (including KIT) compared with other receptor tyrosine kinases and intracellular kinases. Axitinib has been shown to inhibit VEGF-mediated endothelial cell proliferation and survival. Axitinib inhibited the phosphorylation of VEGFR-2 in xenograft tumor vasculature that expressed the target in vivo and produced tumor growth delay, regression, and inhibition of metastases in many experimental models of cancer.

2.4.1 Non-clinical Aspects and Clinical Pharmacology:

Major toxicity findings in mice and dogs following repeated dosing for up to 9 months were in the gastrointestinal, hematopoietic, reproductive, skeletal, and dental systems. Elevated systolic, diastolic, and mean arterial blood pressure was observed in mice and rats and possibly in dogs. Axitinib was not mutagenic or clastogenic in conventional genotoxicity assays in vitro. Concerning reproduction and developmental toxicity, axitinib-related findings in the testes and epididymis included decreased organ weight, atrophy or degeneration, decreased numbers of germinal cells, hypospermia or abnormal sperm forms, and reduced sperm density and count. Findings in women included signs of delayed sexual maturity, reduced or absent corpora lutea, decreased uterine weights, and uterine atrophy at exposures approximately equivalent to the expected human exposure. Reduced fertility and embryonic viability were observed in female mice. Axitinib showed an increased occurrence of cleft palate malformations and skeletal variations, including delayed ossification, in fetuses and/or offspring at exposure levels in pregnant mice below the expected human exposure. In juvenile animals, reversible physeal dysplasia was observed in mice and dogs given axitinib for at least 1 month at exposure levels approximately 6-fold higher than the expected human exposure. Partially reversible dental caries were observed in mice treated for .1 month at exposure levels similar to the expected human exposure. In humans, after oral administration, maximal plasma concentrations occurred within 4 hours (range of median time to peak concentration across studies: 2.5–4.1 hours). Mean absolute bioavailability was found to be 58%in the fasted state and 54% in the fed state. The plasma protein binding of axitinib at therapeutic concentrations was .99%. Axitinib is metabolized primarily in the liver by CYP3A4/5 and, to a lesser extent (10%), by CYP1A2, CYP2C19, and UGT1A1. Hepatobiliary elimination is the major route of elimination for axitinib. Approximately 20% of the administered dose is excreted renally as metabolites. In clinical studies with axitinib, the systemic exposure to axitinib was approximately 2-fold higher in subjects with moderate hepatic impairment (Child-Pugh class B) compared with subjects with normal hepatic function.

2.4.2 Effects in Humans

Pivotal study A4061032 (AXIS) was an open-label, multicenter, randomized controlled trial of axitinib compared with sorafenib in patients with advanced RCC after failure of treatment with one prior systemic therapy including sunitinib, bevacizumab plus IFN-a, temsirolimus, cytokine, or combination of these.

The study enrolled patients aged >18 years with histologically or cytologically confirmed diagnosis of RCC with a component of clear cell subtype and evidence of metastatic disease.

Prior treatment must have contained one or more of the following agents: sunitinib, bevacizumab plus IFN-a, temsirolimus, or cytokine. Patients who had prior treatment of advanced RCC with more than one systemic first-line regimen, treatment with any neoadjuvant or adjuvant systemic therapy, or major surgery,4 weeks or radiation therapy ,2 weeks prior to starting the study treatment were excluded from the study. Subjects were randomized at a 1:1 ratio to receive either axitinib (starting dose 5 mg b.i.d. with food) or sorafenib (starting dose of 400 mg b.i.d. without food). Treatment was administered continuously in 4-week cycles. The primary endpoint was progression-free survival (PFS) by blinded independent central review.

A total of 723 patients were randomized. The distribution of demographics and baseline characteristics and other important factors like previous malignancy and disease history were well balanced between groups. A predominance of men versus women and white versus other races characterized the study.

In the primary analysis (August 31, 2010), the median PFS was 6.7 months for the axitinib group and 4.7 months for the sorafenib group (hazard ratio [HR]: 0.665; 95% confidence interval [CI]: 0.544–0.812;p,.0001).The benefit in PFS was confirmed in an updated analysis (cutoff of June 3, 2011), showing median PFS of 6.8monthsfor the axitinib group versus 4.7 months for the sorafenib group (HR: 0.670; 95% CI: 0.558–0.805; p< .0001). In the updated analysis of PFS according to prespecified subgroups of prior treatment based on review by a blinded independent review committee (June 3, 2011), the difference in median PFS between the two groups in the prior sunitinib treated patients was 1.4 months (HR: 0.736; 95% CI: 0.578–0.937; p= .0063), whereas the difference was 5.4 months (HR: 0.519; 95% CI: 0.375–0.720; p=.0001) in the patients with prior cytokine treatment.

In the full analysis set, median overall survival (OS) was 20.1 months versus 19.2 months for axitinib versus sorafenib, respectively (HR: 0.969; 95% CI: 0.800–1.174; p5.3744; cutoff of November 1, 2011).There was no survival benefit of axitinib over sorafenib in the prior sunitinib treatment group (HR: 0.997; 95% CI: 0.782–1.270), but a positive trend for OS was observed for axitinib over sorafenib in the prior cytokine treatment group (HR: 0.813; 95% CI: 0.555–1.191), with median OS of 29.4 months in the axitinib arm and 27.8 months in the sorafenib arm.

The analysis of objective response rate (ORR) showed a statistically significant improvement of 13.9% for axitinib compared with sorafenib in patients pretreated with cytokines. In the prior sunitinib treatment group, the difference in ORR between axitinib and sorafenib was 3.6%.The groups of patients previously treated with temsirolimus and bevacizumab plus IFNa were very small (n524 and n559, respectively); therefore, no firm conclusions could be made regarding the efficacy in these subgroups. There were no differences between treatment groups in terms of patient-reported outcomes (Functional Assessment of Cancer Therapy-Kidney Symptom Index; EuroQol Group's Self-Reported Health Status Measure) in the overall population.[21]

Clinical Safety

A total of 3,655 subjects (phase I–III studies) were evaluated for safety, including 2,507 (68.6%) who received at least one dose of axitinib. Updated data from 3,944 subjects treated in 42 clinical trials were also provided.

The most common adverse events reported in the axitinib group (in $20% subjects) were diarrhea, hypertension, fatigue, dysphonia, nausea, decreased appetite, and palmar plantar erythrodysaesthesia (hand-foot) syndrome. Most of these events occurred with grade 1 or 2 severities.

The most important serious adverse reactions reported in patients receiving axitinib were thromboembolic events, hemorrhage, gastrointestinal perforation and fistula formation, hypertensive crisis, and posterior reversible encephalopathy syndrome. In total, 36deaths occurred in the axitinib arm versus 25 in the sorafenib arm. The majority of these events were due to progressive disease. Five events in each arm were considered treatment related. There is no indication that axitinib promotes disease progression or the development of new lesions.

Axitinib affected the incidence of hypertension and thyroid dysfunction, and sometimes aggravated these conditions if they were pre-existing. The hypertension reported during the study was largely manageable, but hypertension is still considered an unfavorable effect of axitinib.

There did not seem to be any clear signal of a clinically meaningful prolongation of the QT interval observed with axitinib; however, two patients had grade 3QTcprolongation at cycle 1, day 15, and two additional patients had on treatment increase in QTc .60 ms in the pivotal study. Consequently, to get the most optimal information about new suspected cases, applicant Pfizer included enhanced pharmacovigilance activities with use of a questionnaire to systematically collect follow-up data of individual case safety reports that can be associated with QT prolongation.[22]

A risk management plan was submitted to address additional important potential risks (wound healing complications; congestive heart failure and cardiomyopathy; carcinogenicity; and drug interactions with CYP1A2, 2C8, and P-glycoprotein substrates) and important missing information (safety in pregnant and lactating women, in pediatric patients, in relevant malignancies, in patients with moderate and severe renal impairment, and in patients with severe hepatic impairment).

2.4.3 Clinical Efficacy in Neoadjuvant Setting

Karam et al. performed a single-institution, single-arm phase 2 clinical trial. Patients with locally advanced nonmetastatic biopsy-proven ccRCC were eligible. Patients received axitinib 5mg for up to 12 wk. Axitinib was continued until 36h prior to surgery. Patients underwent partial or radical nephrectomy after axitinib therapy.

The primary outcome was objective response rate prior to surgery. Secondary outcomes included safety, tolerability, and quality of life. A dedicated radiologist independently reviewed all computed tomography scans to evaluate for response using Response Evaluation Criteria in Solid Tumors (RECIST).

A total of 24 patients were treated. Twenty-two patients continued axitinib for 12 wk; 1 patient continued axitinib for 11 wk and underwent surgery as planned. One patient stopped treatment at 7 wk due to adverse events (AEs). Median reduction of primary renal tumor diameter was 28.3%. Eleven patients experienced a partial response per RECIST; 13 had stable disease. There was no progression of disease while on axitinib. The most common AEs were hypertension, fatigue, oral mucositis, hypothyroidism, and hand-foot syndrome. Postoperatively, 2 grade 3 and 13 grade 2 complications were noted. No grade 4 or 5 complications occurred. Functional Assessment of Cancer Therapy-Kidney Specific Index-15 changed over time, with quality of life worsening while on therapy, but by week 19, it was not statistically different from screening. Limitations include single-arm design and small patient numbers. The authors concluded that axitinib was clinically active and reasonably well tolerated in the neoadjuvant setting in patients with locally advanced nonmetastatic ccRCC, though larger studies are needed prior to further clinical use.[19]

3.0 REGISTRATION PROCEDURES

To enter eligible patients on study, investigators register patients by contacting the study research coordinator, Arlene Araneta at (858) 822-5374. .All patients will be registered in ONCORE. ONCORE will also act as the data management system. Please refer to the calendar for data collection details.

4. TREATMENT PLAN

Inclusion Criteria:

1. Localized clear cell renal carcinoma without evidence of distant metastases
2. Imperative indication for nephron sparing surgery
    - baseline CKD (stage 3, GFR <60 ml/min/1.73m2), **or** anatomically or functional solitary kidney (defined by renal scintigraphy of contralateral renal unit with <15% function) or bilateral synchronous disease); **and**
    - RENAL score ≥10 or proximity to renal hilum (defined as <2 mm away from at least 2 renal hilar vessels-the main artery/vein or first order branches); **and**
    - Radical nephrectomy would lead to severe CKD (stage 4, GFR <45 ml/min/1.73m2).[23]
3. Male or female, age ≥ 18 years
4. Karnofsky performance status ≥ 70 %.
5. Adequate organ function as defined by:
    a. Absolute neutrophil count (ANC) ≥1,000/μL
    b. Platelets ≥100,000/μL
    c. Hemoglobin ≥9.0 g/dL
    d. Serum calcium ≤12.0 mg/dL
    e. Serum creatinine ≤1.5 x ULN
    f. Total serum bilirubin ≤1.5 x ULN
    g. SGOT≤2.5 x ULN and SGPT ≤2.5x ULN
6. Signed informed consent and willingness/ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

Exclusion Criteria:

1) Presence of Metastatic Disease
2) Elective indication for nephron sparing surgery
3) Non-clear cell histology
4) Simple or intermediate renal mass on imaging (R.E.N.A.L score ≤9)
5) Prior systemic treatment of any kind or radiotherapy for RCC

6) NCI CTCAE Version 4.03 grade 3 hemorrhage within 4 weeks of starting the study treatment
7) Ongoing cardiac dysrhythmias of NCI CTCAE Version 4.03 grade ≥2. Controlled atrial fibrillation is permitted.
8) Pregnancy or breastfeeding. Female subjects must be surgically sterile or be postmenopausal,or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum) prior to enrollment. Male subjects must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate.
9) Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.
10) Uncontrolled HTN
11) HTN with need for 2 or more anti-hypertensives to control it at baseline (because there isn't room to add more antihypertinsives if axitinib causes increased BP)
12) CHF since axitinib can cause CHF
13) Baseline abnormal thyroid function tests
14) subjects with arterial thrombotic events in the prior 12 months (axitinib has never been studied in this population)
15) subjects who have had venous thrombotic events in the prior 6 months (axitinib has never been studied in this population)

4.1 Axitinib Administration

Pfizer will supply Axitinib and it will be shipped in labeled boxes, with unlabeled bottles inside. The pharmacy must have labeling capabilities and fax all requests to Pfizer using the Drug Supply Request FormContact information is as follows:

Daniel Matulich, CCRC
daniel.matulich@pfizer.com
Fax: (646) 348-8322
Phone: (212) 733-0149

Pfizer will be provided with detailed mailing instructions, address/location of Pharmacy, Pharmacist in charge, or anything else that may be helpful for shipping.

Treatment will be administered on an outpatient basis. Axitinib will be initially dosed at 5 mg po BID with or without food. Patients tolerating axitinib at week 4 with no more than grade 2 toxicity and blood pressure controlled to <140/90 mmHg (medication permitted) will have axitinib dose increased to 7mg BID. Axitinib will be dosed for a total of 8-10 weeks.

Swallow axitinib whole with a glass of water; do not split, crush, or chew. If the patient vomits

or misses a dose, an additional dose should not be taken; the next prescribed dose should be taken at the usual time

No investigational or commercial agents or therapies other than axitinib may be administered with the intent to treat the patient's malignancy.
Axitinib should be held for 1 day prior to surgery.

No axitinib will be administered after nephrectomy for any patient.

4.2 General Concomitant Medication and Supportive Care Guidelines

Patients may receive Epogen/Procrit/Aranesp for anemia as required. Anti-emetic therapy of any kind is permitted. Full transfusional support is permitted. The prophylactic use of growth factors is not allowed. The use of pyridoxine (vitamin B6) for the treatment of hand-foot syndrome is permitted.

No other approved or investigational anticancer treatment will be permitted during the study period, including chemotherapy, biological response modifiers, hormone therapy or immunotherapy. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

Axitinib is metabolized primarily by liver enzymes, in particular CYP3A4. Agents known to induce CYP3A4 including dexamethasone should be avoided. Agents known to inhibit this enzyme (e.g., grapefruit juice) should also be avoided. In particular, ketoconazole should be avoided if possible, since a clinical interaction study of axitinib indicated that up to a 2-fold increase in plasma levels of axitinib was induced by ketoconazole. In addition, concomitant treatment with the following drugs with dysrhythmic potential (i.e., terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, risperidone, and indapamide) is not recommended.

4.3 Duration of Therapy

Treatment may continue until one of the following criteria applies:

- A total of 8-10 weeks of axitinib therapy (at which point partial/radical nephrectomy would be undertaken at the discretion of the operating surgeon). A decision regarding nephrectomy will be made at re-staging done at week 8 of therapy.
- Disease progression, as defined by RECIST criteria, v1.1,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for

further treatment in the judgment of the investigator.

- If axitinib treatment is unsuccessful (i.e. is unable to render a large and complex mass for a partial nephrectomy), radical nephrectomy would be offered. The large size of the masses will mean that they are of significant risk oncologically to the patient and as such would not be candidates for an alternative approach such as radiofrequency or cryoablation (utilized when tumors are less than <3.5 cm in size) or active surveillance.

5. STUDY CALENDAR

	≤ 4 weeks prior to dosing	Baseline	Day 14 (± 3 days)		Day 28 (± 3 days)	End of Cycle (Day 58 ± 3 days)	End of Treatment[1]
Informed Consent	X						
Vital Signs/ECOG	X	X	X		X	X	X
History / Physical	X	X	X		X	X	X
Hematology[2]	X	X*	X		X	X	X
Chemistries[3]	X	X*	X		X	X	X
Coagulation[4]	X					X	
Pregnancy Test[5]	X						
Urinalysis[6]	X				X	X	X
Drug Related AE's		X	X		X	X	X
TSH, T3, T4	X					As clinically indicated	X
Axitinib**		X----------				----------X	
Tumor Imaging[7]	X				X	X	

* Cycle 1, day 1 labs need not be repeated if done within 14 days. ;** Nephrectomy will be performed ≥ 1 days after the last dose of Axitinib

Footnotes for Schedule of Events	
1.	**End of Treatment/Withdrawal:** These assessments will occur at least 30 days after nephrectomy date.
2.	**Hematology:** CBC with differential, platelets
3.	**Blood Chemistry:** Albumin, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, magnesium, phosphorus, potassium, SGOT [AST], SGPT [ALT], sodium, ALP, LDH (baseline only).
4.	**Coagulation:** PT/INR and PTT
5.	**Pregnancy Test:** Serum or urine test must be performed for all women of childbearing potential.
6.	**Urinalysis:** with 24 hour urine to ensure protein < 2 grams for anyone with 2+ or greater protein on urinalysis.
7.	**Tumor Imaging:** CT or MRI scan of the chest, abdomen and pelvis (with IV contrast, if possible) to be performed to assess disease status at screening, prior to nephrectomy and whenever disease progression is suspected. CT or MRI scan of the chest is optional at day 28 based on symptoms or pre-enrollment findings. CNS and bone imaging needed only if clinical signs/symptoms are suggestive. Follow up imaging after nephrectomy at the discretion of the treating MD and not part of this protocol.

6. DOSING DELAYS AND MODIFICATIONS

Patients will be monitored closely for toxicity, and the axitinib dose may be adjusted according to individual patient tolerance.

Table 2: Suggested Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Hypertension: If persistent hypertension occurs despite antihypertensive medications, reduce dose; discontinue if hypertension is severe and persists despite dose reduction	Step 1. Continue investigational product (IP) at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Hypertensive crisis:	Discontinue Axitinib
(C). Hemorrhage	If any bleeding requires medical intervention, temporarily interrupt axitinib dose.
(D). Reversible posterior leukoencephalopathy syndrome:	Discontinue axitinib
(E) Moderate-to-severe proteinuria	Reduce dose or temporarily interrupt treatment
(F) Strong CYP3A 4/5 inhibitors:	Avoid coadministration if possible, if axitinib must be coadministered, decrease dose by ~50% and then adjust according to safety and tolerance; if strong CYP3A4/5 inhibitor is discontinued, may increase to prior axitinib dose after waiting 3-5 half-lives of the inhibitor
(G) Renal Impairment	Based on population pharmacokinetic analyses, no significant difference in clearance observed in patients with pre-existing mild-to-severe renal impairment
(H) Hepatic Impairment	Mild (Child-Pugh A): No adjustment of initial dose is required Moderate (Child-Pugh B): Decrease initial dose by ~50%; subsequent doses can be increased or decreased based on individual safety and tolerability Severe (Child-Pugh C): Has not been studied

7. ADVERS E EVENT REPORTING REQUIREMENTS

Adverse events will be assessed and will be graded according to the NCI CTC v4.0. CTC v4.0 can be accessed on the Internet at http://ctep.info.nih.gov. All Grade 4 toxicities should be reported (using a MedWatch form) to the Principal Investigator, the Data Safety and Toxicity Committee and the IRB.

Expedited Reporting Requirements:

A. The Study Chair and Site Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

B. The UCSD Human Research Protections Program (HRPP) and the Data and Safety Toxicity Committee must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

The **Institutional Review Board (IRB) of each site** must be notified by the site principal investigator according to their local policies.

The **FDA** must be notified according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

Routine Reporting Requirements

A. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

B. The **IRB of each site** must be notified by the site principal investigator according to their local policies.

The **FDA** must be notified of all non-serious adverse events annually at the time of the annual report.

For this protocol, hospital admission for the nephrectomy procedure will not be considered an SAE. Complications secondary to surgery delaying discharge will be considered an SAE. Patients will be followed for toxicity (of drug and/or surgical procedure) until 30 days after the date of partial nephrectomy, unless there is drug-related toxicity in which case patients will be followed until toxicity resolution to grade 1 or less.

Reporting to Pfizer:

Any serious adverse events which occur during the clinical study or within 5 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

All serious adverse events must be reported by facsimile within 24 hours to Pfizer. MDC - Oncology Fax: (212) 733-0149.
For medical emergencies contact: Site PI

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Pfizer within 24 hours.

SAEs brought to the attention of the investigator at any time after cessation of pazopanib and considered by the investigator to be related or possibly related to pazopanib must be reported to GSK if and when they occur. Additionally, in order to fulfill international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is off study.

Data Safety Monitoring Plan

This protocol will adhere to the policies of the Cancer Center Data and Safety Monitoring Plan, version 2 guidelines in accordance with NCI regulations. The Data and Safety Toxicity Committee will compose of the principal investigator and the sub-investigators participating in this research study. The committee will convene electronically and by phone on a monthly basis to review safety and toxicity information.

8. PHARMACEUTICAL INFORMATION

8.1 Description of Investigational Product

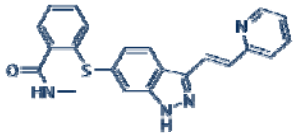
Axitinib

Axitinib is supplied as a series of aqueous film-coated tablets containing 5mg of agent

8.2 Physical and Chemical Properties of the Drug Substance

NDC Codes:	0069-0145-01, 0069-0151-11, 63539-026-01, 63539-044-01, 63539-044-02.
Approved Names:	Inlyta
Chemical Name:	N-methyl-2-[[3-[(E)-2-pyridin-2-ylethenyl]-1H-indazol-6-yl]sulfanyl]benzamide

Structural Formula:



Molecular Formula: $C_{22}H_{18}N_4OS$

Molecular Weight: 386.46952 g/mol

Physical Form: White to light yellow powder

Solubility: In aqueous media with a pH between 1.1 to 7.8, axitinib has a solubility of over 0.2 ?g/mL.

Refer to the FDA label regarding the physical and chemical properties of axitinib and a list of excipients.

8.3 Dosage and Administration

Axitinib

Axitinib will be provided by Pfizer. For purposes of this study, Axitinib dosing will be defined by one 8 week cycle: Dosing will continue until prior to partial/radical nephrectomy, unacceptable toxicity, or withdrawal of consent .

Axitinib should be taken twice daily approximately 12 hr apart. May be taken with or without food. It may be swallowed whole with a glass of water; do not split, crush, or chew. If the patient vomits or misses a dose, an additional dose should not be taken; the next prescribed dose should be taken at the usual time

Specific recommendations regarding anticoagulants:
No interactions have been reported between axitinib and warfarin, aspirin, clopidogrel, ticagrelor, or rivaroxaban.

Specific recommendations regarding hypoglycemic medications including insulin:
Results from drug-drug interaction studies conducted in subjects with cancer suggest that here will be no clinically relevant pharmacokinetic interaction between axitinib and hypoglycemic agents. Decreases in serum glucose, however, have been reported in clinical studies with axitinib. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating).

Overdose
There is no specific antidote for over dosage of axitinib, and treatment of overdose should consist of general supportive measures. Hemodialysis is not expected to enhance the elimination of axitinib, as axitinib is not significantly renally excreted.

9. MEASUREMENT OF EFFECT

9.1 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 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 when both methods have been used to assess the antitumor effect of a treatment.

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

9.2 Response Criteria

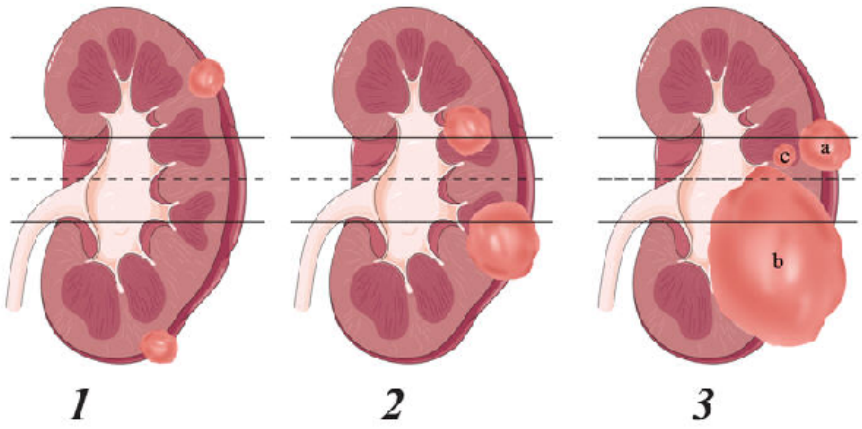
Response to axitinib will be measured according to 3 mechanisms:

1. Percent in reduction of longest diameter of tumor.

2. RECIST criteria-Tumor response to therapy will be assessed by CT/MRI during second cycle of treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.1.[24] Clinical response of primary tumor will be classified by treating physicians as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), where:
    a) Complete Response (CR): Disappearance of all target lesions
    b) Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
    c) Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
    d) Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

3. RENAL score-morphometric measure which has been correlated with oncological prognosis, surgical risk stratification and renal functional outcomes in addition to response to primary TKI.[20]

	1pt	2pts	3 pts
(R)adius (maximal diameter in cm)	≤4	>4 but < 7	≥ 7
(E)xophytic/endophytic properties	≥ 50%	<50%	Entirely endophytic
(N)earness of the tumor to the collecting system or sinus (mm)	≥7	>4 but <7	≤4
(A)nterior/Posterior	No points given. Mass assigned a descriptor of a, p, or x		
(L)ocation relative to the polar lines* * suffix "h" assigned if the tumor touches the main renal artery or vein	Entirely above the upper or below the lower polar line	Lesion crosses polar line	>50% of mass is across polar line (a) or mass crosses the axial renal midline (b) or mass is entirely between the polar lines (c)



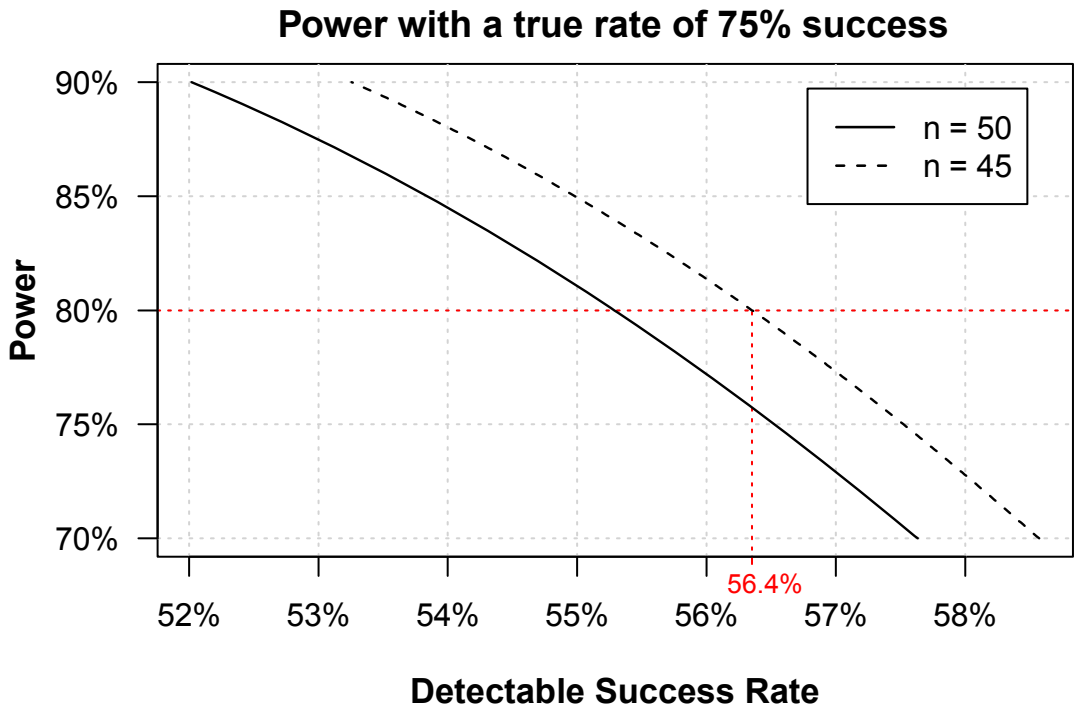
For difficult to qualify/document cases, the primary surgeon may seek confirmation of the surgical Co-PIs (Dr. Derweesh/Dr. Campbell) to confirm the change between baseline and post Rx status.

10. STATISTI CAL CONSIDERATIONS

Sample Size/Power Calculation:

Our sample size calculation is based on the data of Rini et al. (2015) who reported that 80% (20/25) of patients successfully underwent partial nephrectomy; from our institutional database the success rate was utilizing Sunitinib the success rate in imperative indications was 78.6% (11/14).

Assuming a true rate of successful intervention of 75%, a one proportion z-test will have 80% power (Beta 20%) at the two-sided 0.05 (alpha) significance level to detect a rate of success of at least 56.4%. To account for a potential dropout rate of 10%, we will have total sample size to 50 (Figure)



Statistical Analysis:

We will examine patients in whom the operation was feasible vs. those in which it was not. Summary statistics (mean, standard deviation, quintiles, counts, and percentages) and plots will be produced for all demographic (i.e. age, sex, race, BMI, Charlson score, etc), clinical disease characteristics (tumor size prior to treatment, RENAL score), surgical outcomes (margin status, estimated blood loss, transfusions) and complications, and renal functional outcomes (change in eGFR, decline in GFR >50% of preoperative value, and dialysis dependence). In comparing any of these measures between patient groups, we will use either Fisher's Exact test or the Chi-Squared test for categorical variables and a t-test for continuous variables. We will consider the use of the Mann-Whitney U-test as a robust alternative if the assumptions of the t-test are not met.

We will use a logistic regression to examine the impact of factors associated with complications / blood transfusions and GFR decline > 50%, and a linear regression to examine factors associated with changes in GFR. Standard model diagnostics will be assessed before any inference is derived. All statistical analysis will be conducted using the latest version of R (R Foundation for Statistical Computing, Vienna, Austria. http://www.r-project.org/).

11.0 DATA REPORTING AND MONITORING REQUIREMENTS

This monitoring committee will include the three senior co-investigators, Ithaar H. Derweesh, MD, Brian I. Rini, MD, and Steven C. Campbell, MD, PhD. The committee will convene electronically and by phone on a monthly basis to review safety and toxicity information.

If 10 out of the first 15 participants are not able to safely proceed to nephron sparing surgery, the study will be stopped.

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Appendix 1: Axitinib Guidance Document: Concomitant Medication

Concomitant Medications and Non-Drug Therapies

Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the previous 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

All concomitant medications taken during the study will be recorded in the case report form (CRF) with indication, dose information, and dates of administration.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

Permitted Medications – Use with Caution

Specific recommendations regarding anticoagulants:

Results from drug-drug interaction studies conducted in subjects with cancer suggest that pazopanib has no effect on the metabolism of S-warfarin. Hemorrhagic events, however, have been reported in clinical studies with tyrosine kinase inhibitors; therefore, axitinib should be used with caution in subjects with increased risk of severe bleeding or who are receiving concomitant anticoagulant therapy (e.g., warfarin or its derivatives, low molecular weight heparin, unfractionated heparin). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for

any clinical bleeding episodes.

Specific recommendations regarding hypoglycemic therapy including insulin:

Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between axitinib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with sunitinib. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

The Effects of Axitinib on Other Drugs[1,2]

Axitinib is metabolized primarily in the liver by cytochrome P450 (CYP) 3A4/5 and, to a lesser extent (<10 % each), by CYP1A2, CYP2C19, and uridine diphosphate glucuronosyltransferase (UGT) 1A1. The two major human plasma metabolites, M12 (sulfoxide product) and M7 (glucuronide product), are considered pharmacologically inactive. Axitinib is eliminated via hepatobiliary excretion with negligible urinary excretion. Although mild hepatic impairment does not affect axitinib plasma exposures compared with subjects with normal hepatic function, there was a 2-fold increase in AUC from time zero to infinity (AUC∞) following a single 5-mg dose in subjects with moderate hepatic impairment. In the presence of ketoconazole, a strong CYP3A4/5 inhibitor, axitinib C max and AUC∞ increased by 1.5- and 2-fold, respectively, whereas co-administration of rifampin, a strong CYP3A4/5 inducer, resulted in a 71 and 79 % decrease in the C max and AUC∞, respectively. Axitinib does not inhibit CYP3A4/5, CYP1A2, CYP2C8, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or UGT1A1 at concentrations obtained with the clinical doses and is not expected to have major interactions with drugs that are metabolized by these enzymes.

In addition, the potential for drug interaction with such medications, although diminished, may persist after the last dose of axitinib even with its relatively short half-life (i.e., 2.5-6.1 hours); therefore, continue to exercise **CAUTION** for at least 1 day and up to 2 days after the last dose of axitinib when administering these medications. These medications include

(but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: caution should be exercised when utilizing bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (in tyrosine kinase inhibitors as a class, potential increased risk for QT interval prolongation and Torsade de Pointes; notheless a study by Ruiz-Garcia et al. in Cancer Chemother Pharmacol in 2015 noted that in healthy volunteers with Axitinib concentrations exceeded the range observed in RCC patients, axitinib was not associated with clinically significant QTc prolongation)[2]
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

The Effects of Other Drugs on Axitinib

Results from *in vitro* studies suggest that the oxidative metabolism of pazopanib in human liver microsomes is mediated primarily by CYP3A4/5, with minor contributions from CYP1A2 and CYP2C19.[3] Furthermore, *in vitro* data suggest that axitinib is an inhibitor for p-glycoprotein. Substances that induce or inhibit CYP3A4 may alter the pharmacologic effects of pazopanib and should be used with **CAUTION**.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section on Prohibited Medications); therefore selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

CYP3A4 inducers may decrease plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended. **Drugs that induce CYP3A4 and may decrease axitinib plasma concentrations include (but are not**

limited to):

- Glucocorticoids: cortisone (>50 mg), hydrocortisone (>40 mg), prednisone (>10 mg), methylprednisolone (>8 mg), dexamethasone (>1.5 mg)
- Anticonvulsants: phenytoin, carbamezepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone, troglitazone

Prohibited Medications[4]

Subjects should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] while on treatment in this study.
Medications that inhibit CYP3A4 and 1A2 inducers may result in increased plasma pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study.
Strong CYP3A4 inhibitors include (but are not limited to):

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone

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