CLINICAL PROTOCOL

ADJUVANT AXITINIB TREATMENT OF RENAL CANCER: A RANDOMIZED DOUBLE-BLIND PHASE 3 STUDY OF ADJUVANT AXITINIB VS. PLACEBO IN SUBJECTS AT HIGH RISK OF RECURRENT RCC

Compound:	AG-013736
Compound Name (if applicable):	Axitinib
Protocol Number:	AP311736
Phase:	3
Version and Date	version - #10 March 21, 2017
Good Clinical Practice Statement:	This study is to be performed in full compliance with all International Conference on Harmonization (ICH) and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived per regulatory authorities' requirements.

SUMMARY

Indication:

Adjuvant treatment of patients at high risk of recurrent renal cell carcinoma (RCC) following nephrectomy.

Background:

Kidney cancer is diagnosed in approximately 270,000 people each year worldwide, and results in 120,000 deaths. RCC is the most common form of kidney cancer. Up to 30% of patients treated by nephrectomy for localized disease will relapse. Hormonal, chemotherapeutic, and radiation therapy approaches have failed to significantly improve clinical outcomes, particularly for patients with metastatic disease.

Approximately 45% of RCC patients present with "localized" disease (tumor, nodes, metastatis [TNM] Stage I/II) at the time of diagnosis, 25% "locally advanced" disease (Stage III) and 30% "metastatic" disease (TNM Stage IV). Additionally, approximately 30% of patients with "localized" and "locally advanced" disease at the time of diagnosis will develop metastatic disease later on. TNM Stage II, III and IV RCC patients have 5-year survival rates of 65-80%, 40-60% and 0-20%, respectively.

Axitinib is an oral, potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. The safety and efficacy of axitinib is being evaluated in patients with a variety of solid tumors.

VEGF receptors are critical components of the processes leading to the branching, extension, and survival of endothelial cells which form new blood vessels during angiogenesis, an absolute necessity for tumor growth beyond microscopic size. In nonclinical tumor mouse models, twice daily (BID) oral administration of axitinib demonstrated consistent and significant anti-tumor efficacy (marked inhibitory effect on local and distant tumor metastasis and prolonged animal survival).

A Phase 2 study of single-agent axitinib in patients with cytokine-refractory metastatic RCC (mRCC) showed an objective response rate (ORR) of 44.2%, with 21 partial responders (PRs) and 2 complete responders (CRs) out of 52 patients. The median time to progression (TTP) was 15.7 months and median overall survival (OS) was 29.9 months. Another Phase 2 study of single-agent axitinib in Japanese patients with cytokine-refractory mRCC demonstrated ORR of 50.0%, with 32 PRs out of 64 patients. The median progression-free survival (PFS) was 11.0 months. Both data were based on the assessment by an Independent Review Committee (IRC). A third Phase 2 study of single-agent axitinib in patients with sorafenib-refractory mRCC showed ORR of 23% and a median PFS of 7.4 months (N=62). In a subset of 14 patients previously treated with both sorafenib and sunitinib, one patient achieved a PR and the median PFS was 7.1 months. These results suggest that axitinib may provide clinical benefit to patients with mRCC following failure of prior systemic first-line therapy.

In a Phase 3 study, efficacy and safety of axitinib versus (vs) sorafenib were confirmed in patients with advanced RCC following failure of one prior systemic first-line therapy.

Axitinib demonstrated a significantly longer PFS and higher ORR vs sorafenib with an acceptable safety profile as second-line therapy for mRCC. Axitinib was approved by US Food and Drug Administration (FDA) in January 2012 with an indication for the treatment of advanced RCC after failure of one prior systemic therapy. Axitinib was also approved in Japan, Korea and other countries in 2012 for the same indication.

Objectives:

Primary Objective:

- To demonstrate an improvement in disease free survival (DFS) in patients at high risk of recurrent RCC randomly assigned to adjuvant axitinib (Arm A) vs. Placebo (Arm B) after nephrectomy.

Secondary Objectives:

- Compare OS associated with Arm A to that associated with Arm B
- Assess safety/toxicity profile of administration of axitinib

Trial Design:

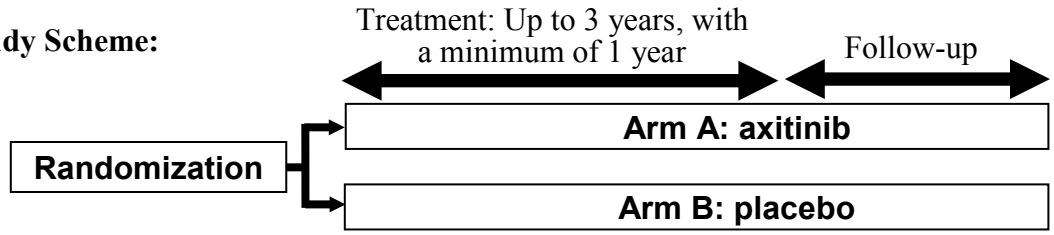
This is a prospective, randomized, double-blind placebo controlled Phase 3 trial of oral axitinib starting at 5 mg twice daily vs. placebo given for up to 3 years, with a minimum of 1 year. The dose may be increased or decreased depending on individual patient tolerance of axitinib.

A total of approximately 700 patients will be randomized in a 1:1 ratio between axitinib vs placebo. Patients should begin study treatment within 7 days after randomization. Randomization will occur no sooner than 4 weeks post-nephrectomy and no later than 12 weeks post-nephrectomy.

Recurrence or occurrence of a secondary malignancy will be followed up, by clinic visit (See Section 6.4 for further details), until the time of the final analysis (regardless of the duration of treatment) every 16 weeks for the first 3 years from initiation of study treatment (also, at the end of treatment) and every 6 months thereafter for the remainder of the follow-up period.

All patients will be followed up for OS status (regardless of the duration of treatment) every 16 weeks until the time for final DFS analysis. Survival status can be ascertained by telephone contact. At the time of final DFS analysis, OS results will be analyzed and summarized.

Study Scheme:



Endpoints:

Primary Endpoint:

- DFS is defined as the time interval from the date of randomization to the first date of recurrence (distant or local recurrence of RCC) or the occurrence of a secondary malignancy or death. The primary DFS analysis will be based on assessments by the Independent Review Committee (IRC). IRC will review all imaging data. Additionally, in cases for which there is site confirmation of recurrence or occurrence of a secondary malignancy in the absence of IRC imaging confirmation, available local histo-/cytopathology reports will also be reviewed by the IRC oncologist to determine confirmation of recurrence or occurrence of a secondary malignancy.

- Recurrence refers to relapse of the primary tumor in situ or at metastatic sites. The date of recurrence or the occurrence of a secondary malignancy is defined as the date of the tumor scan or the date of collection of the histo-/cytopathological specimen (for patients who have site confirmation of recurrence or occurrence of secondary malignancy in the absence of IRC imaging confirmation) that demonstrated unequivocal recurrence or a secondary malignancy according to protocol criteria. If both imaging and histo-/cytopathological confirmation of recurrence or secondary malignancy are available, the earlier of the two dates will be considered.

- For patients with no DFS event, DFS time will be censored at the date of the last scan prior to the time of the analyses. Patients alive who do not have post-baseline disease assessments will have their DFS times censored at randomization. For patients receiving further anti-tumor therapy prior to recurrence or occurrence of a secondary malignancy or death, DFS will be censored on the date of the last scan prior to taking the anti-tumor medication. Patients who miss 2 or more consecutive tumor scans immediately followed by an event will be censored at the date of the last objective tumor assessment prior to the missing/not readable scans.

Secondary Endpoints:

- OS, defined as the time from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond randomization will have their survival times censored at randomization.

- Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0), timing, seriousness, and relatedness of adverse events, and laboratory abnormalities.

Trial Treatments:

Patients will receive a starting dose of 5 mg of axitinib or placebo twice daily (BID) taken orally with or without food. Study drug will 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. If a patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual

time. Missed or vomited doses must be indicated in the source documents and Case Report Forms (CRFs). Study drug will be administered in cycles of 4 weeks in duration.

Patients who tolerate axitinib or placebo with no adverse events related to study drug above CTCAE Grade 2 for a consecutive 2 week period may have their dose increased by one dose level to a maximum of 10 mg BID (unless the patient's blood pressure is >150/90 mm Hg or the patient is receiving antihypertensive medication). The clinical judgment of the treating investigator should be exercised in titrating axitinib dose.

Patients experiencing drug reaction should undergo dose modification as recommended in Section 5.3.4.

Available Axitinib/Placebo Dose Levels:

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 (twice daily)**
-1	3 mg BID	3 X 1 mg Tablets BID
-2	2 mg BID	2 X 1 mg Tablets BID
-3	1 mg BID	1 X 1 mg Tablet BID

Statistical Methods:

Two analysis populations will be defined:

1. Intent-to-Treat Population: This population will include all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized. This will be the primary population for evaluating all efficacy endpoints as well as patient characteristics;

2. As-Treated Population: The as-treated population consists of all patients who received at least 1 dose of study drug with treatment assignments designated according to actual study drug received. This population will be the primary population for evaluating study drug administration/compliance and safety.

Sample Size Calculation:

The patient population in this study can be classified into 4 risk groups based on American Joint Committee on Cancer (AJCC) TNM staging version 2010, Eastern Collaborative Oncology Group (ECOG) performance status (PS). Any Fuhrman grades are eligible. The patient risk groups will be as follows. Group a will be closed for further enrollment, to keep the number of patients of groups b, c, and d with about 90% or more:

~~a. pT2, pN0 or pNx, M0 and ECOG PS 0-1~~

b. pT3, pN0 or pNx, M0 and ECOG PS 0-1

c. pT4, pN0 or pNx, M0 and ECOG PS 0-1

d. Any pT, pN1, M0 and ECOG PS 0-1

Sample size was determined based on the analysis on the primary endpoint, DFS.

The sample size for this study was calculated based on the following assumptions:

- Time to DFS event follows an exponential distribution.
- The percentage of patients randomized from the 4 risk groups, 2-year DFS rates for placebo arm and axitinib arm are assumed below:

Categories	Risk groups	Percentage of patients	2-year DFS rate for placebo arm	2-year DFS rate for axitinib arm
1	a. pT2/pN0 or pNX/M0 b. pT3/pN0 or pNX/M0	90%	70%	79%
2	c. pT4/pN0 or pNX/M0	1%	35%	61%
3	d. Any pT/pN1/M0	9%	33%	51%

The assumptions of 2-year DFS rates for the placebo arm and axitinib arm are equivalent to the assumptions of hazard ratios to be 0.66, 0.47, and 0.61 for the 3 categories 1, 2 and 3 respectively. Given the assumed distribution of patients randomized (1:1) into each of these categories, the overall hazard ratio is estimated to be 0.654.

Based on the above assumptions, a minimal number of 245 DFS events will be required to provide 90% power to detect the statistical difference in DFS with HR $\leq$ 0.654 between the two treatment groups with 2-sided significance level of 0.05.

Applying a 1:1 randomization and a planned accrual period of 24 months, a maximum study period of 60 months (5 years), and an assumed 23% drop-out rate by 18 months, it was estimated that approximately 700 patients will be enrolled.

The final analysis will take place when approximately 245 DFS events are observed.

Interim Analysis:

A single interim analysis (IA) of efficacy and safety will be performed after approximately 184 DFS events (approximately 75% of the total number of required events as assessed by the IRC) have occurred. If the event occurrence pace is much slower than anticipated, the IA could be performed when less than 184 events observed (<75% of the total required) at sponsor's discretion with the Data Monitoring Committee's (DMC) consensus. To protect the integrity of the study and to preserve the Type 1 error, a fraction of alpha will be spent at the interim analysis based on an O'Brien-Fleming stopping boundary.

The objectives of the interim analysis will be:

- To assess the safety, including any unexpected toxicity.
- To allow for early stopping of the trial due to futility.
- To assess the efficacy of the study drug to allow stopping of trial for success of efficacy.

Schedule of Assessments	Screening	Treatment with axitinib or placebo[1]			Post-Treatment			
Protocol Activities and Forms to be Completed	(See Protocol Section 6.1)	Cycle 1 (1 cycle = 4 weeks)		Subsequent Cycles[2]	EOT or Withdrawal[3]	28 Days Post-Treatment	DFS Follow-up	Survival Follow-Up
		Day 1	Day 15 (-7/+2 days)	Day 1 (-7/+2 days)		(0/+7 days)	(-7/+7 days)	
Informed Consent[4]	X							
Medical History, illnesses and demographics	X							
Physical Examination	X*	X	X[5]	X	X			
Vital signs[6], body weight	X*	X	X[5]	X	X			
Home Blood Pressure Monitoring[7]		Throughout the study period						
Height	X*							
Hematology[8]	X*			X	X			
Blood Chemistry[8]	X*			X	X			
Urinalysis[8]	X*			X	X			
Thyroid Function Tests[9]		X	X[5]	X	X			
Pregnancy Test if applicable[10]	X*							
12-lead electrocardiogram[11]	X*							
ECOG Performance Status[12]	X	X		X	X			
CT or MRI of brain[13]	X							
Tumor Imaging[14]	X			X Every 16 weeks	X		X	
Histo-/cytopathology[15]	X				X			
Study Randomization[16]	X (Day -7 to 1)							
Study Treatment[17]		X		X				
Adverse Events[18]	X	X	X[5]	X	X	X		
Study Drug Compliance[19]				X	X			
Prior/Concomitant Medications and Treatments[20]	X	X	X[5]	X	X	X		
Follow-up Survival Status[21]								X

*: Should be assessed within 14 days of randomization.

Footnotes for Schedule of Assessments	
1.	**During Treatment**: Acceptable time windows for performing each assessment are described in the column headings.
2.	**Subsequent Cycles**: Assessments other than tumor imaging should be done at Day 1 of every cycle (4 weeks) until Cycle 5 Day1, then every 8 weeks thereafter starting from Cycle 7 Day 1.
3.	**End of Treatment (EOT)/Withdrawal**: At the end of the study or at withdrawal, these assessments should be performed if they were not performed within 7 days of the end of the study or at withdrawal. Tumor imaging should be obtained if they were not performed within 8 weeks of the end of the study or at withdrawal for patients who discontinue treatment for reasons other than disease progression.
4.	**Informed Consent**: Must be obtained before undergoing any study specific procedure and may occur prior to the screening period.
5.	**Cycle 1 Day 15**: Assessments should be performed via telephone contact or visit. In case of telephone contact, only adverse events assessment should be performed.
6.	**Vital signs**: Temperature, blood pressure and pulse rate will be measured. Blood pressure should be measured with the patient in the seated position after the patient has been sitting quietly for 5 minutes.
7.	**Home Blood Pressure Monitoring**: All patients will be provided a blood pressure monitoring device. Patients should measure their blood pressure prior to taking each dose of study drug (twice daily) for the first 3 months, and once a week thereafter. Following dose modification of study drug or anti-hypertensive medication, or changes of anti-hypertensive medication, patients should restart blood pressure measurements prior to taking each dose of study drug for the first 3 months and once a week thereafter. Patients should record all blood pressure measurements in their patient diary. Patients should be instructed by the study staff to contact their investigator immediately for guidance if their systolic blood pressure rises above 150 mm Hg, diastolic blood pressure rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated blood pressure (eg, headache, visual disturbance).
8.	**Hematology, Blood Chemistry, Urinalysis**: See Appendix 1 of the protocol for required tests. Hematology, chemistry and urinalysis will be done 2 weeks prior to starting treatment (screening). Results of the tests must be awaited before randomizing patients. Thus, days for test results should be taken into consideration. After the first cycle, the hematology, chemistry and urinalysis will be repeated at Day 1 of every cycle (4 weeks) until Cycle 5 Day1, then every 8 weeks thereafter starting from Cycle 7 Day 1. If urine protein is ≥2+ by semi-quantitative method (ie, dipstick) at screening or on study, then urine protein:urine creatinine ratio should be performed. PT/INR should be performed to monitor patients receiving concomitant warfarin or other anti-coagulants and when clinically indicated.
9.	**Thyroid Function Tests**: Thyroid Function Tests (TSH, free T_3 and free T_4) should be performed for all patients at baseline (Cycle 1 Day 1 pre-dose). Subsequently, TSH should be done at Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, then every 8 weeks thereafter starting from Cycle 7 Day 1. TSH, Free T_3 and free T_4 should be performed on the next visit for any patient who has elevated TSH. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state with a normal TSH.
10.	**Pregnancy Testing:** Patient of childbearing potential must have a negative pregnancy test within 14 days prior to the date of randomization and must be using appropriate birth control or practicing abstinence. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
11.	**12-lead electrocardiogram (ECG):** To determine the QTc interval at screening, the average of three consecutive 12-lead ECGs should be done. Screening ECG should be performed no more than 2 weeks prior to randomization. If the QTc interval is prolonged (>500 msec), the ECG should be re-read by a cardiologist at the site for confirmation. ECGs should be repeated as clinically indicated.
12.	**ECOG Performance Status (ECOG PS):** Evaluation of ECOG PS at screening should reflect the patient condition just prior to nephrectomy. Baseline ECOG PS should be made prior to randomization and start of treatment. Follow-up assessments will be done at Day 1 of every cycle (4 weeks) until Cycle 5 Day1, then every 8 weeks thereafter starting from Cycle 7 Day 1.
13.	**CT or MRI of brain**: To be done at screening and the images sent to the IRC for retrospective confirmation. Patients with any evidence of brain metastasis must be excluded from the study. Images should be submitted for IRC review before Week 8 post-nephrectomy to allow for return of the results before Week 12 and in the event a repeat scan is needed. Brain CT or MRI within 12 weeks prior to randomization is acceptable regardless of whether it is before or after nephrectomy. Subsequent CT or MRI of brain is not required, but may be performed if clinically indicated.
14.	**Tumor Imaging**: Pre-surgery images are requested, if available, and should be submitted for IRC review. Screening visit imaging will be reviewed by IRC, designated by the sponsor, and must be performed at least 3 weeks after nephrectomy. Images should be submitted for IRC review before Week 8 post-nephrectomy to allow for return of the results before Week 12 and in the event a repeat scan is needed. CT or MRI of the chest, abdomen and pelvis for DFS should be performed (regardless of the duration of treatment) every 16 weeks for the first 3 years from initiation of study treatment (also, at the end of treatment). Allowable window for assessment is +/- 7 days. Thereafter,

Footnotes for Schedule of Assessments
imaging should be repeated every 6 months for the duration of the DFS follow-up period. Additional imaging of potential disease sites should be performed whenever recurrence or occurrence of a secondary malignancy is suspected. Bone scan (confirmatory imaging in addition to bone scan may be required), if clinically indicated.
15. **Histo-/cytopathology:** Local histopathology confirmation of eligibility is required. After randomization, in cases for which there is site confirmation of recurrence or occurrence of a secondary malignancy in the absence of IRC imaging confirmation, available local histo-/cytopathology reports should be submitted to the IRC for review.
16. **Study Randomization**: Patients must be randomized by 12 weeks after nephrectomy. Patient eligibility must be confirmed by IRC review for imaging and by a sponsor designated laboratory. Patients must be randomized based on the assessment by the IRC when there is a discrepancy between the local and the IRC imaging review.
17. **Study Treatment**: Should be started within 7 days after randomization. It is not necessary to repeat the Day 1 procedures if treatment is not started on the same day as randomization. Patients will receive either axitinib tablets at a starting dose of 5 mg BID or placebo according to randomization. The axitinib/placebo dose may be adjusted up or down according to individual patient tolerance per protocol dose modification procedure. Study drug are dispensed on Day 1 of each cycle.
18. **Adverse Events (AEs)**: Will be collected from the first day of study treatment until at least 28 days after the last on-study drug administration (Allowable window for assessment is 0/+7 days.), or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported from the time that the patient provides informed consent and as described in the protocol.
19. **Study Drug Compliance**: The study drug bottle(s) including any unused tablets will be returned to the clinic for drug accountability.
20. **Prior/Concomitant Medications and Treatments**: Will be recorded from the time the patient has signed informed consent until 28 days after last treatment. Allowable window for assessment is 0/+7 days. Anti-tumor therapy should be recorded even after 28 days after last treatment.
21. **Follow-up Survival Status**: Survival status information should be collected, approximately every 16 weeks (+/- 2 weeks) from DFS events, until the time for final DFS analysis. Survival information can be done via telephone contact.

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1. INTRODUCTION

1.1. Background

1.1.1. Renal Cell Carcinoma Epidemiology and Treatment

Kidney cancer is diagnosed in approximately 270,000 people each year worldwide, and results in 120,000 deaths. Renal cell carcinoma (RCC) is the most common form of kidney cancer.[1] Up to 30% of patients treated by nephrectomy for localized disease will relapse.[2] Hormonal, chemotherapeutic, and radiation therapy approaches have failed to significantly improve clinical outcomes, particularly for patients with metastatic disease.

Clear cell RCC, which represents 75% to 85% of the RCC population, frequently displays allelic loss on chromosome 3p, accompanied by mutational inactivation of the Von Hippel-Lindau (VHL) tumor suppressor gene.[3, 4] VHL-associated RCC are known for their vascularity and these tumors produce high levels of vascular endothelial growth factor (VEGF).[5, 6, 7] In addition, recent studies suggest that in sporadic clear cell RCC, increased expression of VEGF is closely correlated with neovascularization, which is a prerequisite of tumor growth and metastasis.[8] RCC tumors overexpress the receptors for these peptides. These ligands and receptors may be involved in the autocrine stimulation of tumor cell growth, or in the paracrine stimulation of neovascular or stromal fibroblast growth that supports tumor expansion.

Approximately 45% of RCC patients present with “localized” disease (tumor, nodes, metastatis [TNM] Stage I/II) at the time of diagnosis, 25% “locally advanced” disease (Stage III) and 30% “metastatic” disease (TNM Stage IV). Additionally, approximately 30% of patients with “localized” and “locally advanced” disease at the time of diagnosis will develop metastatic disease later on. TNM Stage II, III and IV RCC patients have 5 year survival rates of 65-80%, 40-60% and 0-20%, respectively.

Hormonal, chemotherapeutic, and radiation therapy approaches have failed to significantly improve clinical outcomes for patients with metastatic RCC (mRCC). Recently-published trials included reports on thalidomide, 5-FU, and cis-retinoic acid, none of which showed clear benefit. Studies of chemotherapy combined with cytokine therapy have also been discouraging. Notwithstanding, cytokine therapies have been commonly used in the treatment of mRCC albeit with limited anti-tumor response. Interferon-α (IFN-α) has an approximately 15% objective response rate (ORR) in appropriately selected individuals.[10] In general, these patients have non-bulky pulmonary and/or soft tissue metastases with excellent PS (Eastern Collaborative Oncology Group (ECOG) performance status (PS) 0 or 1) without weight loss. These responses are rarely complete or durable, but the result of a study suggests that IFN-α improves survival.[11] Administration of high-dose interleukin-2 (IL-2) appears to have a similar overall response rate to IFN-α, but with approximately 5% of the appropriately selected patients having durable complete remissions. Combinations of IL-2 and IFN-α have been studied, but have not shown an overall survival (OS) advantage over monotherapy. The optimum dose of IL-2 is unknown. High-dose therapy has been approved in the United States, and while it appears to be associated with higher response rates, the incidence of toxic effects is also high.[12, 13, 14, 15] Low-dose IL-2 regimens produce lower

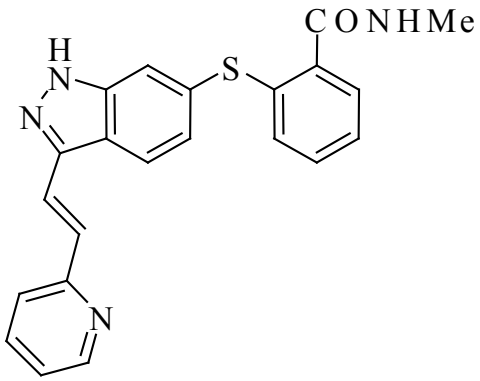
response rates but can be administered with fewer toxic effects, especially hypotension.[16] Attempts to improve relapse-free survival and OS using cytokine or immune-based treatments were equally discouraging providing no evidence for improved relapse-free or OS.[17, 18, 19]

Several anti-angiogenic agents have shown activity in the treatment of mRCC. In the first-line treatment of mRCC, sunitinib has demonstrated dramatically improved median progression free survival (PFS) over IFN (11 months vs 5 months; hazard ratio 0.42; $p < 0.001$)[20] and is now considered to be the standard of care for the first-line treatment of patients with mRCC. In similar first-line setting, the final analysis of a randomized Phase 3 (AVOREN) trial of bevacizumab in combination with IFN versus IFN alone demonstrated that bevacizumab significantly improved PFS and showed a trend toward improvement in OS in patients with mRCC.[21, 22] In second-line setting after cytokine failure, sorafenib has demonstrated superior PFS over placebo with the median PFS of 5.5 months.[23]

1.1.2. Molecular Formula

Axitinib, a substituted indazole derivative, is an oral, potent, and selective inhibitor of VEGF receptors 1, 2, 3. The molecular formula is $C_{22}H_{18}N_4OS$ with molecular weight of 386.47. The chemical name is
N-Methyl-2-[3-((E)-2-pyridin-2-yl-vinyl)-1H-indazol-6-ylsulfanyl]-benzamide:

Figure 1 Molecular Formula



1.1.3. Phase 2 Clinical Trials of Single-Agent Axitinib in mRCC

Three Phase 2 studies have been conducted to explore the safety and efficacy of axitinib in mRCC patients.

1.1.3.1. Cytokine-Refractory mRCC Studies

The Phase 2 study (Protocol A4061012) enrolled 52 patients with mRCC who were refractory to cytokine treatment. Two complete responses (CRs) and 21 partial responders

(PRs) were observed, for an ORR of 44.2%. The median time to progression (TTP) was 15.7 months and the median OS was 29.9 months. [24]

Long-term survival data were collected via an observational study (Protocol A4061065). [25] Of the 52 patients, 35 died of progressive disease, 5 died of "unknown causes," 10 were alive, and 2 were lost to follow-up. Median follow-up for OS was 5.9 yrs. The 5-year survival rate was 20.6% (95% confidence interval [CI], 10.9–32.4%). Treatment-emergent, all-causality grade ≥3 adverse events for the 52 patients included diarrhea (19%), fatigue (19%), hypertension (17%), weight loss (8%), and dehydration, myocardial infarction, and stomatitis (6% each). Hypothyroidism (all grades) was observed in 23%. Comparing the characteristics of the 5-year survivors (n = 10) vs <5-year survivors (n = 40), the former had higher ORR (100% vs 30%), longer axitinib therapy duration (median 5.8 years vs 0.67 years), and better baseline PS (80% vs 53% with PS 0) but were of similar median age (57 vs 60), gender (80% vs 75% males), and risk factors (50% vs 40% with zero MSKCC factors).

Subsequently, the Phase 2 Study (Protocol A4061035) in Japanese patients with advanced RCC who were refractory to first line cytokine containing regimen was conducted. [26] 64 patients were enrolled in this study. Based on the results from IRC, confirmed partial response was observed in 32 patients, and ORR was 50.0%. In addition, median PFS was 11 months as of data cutoff date (February 26, 2010).

1.1.3.2. Sorafenib- and Sunitinib-Failure mRCC Study

The third Phase 2 study (Protocol A4061023) enrolled 62 patients with mRCC who were refractory to sorafenib treatment. In addition to prior sorafenib, most of the patients received prior sunitinib and (or) other drugs before enrollment in this study. The analysis of all 62 evaluable patients indicates 14 PRs (23%) and a median PFS of 7.4 months. The median PFS for the 14 patients who failed both sunitinib and sorafenib was 7.1 months.[27]

1.1.4. Comparative Effectiveness Phase III Study of Axitinib in second line mRCC

The primary objective of this pivotal Phase 3 (AXIS) study was to compare the PFS of patients with mRCC receiving axitinib vs another TKI, sorafenib, following failure of 1 prior systemic first-line regimen.[28] The secondary objectives were to compare the OS and ORR of patients in each arm, evaluate the safety and tolerability of axitinib, estimate the duration of response (DR) of patients in each arm, and compare the FACT-Advanced Kidney Cancer Symptom Index (FKSI) and EuroQoL-5D (EQ-5D).

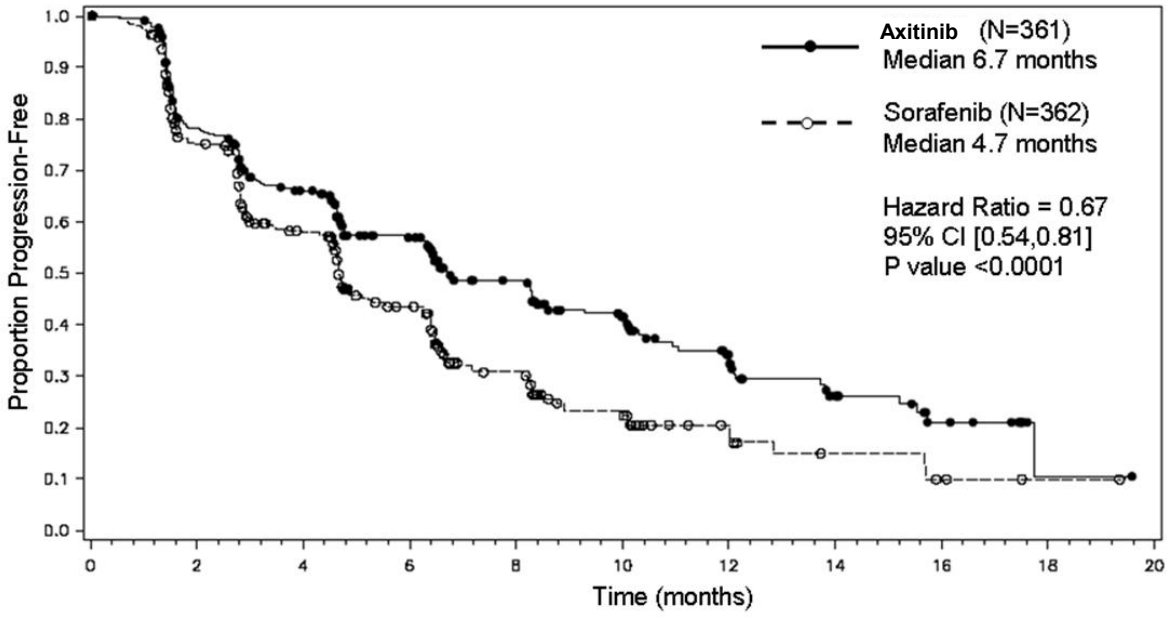
Between 15 September 2008 and 23 July 2010, a total of 723 patients with mRCC were randomized into this Phase 3 study, treated with either axitinib or sorafenib, and were followed for safety and efficacy. Enrolled patients were ≥18 years old, had histologically confirmed mRCC, had an ECOG PS of 0 or 1, and had failed 1 prior systemic, first-line regimen, which must have contained 1 or more of the following: sunitinib, bevacizumab + IFN-α, temsirolimus, or cytokine(s). Demographic and baseline characteristics were well balanced between both treatment arms.

The study enrolled 361 patients in the axitinib arm and 362 in the sorafenib arm. Based on the blinded IRC review of the overall analysis, the median PFS was 6.7 months (95% CI

[6.3, 8.6]) in the axitinib arm and 4.7 months (95% CI [4.6, 5.6]) in the sorafenib arm, with a hazard ratio of 0.665 (95% CI [0.544, 0.812]) and p-value of <0.0001 (1-sided).

In the subgroup of 251 patients who received prior treatment with cytokines (126 in the axitinib arm and 125 in the sorafenib arm), the median PFS in the axitinib arm was 12.1 months (95% CI [10.1, 13.9]) compared with 6.5 months (95% CI [6.3, 8.3]) in the sorafenib arm, with a hazard ratio of 0.464 (95% CI [0.318, 0.676]) and a p-value of <0.0001 (1-sided). The sorafenib control arm replicated prior Phase 3 sorafenib data (median PFS of 5.5 months) in a cytokine-refractory population. In the subgroup of 389 patients who had received prior treatment with sunitinib-containing regimen (194 in the axitinib arm and 195 in the sorafenib arm), the median PFS in the axitinib arm was 4.8 months (95% CI [4.5, 6.4]) compared with 3.4 months (95% CI [2.8, 4.7]) in the sorafenib arm, with a hazard ratio of 0.741 (95% CI [0.573, 0.958]) and a p-value of 0.0107 (1-sided). The study enrolled only 59 patients who received prior treatment with bevacizumab-containing regimen (29 in the axitinib arm and 30 in the sorafenib arm) and 24 patients who received prior treatment with temsirolimus-containing regimen (12 in the axitinib arm and 12 in the sorafenib arm). Due to small numbers of patients in these subgroups, no firm conclusions can be made.

Figure 2 Kaplan-Meier Curve for Progression-Free Survival by Independent Assessment for the Overall Population



Since only a total of 223 patients (approximately 30%) had died as of the data cutoff date (31 August 2010), the data for OS are not mature and likely to change with further followup. As of the data cutoff date, the median OS was not reached in the axitinib arm and was 18.9 months in the sorafenib arm, with a hazard ratio of 1.008 with a 95% CI of (0.774, 1.313) and a 1-sided p-value of 0.525. Further follow-up of OS is continuing.

Table 1 presents adverse reactions reported in patients who received axitinib or sorafenib:

Table 1 Adverse Reaction (Phase III study)

Adverse Reaction [a]	Axitinib N=359		Sorafenib N=355	
	All Grades [b]	Grade 3/4	All Grades [b]	Grade 3/4
	%	%	%	%
Diarrhea	55	11	53	7
Hypertension	40	16	29	11
Fatigue	39	11	32	5
Decreased appetite	34	5	29	4
Nausea	32	3	22	1
Dysphonia	31	0	14	0
Palmar-plantar erythrodysesthesia syndrome	27	5	51	16
Weight decreased	25	2	21	1
Vomiting	24	3	17	1
Asthenia	21	5	14	3
Constipation	20	1	20	1
Hypothyroidism	19	<1	8	0
Cough	15	1	17	1
Mucosal inflammation	15	1	12	1
Arthralgia	15	2	11	1
Stomatitis	15	1	12	<1
Dyspnea	15	3	12	3
Abdominal pain	14	2	11	1
Headache	14	1	11	0
Pain in extremity	13	1	14	1
Rash	13	<1	32	4
Proteinuria	11	3	7	2
Dysgeusia	11	0	8	0
Dry skin	10	0	11	0
Dyspepsia	10	0	2	0
Pruritus	7	0	12	0
Alopecia	4	0	32	0
Erythema	2	0	10	<1

[a] Percentages are treatment-emergent, all-causality events

[b] National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0

1.2. Rationale

The axitinib response rate in cytokine-refractory patients is higher than reported response rates with cytokines or chemotherapeutics in the second-line setting. Additionally, axitinib response rates in the second-line setting are better than response rates reported in the first-line setting with cytokines or chemotherapeutics alone or in combination. The 5-year survival rate was 20.6% (95% CI, 10.9–32.4%) in patients with mRCC who were refractory to cytokine treatment. Axitinib demonstrated a significantly longer PFS and higher ORR vs sorafenib with an acceptable safety profile as second-line therapy for mRCC. Axitinib was approved by US Food and Drug Administration (FDA) in January 2012 with an indication for the treatment of advanced RCC after failure of one prior systemic therapy. Axitinib was also approved in Japan, Korea and other countries in 2012 for the same indication. The efficacy and safety of axitinib in patients with mRCC support further clinical study to pursue clinical benefits of adjuvant axitinib treatment for patients at high risk of recurrent RCC after nephrectomy.

Risk stratification has become increasingly important in the management of patients newly diagnosed with RCC. Tumor stage is currently the principal prognostic factor for patients with RCC. Although various risk stratification systems have been described, none of them has been accepted as the standard of care. This study aims to recruit those patients who are at a potentially relatively increased risk of disease recurrence. Therefore, the target patients in this study are able to be considered patients at high risk of recurrent RCC.

According NCCN Guidelines v1.2014, adjuvant treatment after nephrectomy currently has no established role in patients with renal cell cancer who have undergone a complete resection of their tumor. No systemic therapy has yet been shown to reduce the likelihood of relapse. Randomized trials comparing adjuvant interferon alpha or high-dose interleukin (IL-2) or cytokines combinations with observation alone in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy. Observation remains standard care after nephrectomy, and eligible patients should be offered enrolled in randomized clinical trials.

Without an established adjuvant treatment for patients with high risk of recurrence of their renal cell cancer after nephrectomy and observation or participation in clinical study as recommended standard; several placebo-controlled, randomized, double blind studies are currently ongoing in this indication (http://clinicaltrials.gov), which is ethically justifiable and necessary to meet regulatory standards for drug approval.

2. TRIAL OBJECTIVES

2.1. Primary Objective

- To demonstrate an improvement in disease free survival (DFS) in patients at high risk of recurrent RCC randomly assigned to adjuvant axitinib (Arm A) vs. Placebo (Arm B) after nephrectomy.

2.2. Secondary Objectives

- Compare OS associated with Arm A to that associated with Arm B
- Assess safety/toxicity profile of administration of axitinib

3. TRIAL DESIGN

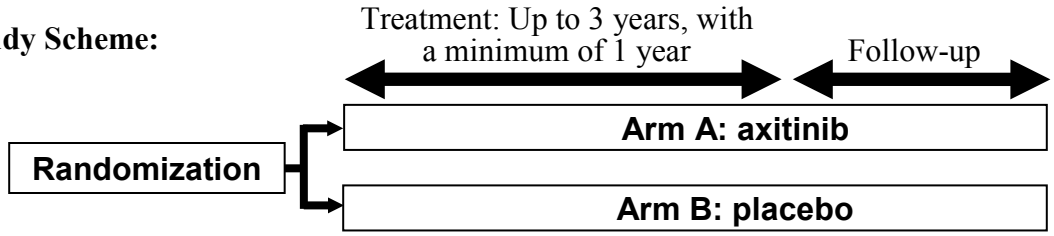
This is a prospective, randomized, double-blind placebo controlled Phase 3 trial of oral axitinib starting at 5 mg twice daily vs. placebo given for up to 3 years, with a minimum of 1 year. The dose may be increased or decreased depending on individual patient tolerance of axitinib.

A total of approximately 700 patients will be randomized in a 1:1 ratio between axitinib vs placebo. Patients should begin study treatment within 7 days after randomization. Randomization will occur no sooner than 4 weeks post-nephrectomy and no later than 12 weeks post-nephrectomy.

Follow-up for recurrence (distant or local recurrence of RCC) or occurrence of a secondary malignancy (occurrence of a second primary cancer other than RCC) must be collected at each clinic visit as per protocol. All patients will be followed up (regardless of the duration of treatment) until the time for the final analysis, every 16 weeks for the first 3 years from initiation of study treatment (also, at the end of treatment) and every 6 months thereafter for the remainder of the follow-up period, by clinic visit (See Section 6.4 for further details).

All patients will be followed up for OS status (regardless of the duration of treatment) every 16 weeks until the time for final DFS analysis. Survival status can be ascertained by telephone contact. At the time of final DFS analysis, OS results will be analyzed and summarized.

Study Scheme:



4. SUBJECT SELECTION

The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1. Inclusion Criteria

Patients must be newly-diagnosed RCC and treated by nephrectomy (complete or partial) and patients must meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Patients must have no evidence of macroscopic residual disease or metastatic disease.

2. Male or female, age ≥18 years (age ≥20 years in Japan, Korea and Taiwan, age ≥18 years and ≤ 65 years in India).

3. Patients must be diagnosed with one of the following based on American Joint Committee on Cancer (AJCC) TNM staging version 2010 [29], Eastern Collaborative Oncology Group (ECOG) performance status (PS). Any Fuhrman grades are eligible. The patient risk groups will be as follows. Group a will be closed for further enrollment, to keep the number of patients of groups b, c, and d with about 90% or more:

   ~~a. pT2, pN0 or pNx, M0 and ECOG PS 0-1~~

   b. pT3, pN0 or pNx, M0 and ECOG PS 0-1

   c. pT4, pN0 or pNx, M0 and ECOG PS 0-1

   d. Any pT, pN1, M0 and ECOG PS 0-1

4. Patients must have histologically confirmed preponderant, defined as >50%, clear cell RCC.

5. Patients must not have received any previous systemic (includes chemotherapeutic, hormonal, or immunotherapeutic) treatment for RCC.

6. Patients must not have received any previous anti-angiogenic treatment.

7. Patients must have adequate organ function defined as:
   - Absolute neutrophil count (ANC) ≥1500 cells/mm3.
   - Platelets ≥75,000 cells/mm3.
   - Hemoglobin (Hgb) ≥9.0 g/dL.
   - AST and ALT ≤2.5 x upper limit of normal (ULN).
   - Total bilirubin ≤1.5 x ULN.
   - Serum creatinine (Scr) ≤1.5 x ULN or calculated creatinine clearance (Clcr) ≥30 mL/min (by the Cockcroft-Gault equation*).
     * For males; the Cockcroft-Gault equation, using Scr : Clcr (mL/min) = (140 - Age in years) × weight (in kilograms) / [72 × Scr (in mg/dL)]
     The calculated Clcr should be multiplied by 0.85 to adjust for female gender.
   - Urinary protein <2+ by urine dipstick. If dipstick is ≥2+ then a urine protein: urine creatinine ratio (UPC) should be done and the patient may enter only if UPC is < 2.0.

8. At screening, no evidence of preexisting uncontrolled hypertension as documented by 2 blood pressure (BP) readings taken at least 1 hour apart in the seated position after the patient has been sitting quietly for 5 minutes. The systolic blood pressure (sBP) readings must be ≤140 mm Hg, and the diastolic blood pressure (dBP) readings must be ≤90 mm Hg. Patients whose hypertension is controlled by antihypertensive therapies are eligible.

9. Women of childbearing potential and men must use adequate contraception during the study and for 6 months after discontinuing or completing study treatment. Acceptable contraception for women include implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence, or a partner who has been vasectomized for at least 6 months. Acceptable contraception for a male includes having had a vasectomy for at least 6 months, sexual abstinence, or condoms plus spermicide.

10. Signed and dated informed consent document (ICD) indicating that the patient (or legally acceptable representative) has been informed of all pertinent aspects of the trial prior to enrollment.

11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

Patients presenting with any of the following will not be included in the trial:

1. Histologically undifferentiated carcinomas, sarcomas, collecting duct carcinoma, lymphoma, or patients with any metastatic renal sites.

2. Active bleeding (other than menstrual bleeding) at randomization.

3. Diagnosis of any non-RCC malignancy within the 5 years from date of randomization, except basal cell carcinoma, squamous cell skin cancer, or in situ carcinoma of the cervix uteri that has been adequately treated with no evidence of recurrent disease for 12 months.

4. 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.

5. Gastrointestinal abnormalities including:
   - inability to take oral medication
   - requirement for intravenous alimentation
   - prior surgical procedures affecting absorption including total gastric resection
   - treatment for active peptic ulcer disease in the past 6 months

- active gastrointestinal bleeding, unrelated to cancer, as evidenced by hematemesis, hematochezia or melena in the past 3 months without evidence of resolution documented by endoscopy or colonoscopy
- malabsorption syndromes
- chronic diarrhea that persists at Grade 3 or 4 despite maximal medical therapy

6. Major surgery <4 weeks, or radiation theapy <2 weeks, of starting the study treatment or incomplete healing of surgical or superficial wounds.

7. Current use or anticipated need for treatment with drugs that are known potent CYP3A4/5 inhibitors (eg, grapefruit juice, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin).

8. Current use or anticipated need for treatment with drugs that are known CYP3A4/5 or CYP1A2 inducers (eg, rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort).

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

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

11. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness.

12. Pregnancy or breastfeeding. Urinary pregnancy test should be performed by sites on female patients who have not experienced at least one consecutive year of amenorrhea without ovarian dysfunction, or have been taking hormonal therapy, or have been rendered surgically sterile. If positive, serum pregnancy test should be performed at central laboratories. All female patients of childbearing potential must have a negative pregnancy test within the 14 days prior to date of randomization. (Definition of surgical sterilization: patients who underwent hysterectomy or bilateral oophorectomy, or bilateral tubal ligation)

13. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent and compliance with the requirements of this protocol.

14. 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 patient inappropriate for entry into this study.

15. Receipt of any investigational oncology or, approved or investigational anti-angiogenic agent prior to study entry.

16. Current treatment on another therapeutic clinical trial. Supportive care trials or non-treatment trials, eg, Patient Reported Outcomes (PRO) methods studies, are allowed.

4.3. Randomization Criteria

Patients must be randomized no earlier than 4 weeks and no later than 12 weeks after nephrectomy and treatment should be started within 7 days after randomization. Patient eligibility must be confirmed by independent review committee (IRC) assessment of imaging by a sponsor designated center prior to randomization.

Patients must be randomized based on the assessment by the IRC when there is a discrepancy between the local and the IRC imaging review.

A centralized system will be used to assign patient numbers and randomize patients into blinded study drug: axitinib, or blinded placebo identical in appearance to the active study drug.

After a patient has provided written informed consent and has completed the necessary screening assessments, the clinical site must contact a centralized internet/telephone registration system (IWRS/IVRS), to enroll the patient into study.

For those patients who failed screening, the reason for screen failure should be entered in the source documentation. The following information should also be collected in the source documents: Patient age, sex, ECOG PS, tumor size (eg, T1, T2, T3), nodal disease (Yes/No), metastatic disease (Yes/No), histological type (eg, clear cell).

At the time of registration, the clinical site staff must provide site and patient identifiers and demographic information. The registration system will assign a unique patient identification number. The system will also be used to assign blinded study drug bottles. Patients will be randomized to one of two arms:

Arm A: axitinib 5 mg BID taken orally (doses should be taken approximately 12 hours apart continuous dosing)

Arm B: Placebo tablets BID taken orally

Patients will be stratified by:

1. Risk group
    a. pT2, pN0 or pNx, M0 and ECOG PS 0-1
    b. pT3, pN0 or pNx, M0 and ECOG PS 0-1
    c. pT4, pN0 or pNx, M0 and ECOG PS 0-1
    d. Any pT, pN1, M0 and ECOG PS 0-1
2. Country

Eligible patients will be randomized in a 1:1 ratio to one of the two treatments using the registration system. Patients in risk group a or b will be stratified by risk group and by country. Patients in risk group c or d will be stratified by risk group only.

Randomization shall continue until a minimum of 10% of subjects are represented in this study from groups c and d. Risk group a will be closed for from further enrollment, to keep the number of patients of risk groups b, c, and d with about 90% or more.

4.4. Life Style Guidelines

During the study female patients of childbearing potential must take precautions to prevent pregnancy since the effects on the fetus are unknown. Male patients with partners of childbearing potential must take precautions to prevent pregnancy of the partner since the effects of these drugs on sperm are unknown. These restrictions should remain in force for 6 months from the last dose of investigational agent. Drug interaction studies with oral contraceptives have not been performed, so barrier methods of contraception or abstinence should be considered. Adequate contraception should be discussed with the investigator before the treatment start and should be in agreement with local law.

5. TRIAL TREATMENTS

5.1. Allocation to Treatment

Axitinib for up to 3 years, with a minimum of 1 year until recurrence, occurrence of a secondary malignancy, significant toxicity, or withdrawal of consent.

OR

Placebo for up to 3 years, with a minimum of 1 year until recurrence, occurrence of a secondary malignancy, significant toxicity, or withdrawal of consent.

5.2. Breaking the Blind

At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be an electronic process. Blinding codes should only be broken in emergency situations for reasons of patient safety, or if the patient has a confirmed recurrence or occurrence of a secondary malignancy with limited alternative treatment option and knowledge of study drug is required to facilitate further treatment decision. For those with suspected recurrence, the site must await results from the Independent Review Committee (IRC). The decision to break the blind must be approved by the Sponsor prior to doing so. When the blinding code is broken, the reason must be fully documented in the site source document.

5.3. Drug Supplies

In this clinical trial, study drug or investigational agent refers to axitinib and placebo.

5.3.1. Formulation and Packaging

Axitinib will be supplied as 1 mg and 5 mg film-coated tablets for oral administration in light-protecting bottles. Placebo will match all dose formulations.

5.3.2. Preparation and Dispensing

Axitinib and matching placebo will be dispensed as tablets in opaque plastic bottles to protect the compounds from light. Axitinib is a hazardous drug (due to possible reproductive toxicity), and should be handled according to the recommended procedures described in the current edition of the American Society of Hospital Pharmacists (ASHP), Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, American Hospital Formulary Service (AHFS) Drug Information (1999) and its references. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

5.3.3. Administration

Patients will receive blinded study drug: Axitinib or blinded matching placebo identical in appearance to the active study drug twice daily.

Patients will receive a starting dose of 5 mg of axitinib or placebo twice daily taken orally with or without food. Dose adjustments, including dose increase or dose reduction will be based on adverse events experienced by the individual patient. Study drug will be taken beginning on Day 1 of the study. Doses should be taken approximately 12 hours apart continuous dosing. Patients should be instructed to take their doses at approximately the same times each day. If a patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Missed or vomited doses must be indicated in the source documents and Case Report Forms (CRFs). Study drug will be administered in cycles of 4 weeks in duration.

Patients who tolerate axitinib or placebo with no adverse events related to study drug above CTCAE Grade 2 for a consecutive 2-week period may have their dose increased by one dose level to maximum of 10 mg BID (unless the patient's BP is >150/90 mm Hg or the patient is receiving antihypertensive medication). The clinical judgment of the treating investigator should be exercised in titrating axitinib/placebo dose.

Patients experiencing drug reaction should undergo dose modification as recommended in Section 5.3.4.

Once the dosage is reduced, it can be uptitrated again.

Concomitant medications that are known to substantially inhibit the enzyme, CYP3A4/5, should be avoided as much as medically possible on this study as in Section 5.5.1. If a strong CYP3A4/5 inhibitor must be co-administered, based on investigator judgment, the dose of study drug (axitinib/placebo) should be decreased by one or more dose levels.

Table 2 Available Axitinib/Placebo Dose Levels

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 (twice daily)**
-1	3 mg BID	3 X 1 mg Tablets BID
-2	2 mg BID	2 X 1 mg Tablets BID
-3	1 mg BID	1 X 1 mg Tablet BID

5.3.4. Dose Interruption and Reduction

Adverse events and other symptoms will be graded according to the current CTCAE v4.0 (See URL: http://ctep.cancer.gov/reporting/ctc.html).

5.3.4.1. Management of Axitinib/Placebo-Related Adverse Events

This section contains management of adverse events except hypertension and proteinuria which are discussed in subsequent sections.

The criterion for dose modification for study-drug-related adverse events is summarized in the table below:

Table 3 Criteria for Dose Modification for Axitinib/Placebo – Related Adverse Events Other Than Hypertension Or Proteinuria

Related Adverse Events	**Intervention**
Grade 1	Continue at same dose level.
Grade 2*	Continue at same dose level or decreased dose to one lower dose level.[a)]
Grade 3*	Interrupt dosing; re start at one or two lower dose level as soon as improvement to CTCAE Grade ≤1 or baseline.[b)] Discontinue dosing in case of grade 3 persisting for ≥ 2 weeks or grade 3 despite dose reduction to 1 mg BID.
Grade 4 or RPLS**	Discontinue dosing

* Patients who have a grade 3 arterial event, grade 3 hemorrhagic event, grade 3 perforation/fistula, grade 3 palmar-planter erythrodysesthesia syndrome (PPE), or persistent grade 2 PPE despite dose reduction to 1 mg BID, should be discontinued dosing.

** Treatment interruption for patients with signs/symptoms of reversible posterior leukoencephalopathy (RPLS). RPLS is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances. Mild to severe hypertension may be present. Magnetic resonance imaging is necessary to confirm the diagnosis of RPLS. In case of confirmed diagnosis discontinue permanently.

a) Dose may be decreased to one lower dose level if the investigator considers it is difficult to continue treatment at same dose level.

b) Dose may be decreased to two lower dose level if the investigator considers it is difficult to continue treatment at one lower dose level.

Dose may also be interrupted or decreased at the discretion of the investigator even if none of the above criteria applies.

Guidelines for dose reductions for specific adverse events are provided in the following sections.

5.3.4.2. Axitinib/Placebo Dose Reduction for Hypertension

Patients treated with axitinib/placebo will be issued blood pressure cuffs (provided by Sponsor) for home monitoring and instructed to measure their blood pressure prior to taking each dose of study drug (twice daily) for the first 3 months, and once a week thereafter. Following dose modification of study drug or anti-hypertensive medication, or changes of anti-hypertensive medication, patients must restart blood pressure measurements prior to taking each dose of study drug for the first 3 months and once a week thereafter. All BP measurements will be recorded in a diary by the patient themselves and brought to the nurse or study coordinator at each clinic visit. Patients should be instructed by the study staff to contact their investigator immediately for guidance if their sBP rises above 150 mm Hg, or dBP rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance). See below for dose modifications for hypertension.

New or additional antihypertensive therapy (See Section 5.5.1, Concomitant Medication) should be started if 2 BP readings, taken at site and separated by at least 5 minutes in the seated position after the patient has been sitting quietly for 5 minutes, show the following: 2 sBP readings >150 mm Hg or 2 dBP readings >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/placebo dose should be reduced by 1 dose level.

Patients who have 2 sBP readings, separated by at least 5 minutes, greater than 160 mm Hg, or 2 dBP readings, separated by at least 5 minutes in the seated position after the patient has been sitting quietly for 5 minutes, greater than 105 mm Hg, will have treatment with axitinib/placebo interrupted. (Note: if axitinib/placebo is interrupted, patients receiving antihypertensive medications should monitor closely for hypotension and restart axitinib/placebo at one lower dose level as soon as BP is ≤150/100 mm Hg. Plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dose interruption.) Treatment with axitinib/placebo should be restarted at 1 lower dose level as soon as the sBP reduces to less than or equal to 150 mm Hg and the dBP reduces to less than or equal to 100 mm Hg.

Patients who develop recurrent systolic hypertension (2 BP readings separated by at least 5 minutes show sBP >150 mm Hg) or recurrent dBP >100 mm Hg following previous axitinib/placebo dose reduction should undergo another dose reduction by one dose level.

Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments until recurrence or occurrence of a secondary malignancy or start of new treatment, and for survival thereafter. Guidance on dose interruption and reduction for

hypertension is summarized in the table below. The BP readings stated in this table is based on BP measurement taken at the site.

Table 4 Hypertension Management Plan for Axitinib/Placebo

Degree of Blood Pressure Elevation			Management
Systolic Blood Pressure		Diastolic Blood Pressure	
2 BP readings separated by at least 5 minutes show sBP >150 mm Hg	OR	2 BP readings separated by at least 5 minutes show dBP >100 mm Hg	If not on maximal antihypertensive treatment, institute new or additional antihypertensive medication* and maintain dose of axitinib/placebo. If on maximal antihypertensive treatment, reduce axitinib/placebo to one lower dose level.
2 BP readings separated by at least 5 minutes show sBP >160 mm Hg	OR	2 BP readings separated by at least 5 minutes show dBP >105 mm Hg	Interrupt dosing**; Adjust antihypertensive medication; As soon as BP is less than or equal to 150/100 mm Hg, restart axitinib/placebo at one lower dose level.
Recurrent hypertension following previous dose reduction (2 BP readings separated by at least 5 minutes show sBP >150 mm Hg)	OR	Recurrent dBP >100 mm Hg (2 BP readings separated by at least 5 minutes) following previous dose reduction	Repeat axitinib/placebo dose reduction by one lower dose level.

* If no contraindication – consider preferred anti-hypertensive monotherapy: Angiotensin system inhibitors (ASI) or preferred combination anti-hypertensive therapy: Diuretic and angiotensin system inhibitor [please check local guidelines]
Based on current international guidelines: ASI- Angiotensin Converting Enzyme (ACE) Inhibitor or Angiotensin receptor blocker; Diuretics; Beta-blocker or Calcium antagonists: All suitable and recommended for initiation + maintenance of antihypertensive treatment as monotherapy or in some combinations. Additional aspects for consideration within this study:
- No drug-drug interaction between axitinib and ASI expected (e.g. enalapril, captopril, losartan, valsartan). Retrospective data [McKay et al.J Clin Oncol 32, 2014 (suppl 4; abstr 437)] indicate that ASI may improve outcome in patients with renal cell cancer.
- No interference between axitinib and beta blockers (atenolol, metoprolol, labetalol), or diuretics (hydrochlorothiazide, furosemide) expected.
- Not first choice based on potential interference with axitinib plasma level: calcium channel blockers (verapamil) and to a lesser extent nifedipine, nicardipine, and diltiazem.
- Other calcium channel blockers (amlodipine, bepridil, felodipine) are less likely to interfere with axitinib plasma levels.
** If axitinib/placebo is interrupted, patients receiving antihypertensive medications should be monitored closely for hypotension. Plasma half-life of axitinib is 2-4 hours and BP usually decreases within 1-2 days following dose interruption.

5.3.4.3. Axitinib/Placebo Dose Reduction for Proteinuria

- If dipstick shows ≥2+ proteinuria, perform UPC. Dosing may continue while waiting for test results.

- If UPC < 2.0 is reported, continue dosing at the same dose level.

- If UPC ≥ 2.0 is reported, hold dosing and repeat UPC (interval at investigator discretion) until UPC is < 2.0. Restart axitinib/placebo at the same dose or one lower dose level at discretion of the investigator. Repeated UPC can be performed during treatment interruption at the site laboratory.

- If UPC ≥ 2 despite dose reduction to 1 mg BID, discontinue dosing.

Patients removed from treatment for intolerable toxicity should still be followed with regular tumor assessments until recurrence or occurrence of a secondary malignancy or start of new treatment, and for survival thereafter.

5.3.4.4. Axitinib/Placebo Dose Interruption for Surgery or Surgical Procedures

If a major surgery or an invasive intervention (eg, endoscopy) is required, treatment with axitinib/placebo must be interrupted at least 24 hours before the procedure and the patient BP should be monitored closely for hypotension. Depending on the investigators assessment patients may resume axitinib/placebo 7 days after surgery/invasive intervention, assuming wound has completely healed and no wound healing complications (eg, delayed healing, wound infection or fistula).

5.3.5. Compliance

Patients will maintain diaries to include missed or changed doses. Pill counts on returned study drug bottles should be performed.

5.4. Drug Storage and Drug Accountability

Axitinib/placebo will be supplied for the study. Study drug will be shipped to the study sites.

The investigator, or an approved representative (eg, pharmacist), will ensure that all axitinib/placebo is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Drug should be stored at controlled room temperature (ie, 15-30°C) and protected from light and moisture.

To ensure adequate records, all axitinib/placebo will be accounted for in the CRFs and drug accountability inventory forms as instructed by sponsor. Unless otherwise authorized by sponsor, at the end of the clinical trial all drug supplies unallocated or unused by the patients must be returned to sponsor or its appointed agent (eg, a contract research organization).

Axitinib is considered a hazardous drug (due to possible reproductive toxicity), and should be handled according to the recommended procedures described in the current edition of the ASHP, Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, AHFS Drug Information (1999) and its references. Procedures described in each institution's pharmacy or hospital standard operating procedure manual should be followed when handling hazardous drugs.

5.5. Prior/Concomitant Therapy

5.5.1. Prior/Concomitant Medication

No other chemotherapy or experimental anticancer medications will be permitted while the patient is on study. Any disease requiring other forms of systemic anticancer therapy will be cause for discontinuation from study treatment.

Patients may receive loperamide or other medications for treatment or prophylaxis of potential diarrhea. Anti-inflammatory or narcotic analgesics may be offered as needed. Patients with fever or infection may undergo diagnostic tests and treated with antibiotics as appropriate and may receive therapeutic colony-stimulating factors as appropriate. Erythropoietic agents such as epoetin or darbepoetin may be used at the discretion of the treating investigator. Packed red blood cell and platelet transfusions should be administered as clinically indicated. Low-dose oral steroids (defined as $\leq$5 mg per day prednisone or equivalent), short course of oral steroids (defined as < 5 consecutive days or topical or inhaled steroids at any dose) may be taken during the study.

Patients who need to be on anticoagulant therapy before or during study treatment should be treated with low molecular weight heparin. If low dose heparin cannot be administered, the administration of coumadin or other coumarin derivatives or other anti-coagulants may be allowed; however, appropriate monitoring for bleeding risk including prothrombin time/international normalized ratio (PT/INR) should be performed.

In vitro studies with human liver microenzymes and recombinant CYP enzymes indicated that axitinib metabolism was primarily mediated by the drug-metabolizing enzyme CYP3A4/5, and to a lesser extent by CYP1A2. Additionally, the drug also undergoes N-glucuronidation in liver microsomes of some species. Clinically, there is likelihood that axitinib plasma concentrations may be increased in the presence of co-administered potent inhibitors of the CYP3A4/5 and glucuronosyltransferase enzymes. In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2-fold increase in plasma exposure and a 1.5-fold increase in peak plasma concentration of axitinib. Therefore a potential exists for drug-drug interactions with CYP3A4/5 inhibitors such as grapefruit juice, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin. Caution should be exercised in patients receiving axitinib in combination with these and other potent CYP3A4/5 inhibitors until appropriate clinical drug interaction studies are performed. If a strong CYP3A4/5 inhibitor must be co-administered, based on investigator judgment, the dose of study drug (axitinib/placebo) should be decreased by one or more dose levels.

Axitinib metabolism may be induced in patients taking CYP3A4/5 or CYP1A2 inducers (rifampin, dexamethasone, phenytoin, carbamazepine, rifabutin, rifapentin, phenobarbital, and St. John's wort) and this may reduce axitinib plasma concentrations. Patients who require concomitant treatment with potent CYP3A4/5 or CYP1A2 inducers are not eligible for the study. Since CYP1A2 is also known to be induced in chronic smokers, there is likelihood that axitinib plasma concentrations may be reduced in these individuals. (Note: these patients are not excluded from enrolment, however.)

The ability of axitinib to increase concentrations of coadministered drugs was also investigated in studies with human liver microsomes. At expected therapeutic plasma concentrations (0.01 to 1.0 μg/mL), axitinib appears most likely to inhibit the drug metabolizing enzymes CYP1A2 and CYP2C8, 2 enzymes not frequently observed as predominant drug metabolizing enzymes. Theophylline, and tacrine are among the few drugs whose plasma concentrations are likely to be increased by axitinib.

Axitinib is highly bound to proteins in human plasma (99.5% bound at concentrations between 0.2 to 20 μg/mL). Therefore, drug interactions with other agents that are also highly bound to plasma proteins are a possibility.

Axitinib is not likely to have drug-drug interactions with commonly used antihypertensive agents belonging to the class of ACE inhibitors including angiotensin II receptor antagonists (enalapril, captopril, losartan, valsartan), beta-blockers (atenolol, metoprolol, labetalol), or diuretics (hydrochlorothiazide, furosemide). Within the class of calcium channel blockers, verapamil, and to a lesser extent nifedipine, nicardipine, and diltiazem have a potential for increasing axitinib plasma concentrations, due to CYP3A4/5 inhibition and should not be used as first choice in antihypertensive treatment. Other calcium channel blockers (amlodipine, bepridil, felodipine) are less likely to raise axitinib plasma levels.

The above information is based on preclinical data from studies using human and animal metabolizing enzyme systems.

All prior/concomitant medications and blood products, as well as interventions (eg, analgesic use or paracentesis) received by patients from the time the patient has signed informed consent until 28 days after last treatment will be recorded on the CRF. Anti-tumor therapy should be recorded even after 28 days after last treatment.

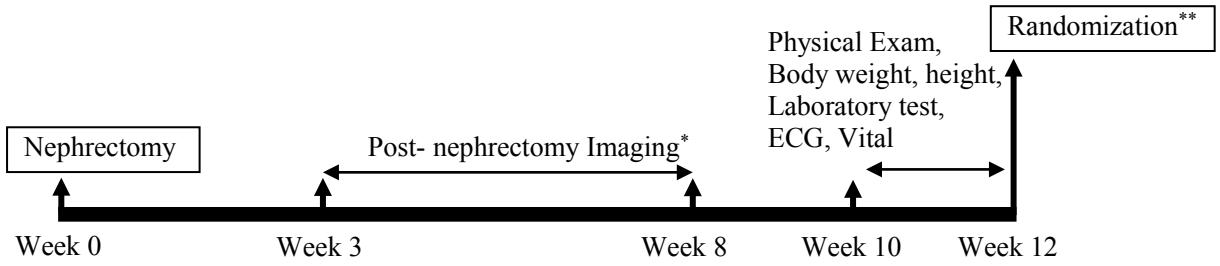
5.5.2. Concomitant Radiotherapy

Investigators are encouraged to await the result of the IRC assessment before making treatment decisions for patients who require palliative radiotherapy because of suspected recurrence or occurrence of a secondary malignancy unless clinical considerations require immediate intervention eg, in the case of brain metastases. In the event that an investigator determines recurrence or occurrence of a secondary malignancy based on local imaging and/or local histo-/cytopathology reports, the patient must continue to receive tumor assessments until the IRC determines recurrence or occurrence of a secondary malignancy.

6. TRIAL PROCEDURES

6.1. Screening

Figure 3 Screening Procedures



*: IRC review of imaging to be returned within 2 weeks post submission of images.
**: Randomization will occur no sooner than 4 weeks post-nephrectomy and no later than 12 weeks post-nephrectomy. This figure shows the latest case after nephrectomy. Study treatment should be started within 7 days after randomization.

6.1.1. Screening Procedures between Nephrectomy and Starting Treatment

One rescreening is acceptable. Patient with screening values/findings outside ranges described in the protocol may, at the discretion of the investigator, have one repeat determination performed and if the repeat value satisfies the criterion they may continue in the screening process. Only the specific out of range value/finding should be repeated (not the entire panel).

a. Medical history including oncologic history, history of other disease processes (active or resolved), signs and symptoms, concomitant medications and treatments, illnesses and demographics.

b. Local histopathology confirmation of eligibility is required.

c. Pre-surgery images are requested, if available or whenever possible should be submitted for IRC review.

d. ECOG PS ascertained at the time of nephrectomy (just prior to nephrectomy) is desired.

e. Local and IRC review of tumor imaging including CT or MRI of the brain, chest, abdomen and pelvis and other applicable sites of disease. CT scans are expected to be with intravenous and/or oral contrast. CT or MRI of the chest, abdomen and pelvis must be performed at least 3 weeks after nephrectomy. Results of the IRC assessment must be awaited before randomizing patients. Thus, images should be submitted for IRC review before Week 8 post-nephrectomy to allow for return of the results before Week 12 and in the event a repeat scan is needed. Brain CT or MRI within 12 weeks prior to randomization is acceptable regardless of whether it is before or after nephrectomy. Bone scan (either Tc-99 or positron emission tomography (FDG-PET)) can be performed if clinically indicated.

6.1.2. Screening Procedures Within 2 Weeks Prior to Randomization

a. Physical examination of major body systems.

b. Body weight, height and vital signs (temperature, 2 BP readings separated by at least 1 hour, pulse rate).

c. Laboratory tests.

- Hematology: Hgb, white blood cell count (WBC), ANC, lymphocyte count and platelet count.
- Chemistry: Total bilirubin, AST, ALT, alkaline phosphatase, albumin, total protein, LDH, sodium, potassium, chloride, calcium, phosphate, BUN/Urea, creatinine, glucose.
- Urine dipstick for protein (patients with ≥2+ protein will have UPC).
- Pregnancy test, if applicable. Urine pregnancy test will be conducted at sites for females of childbearing potential only. If positive, then serum test should be conducted at central laboratories.

d. Triplicate 12 lead ECGs to be performed two weeks prior to randomization. Three consecutive 12 lead ECGs (with a 10 second rhythm strip) will be collected at screening to determine the mean QTc interval. If the QTc interval is prolonged (>500msec), the ECG should be re-read by a cardiologist at the site for confirmation.

e. Assessment of concomitant medications and treatments.

f. Study Registration/Randomization.

6.2. Trial Period

For the purposes of this study, unscheduled assessments may occur coincident with safety events, early discontinuation of study treatment, early study termination, suspected recurrence, or suspected occurrence of the secondary malignancy between protocol-specified study visits.

6.2.1. Treatment Procedures First Cycle

6.2.1.1. Day 1

The following procedures must be performed pre-dose. It is not necessary to repeat the Day 1 procedures if treatment is not started on the same day as randomization:

a. Physical Examination of major body systems.

b. Body weight and vital signs (temperature, BP, pulse rate). Patients who have 2 sBP readings, separated by at least 5 minutes, greater than 140 mm Hg, or 2 dBP readings, separated by at least 5 minutes, greater than 90 mm Hg, will not start treatment.

c. ECOG PS.

d. Thyroid function tests: TSH, free T_3, free T_4.

e. Assessment of adverse events.

f. Assessment of concomitant medications and treatments.

6.2.1.2. Day 15

Assessments should be performed via telephone contact or visit. In case of telephone contact, only adverse events assessment should be performed.

a. Physical Examination of major body systems.

b. Body weight and vital signs (temperature, 2 BP readings separated by at least 5 minutes, pulse rate).

c. Thyroid function tests: TSH (Free T_3 and free T_4 should be performed for any patient who has an elevated TSH at Day1 or the previous visit.) Hypothyroidism should be treated per standard medical practice to maintain euthyroid state with a normal TSH.

d. Assessment of adverse events.

e. Assessment of concomitant medications and treatments.

6.2.2. Treatment Procedures Subsequent Cycles

Assessments other than tumor imaging should be done at Day 1 of every cycle (4 weeks) until Cycle 5 Day 1, then every 8 weeks thereafter starting from Cycle 7 Day 1.

a. Physical examination of major body systems.

b. Body weight and vital signs (temperature, 2 BP readings separated by at least 5 minutes, pulse rate).

c. ECOG PS.

d. Laboratory tests.

- Hematology: Hgb, WBC, ANC, lymphocyte count and platelet count.
- Chemistry: Total bilirubin, AST, ALT, alkaline phosphatase, albumin, total protein, LDH, sodium, potassium, chloride, calcium, phosphate, BUN/Urea, creatinine, glucose.
- Urine Dipstick for protein (patients with ≥2+ protein will have UPC).
- Thyroid function tests: TSH. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state with a normal TSH (TSH, Free T_3

and free T_4 should be performed on the next visit for any patient who has an elevated TSH.).

e. Tumor imaging including CT or MRI of the chest, abdomen, and pelvis should be performed every 16 weeks for the first 3 years from the initiation of study treatment. Additional imaging and/or local histo-/cytopathology confirmation, if clinically indicated, of potential disease sites should be performed whenever recurrence or occurrence of a secondary malignancy is suspected. Brain CT or MRI with contrast or bone scan (confirmatory imaging in addition to bone scan may be required), if clinically indicated.

f. Assessment of concomitant medications and treatments.

g. Assessment of study drug compliance/accountability.

h. Assessment of adverse events and tumor-related signs and symptoms.

6.2.3. End of Study Treatment/Withdrawal from treatment Procedures

At the end of the study or at withdrawal from treatment, the following procedures should be performed if they were not performed within 7 days of the end of the study or at withdrawal:

a. Physical examination of major body systems.

b. Body weight and vital signs (temperature, 2 BP readings separated by at least 5 minutes, pulse rate).

c. ECOG PS.

d. Laboratory tests.

- Hematology: Hgb, WBC, ANC, lymphocyte count and platelet count.
- Chemistry: Total bilirubin, AST, ALT, alkaline phosphatase, albumin, total protein, LDH, sodium, potassium, chloride, calcium, phosphate, BUN/Urea, creatinine, glucose.
- Urine Dipstick for protein (patients with ≥2+ protein will have UPC).
- Thyroid function tests: TSH (Free T_3 and free T_4 should be performed for any patient who has an elevated TSH in the previous visit.)

e. Tumor imaging including CT or MRI of the chest, abdomen, and pelvis and other applicable sites of disease. Local histo-/cytopathology confirmation, if clinically indicated, of potential disease sites should be performed whenever recurrence or occurrence of a secondary malignancy is suspected. Brain CT or MRI with contrast or bone scan if clinically indicated. At the end of the study or at withdrawal, the tumor imaging should be performed if they were not performed within 8 weeks of the

end of the study or at withdrawal for patients who discontinue treatment for reasons other than disease progression.

f. Assessment of concomitant medications and treatments.

g. Assessment of study drug compliance/accountability. Patients must return all used and unused study drug bottles to the clinical site.

h. Assessment of adverse events and tumor-related signs and symptoms.

6.3. 28 Days Post Treatment Follow-Up Visit

Patients should continue to be evaluated up to 28 days after the last dose of study drug. At the post-treatment follow-up visit, the following procedures should be performed:

- Assessment of adverse events and tumor-related signs and symptoms.
- Assessment of concomitant medications and treatments.

During this period, the outcome of adverse events with a date of onset during the study period should be reevaluated, and any new adverse events should be recorded. All serious adverse events, and those non-serious adverse events assessed by the investigator as possibly related to study drug, should continue to be followed even after patient withdrawal from study. These adverse events should be followed until they resolve, or until the investigator assesses them to be “chronic” or “stable”.

6.4. Recurrence or occurrence of secondary malignancy and Survival Follow-Up

Follow-up for recurrence or occurrence of a secondary malignancy must be collected at each clinic visit as per protocol. All patients will be followed up (regardless of the duration of treatment) until the time for final analysis, every 16 weeks for the first 3 years from initiation of study treatment (also, at the end of treatment) and every 6 months thereafter for the remainder of follow-up period*. If new anti tumor therapy is initiated for either recurrence or occurrence of a secondary malignancy at any time during this period, this and all other pertinent data obtained should be recorded on the appropriate CRFs. The final analysis of primary endpoint (DFS) will be performed when approximately 245 DFS events have been reached.

* Patients who complete 3-year treatment will be followed up for DFS every 6 months from the date of CT or MRI at the end of study treatment.
Patients who withdraw from treatment before DFS events will be followed up for DFS every 16 weeks from the date of CT or MRI at the withdrawal. After 3 years from initiation of study treatment, CT or MRI for DFS will be performed every 6 months from the first scan date that is performed after more than 3 years from initiation of study treatment.

All patients will be followed up for OS status (regardless of the duration of treatment) approximately every 16 weeks from DFS events until the time for final DFS analysis. Survival status can be ascertained by telephone contact.

6.5. Patient Withdrawal

Patients may withdraw from the treatment/trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a patient does not return for a scheduled visit, every effort should be made to contact the patient. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the patient return all unused investigational product(s), request that the patient returns for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events.

6.5.1. Withdrawal from treatment

Patients will be withdrawn from treatment in the case of:

- Recurrence or occurrence of a secondary malignancy. Investigators are encouraged to await the result of the IRC assessment before making treatment decisions unless clinical considerations require immediate intervention eg, in the case of brain metastases;
- Unacceptable toxicity;
- Need for anticancer therapy not specified in the protocol;
- Congestive heart failure;
- Repeated noncompliance;
- Patient becomes pregnant;
- Patient lost to follow-up;
- Patient choice to withdraw from treatment (follow-up permitted by patient)

If patients require >2 consecutive weeks of dose interruption, a discussion should be made in consultation with the medical monitor.

Data to be collected for the end of study treatment/withdrawal from treatment are described in the End of Study Treatment/Withdrawal from treatment Procedures section (Section 6.2.3). Patients will be followed up for at least 28 days after the last dose of study drug for adverse events and concomitant medications and treatments.

6.5.2. Withdrawal from trial

If the patient withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. Sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

7.1. Efficacy Assessments

Local and the IRC imaging tumor assessments are to be performed between week 3-8 post-nephrectomy. Brain CT or MRI within 12 weeks prior to randomization is acceptable regardless of whether it is before or after nephrectomy.

During the trial, local and the IRC imaging tumor assessments will be performed (regardless of the duration of treatment) every 16 weeks during the first 3 years of study (also, at the end of treatment) and every 6 months thereafter until the time for final analysis, or recurrence or occurrence of a secondary malignancy, whichever comes first.

Investigators are encouraged to await the result of the IRC assessment before making treatment decisions for patients who require palliative radiotherapy because of suspected recurrence or occurrence of a secondary malignancy unless clinical considerations require immediate intervention eg, in the case of brain metastases. In the event that an investigator determines recurrence or occurrence of a secondary malignancy based on local imaging reviews and/or local histo-/cytopathology reports, the patient must continue to receive tumor assessments until the IRC determines recurrence or occurrence of a secondary malignancy.

Local and IRC imaging assessments at screening and during the trial will include CT or MRI of the brain, chest, abdomen and pelvis, and other applicable sites. Further imaging techniques e.g., bone scan, are to be performed as clinically indicated if metastases are present or suspected.

For patients who present with findings suggestive of a tumor recurrence or secondary malignancy, histo-/cytopathological confirmation of the diagnosis should be obtained except in patients whose suspicious lesions are deemed by the investigator not to be amenable to biopsy. Such available local histo-/cytopathology reports should be submitted to the IRC for review in cases for which there is site confirmation of recurrence or occurrence of a secondary malignancy in the absence of IRC imaging confirmation. For patients with an isolated, suspected intracranial recurrence, histologic documentation of recurrence in surgically accessible lesions is highly recommended, but not required. For such patients, document the recurrent disease using MRI or CT if MRI is not generally available or is contraindicated.

The diagnosis of a recurrence or occurrence of a secondary malignancy can be made only when the imaging, clinical or pathology findings meet at least one of the following acceptance criteria:

Lung

a. Positive cytology or histology.
b. Imaging evidence of lesions felt to be consistent with metastases.
c. Proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

Liver

a. Positive cytology or histology.
b. New focal defects on MRI or CT that are enlarging in size as documented by at least a 4-week interval.
c. Proof of neoplastic abdominal ascites established by cytology or histology.

Central Nervous System

a. Positive brain CT or MRI.
b. Positive cerebral spinal fluid (CSF) cytology.

Subcutaneous and Lymph Node Recurrence

a. Positive histology.
b. Progressively enlarging solid mass or node(s) as evidenced by two CT or MRI separated by at least a 4-week interval.

   ·Nodal lesions must have a short axis diameter ≥10 mm to be considered enlarged.

Skeletal

a. Positive radiographic study such as bone scan (confirmatory imaging in addition to bone scan may be required).
b. For a solitary lesion or equivocal finding on imaging, a positive histology.

Other Organs

a. Histology/aspiration cytology.
b. Progressively enlarging solid mass or node(s) as evidenced by two CT or MRI separated by at least a 4-week interval.

   ·Nodal lesions must have a short axis diameter ≥10 mm to be considered enlarged.
c. Urethral obstruction in the presence of a mass as documented on CT or MRI.

Anything not meeting the above criteria should be considered unacceptable for evidence of recurrence or occurrence of a secondary malignancy and should not be an indication to alter protocol therapy.

7.1.1. Primary Endpoint

DFS is defined as the time interval from the date of randomization to the first date of recurrence (distant or local recurrence of RCC) or the occurrence of a secondary malignancy or death. The primary DFS analysis will be based on assessments by the IRC. IRC will review all imaging data. Additionally, in cases for which there is site confirmation of recurrence or occurrence of a secondary malignancy in the absence of IRC imaging

confirmation, available local histo-/cytopathology reports will also be reviewed by the IRC oncologist to determine confirmation of recurrence or occurrence of a secondary malignancy.

Recurrence refers to relapse of the primary tumor in situ or at metastatic sites. The date of recurrence or the occurrence of a secondary malignancy is defined as the date of the tumor scan or the date of collection of the histo-/cytopathological specimen (for patients who have site confirmation of recurrence or occurrence of secondary malignancy in the absence of IRC imaging confirmation) that demonstrated unequivocal recurrence or a secondary malignancy according to protocol criteria. If both imaging and histo-/cytopatholigical confirmation of recurrence or sencondary malignancy are available, the earlier of the two dates will be considered.

For patients with no DFS event, DFS time will be censored at the date of the last scan prior to the time for the analyses. Patients alive who do not have post-baseline disease assessments will have their DFS times censored at randomization. For patients receiving further anti-tumor therapy prior to recurrence or occurrence of a secondary malignancy or death, DFS will be censored on the date of the last scan prior to taking the anti-tumor medication. Patients who miss 2 or more consecutive tumor scans immediately followed by an event will be censored at the date of the last objective tumor assessment prior to the missing/not readable scans.

7.1.2. Secondary Endpoints

OS is defined as the time from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond randomization will have their survival times censored at randomization.

7.2. Safety Assessments

7.2.1. Adverse Events

Assessment of adverse events will include: type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), timing, seriousness, and relatedness; and laboratory abnormalities.

Baseline tumor-related signs and symptoms will be recorded as adverse events during the trial if they worsen in severity or increase in frequency.

7.2.2. Laboratory Safety Assessments

Hematology and blood chemistry will be drawn at the time points described in the Schedule of Activities and analyzed at central laboratories (Refer to Appendix 1). Investigators may have additional blood tests performed for the purpose of planning treatment administration, dose modification, or following adverse events and should be repeated as clinically needed. PT/INR should be performed to monitor patients receiving concomitant warfarin or other anti-coagulants and when clinically indicated.

Thyroid Function Tests (TSH, free T_3 and free T_4) should be performed for all patients at baseline (Cycle 1Day 1 pre-dose). Subsequently TSH should be done at Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, then every 8 weeks thereafter starting from Cycle 7 Day 1. TSH, free T_3, free T_4 should be performed on the next visit for any patient who has an elevated TSH in the previous visit. Hypothyroidism should be treated per standard medical practice to maintain euthyroid state with a normal TSH.

7.2.3. Other Safety Assessments

Physical examination: A physical examination including, but not limited to, general appearance, head, skin, neck, eyes, ears, nose, mouth, throat, breast, lungs, heart, abdomen, back, lymph nodes, extremities, thyroid, musculoskeletal, pulses and nervous system will be performed. The physical examination will include examination of known and suspected sites of disease.

Height and body weight: Height will be recorded at screening visit only. Body weight will also be recorded at the start of each 4 week period.

Vital Signs: Measurements will be made of temperature, BP and pulse rate. 2 BP readings should be taken at least 5 minutes apart in the seated position after the patient has been sitting quietly for 5 minutes.

All patients will be issued a blood pressure monitor and blood pressure measurement diary. Patients will be asked to record their blood pressure measurements prior to taking each dose of study drug (twice daily) for the first 3 months, and once a week thereafter. Following dose modification of study drug or anti-hypertensive medication, or changes of anti-hypertensive medication, patients should restart blood pressure measurements prior to taking each dose of study drug for the first 3 months and once a week thereafter. Patients should record all blood pressure measurements in their patient diary. BP readings should be taken in the seated position after the patient has been sitting quietly for 5 minutes. Patients should be instructed to inform the investigator immediately if their sBP rises above 150 mm Hg, dBP rises above 100 mm Hg, or if they develop symptoms perceived to be related to elevated BP (eg, headache, visual disturbance).

ECOG PS: The ECOG PS scale will be used (Appendix 2). Evaluation of ECOG PS at screening should reflect the patient condition just prior to nephrectomy.

All safety assessments should be repeated as clinically needed.

8. Adverse Event Reporting

8.1. Adverse Events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (See Section 8.5) requiring immediate notification to sponsor or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and sponsor concurs with that assessment.

8.2. Reporting Period

Serious adverse events require immediate notification to sponsor or its designated representative beginning from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the clinical trial, ie, prior to undergoing any trial-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

Non-serious adverse events should be recorded from the time the patient has taken at least one dose of trial treatment through last patient visit.

If a patient begins a new anticancer therapy, the adverse event reporting period for non-serious adverse events ends at the time the new treatment is started. Death must be reported if it occurs during the serious adverse event reporting period after the last dose of investigational product, irrespective of any intervening treatment.

8.3. Definition of an Adverse Event

An adverse event is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;

- Drug abuse;
- Drug misuse;
- Drug interactions;
- Drug dependency;
- Exposure In Utero.

Worsening of signs and symptoms of the malignancy under trial should be reported as adverse events in the appropriate section of the CRFs. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events. See description of Serious Adverse Events in Section 8.5 with respect to disease progression.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in trial dosing or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

8.5. Serious Adverse Events

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;

- Results in congenital anomaly/birth defect.

Progression of the malignancy under trial (including signs and symptoms of progression) should not be reported as a serious adverse event unless the outcome is fatal during the trial or within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as serious adverse event. If the malignancy has a fatal outcome within the safety reporting period, then the event leading to death must be recorded as an adverse event and as a serious adverse event with CTCAE Grade 5 (See Section 8.7, Severity Assessment). Any histopathologically confirmed secondary malignancy must be reported as SAE.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.[1]

8.6. Hospitalization

Adverse events reported from clinical trials associated with hospitalization or prolongation of a hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

[1] 21CFR 312.32

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a clinical trial (eg, for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (eg, for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

If required on the adverse event CRFs, the investigator will use the following definitions of severity in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 document but may be used in certain circumstances).
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes

significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

8.8. Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on trial records.

In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

8.9. Exposure In Utero

For investigational products within clinical trials, an Exposure In-Utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);

2. A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

If any trial patient or trial patient's partner becomes or is found to be pregnant while receiving the investigational product or within 6 months of the last treatment on study, the investigator must submit this information to sponsor on a Pregnancy Reporting Form. In addition, the investigator must submit information regarding environmental exposure to the investigational product in a pregnant woman (eg a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Pregnancy Reporting Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information on all pregnancy reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify sponsor of the outcome. The investigator will provide this information as a follow up to the initial Pregnancy Reporting Form. The reason(s) for an induced abortion should be specified. A pregnancy

report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the "normality" of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before a Pregnancy Reporting Form can be completed). The "normality" of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- "Spontaneous abortion" includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the in utero exposure to the investigational agent should be reported.

8.10. Withdrawal Due to Adverse Events (See Also Patient Withdrawal)

Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event CRF page.

When a patient withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events in general.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

Adverse events reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations. In this clinical trial, the reference document for determining whether an event is unexpected is the Investigator's Brochure.

All adverse events and serious adverse events will be reported via eCRF. Adverse events should be reported using concise medical terminology in the AE page as well as in the SAE page of the eCRF.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Sponsor is to be notified via eCRF within 24 hours of awareness of the event by the investigator. In particular, if the serious adverse event is fatal or life-threatening, notification to sponsor must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously reported serious adverse event reports as well as to the initial and follow-up reporting of Exposure in Utero cases.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (eg, if an outpatient trial patient initially seeks treatment elsewhere), the investigator is to report the event via eCRF within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

For all serious adverse events, the investigator is obligated to pursue and provide information to sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by sponsor to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured in the SAE page of eCRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be reported as soon as possible to sponsor or its designated representative.

8.12.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the adverse event CRFs, which are to be submitted to sponsor.

9. DATA ANALYSIS/STATISTICAL METHODS

Two analysis populations will be defined:

1. Intent-to-Treat Population: This population will include all patients who are randomized, with study drug assignment designated according to initial randomization, regardless of whether patients receive study drug or receive a different drug from that to which they were randomized. This will be the primary population for evaluating all efficacy endpoints as well as patient characteristics.

2. As-Treated Population: The as-treated population consists of all patients who received at least 1 dose of study drug with treatment assignments designated according to actual study drug received. This population will be the primary population for evaluating study drug administration/compliance and safety.

9.1. Sample Size Determination

The patient population in this study can be classified into 4 risk groups:

a. pT2, pN0 or pNx, M0 and ECOG 0-1

b. pT3, pN0 or pNx, M0 and ECOG 0-1

c. pT4, pN0 or pNx, M0 and ECOG 0-1

d. Any pT, pN1, M0 and ECOG 0-1

Sample size was determined based on the analysis on the primary endpoint, DFS.

The sample size for this study was calculated based on the following assumptions:

- Time to DFS event follows an exponential distribution.
- The percentage of patients randomized from the 4 risk groups, 2-year DFS rates for placebo arm and axitinib arm are assumed below

Categories	Risk groups	Percentage of patients	2-year DFS rate for placebo arm	2-year DFS rate for axitinib arm
1	a. pT2/pN0 or pNX/M0 b. pT3/pN0 or pNX/M0	90%	70%	79%
2	c. pT4/pN0 or pNX/M0	1%	35%	61%
3	d. Any pT/pN1/M0	9%	33%	51%

The assumptions of 2-year DFS rates for the placebo arm and axitinib arm are equivalent to the assumptions of hazard ratios to be 0.66, 0.47, and 0.61 for the 3 categories 1, 2 and 3 respectively. Given the assumed distribution of patients randomized (1:1) into each of these categories, the overall hazard ratio is estimated to be 0.654.

Based on the above assumptions, a minimal number of 245 DFS events will be required to provide 90% power to detect the statistical difference in DFS with HR $\leq$ 0.654 between the two treatment groups with 2-sided significance level of 0.05.

Applying a 1:1 randomization and a planned accrual period of 24 months, a maximum follow-up period of 60 months (5 years), and an assumed 23% drop-out rate by 18 months, it was estimated that approximately 700 patients will be enrolled.

The final analysis will take place when approximately 245 DFS events are observed.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

DFS based on the IRC review of tumor assessments (by imaging or histo-/cytopathology reports in the absence of IRC imaging confirmation) is the primary endpoint in this study. Factors (and levels in each factor) used in the stratified log-rank test will be stated in the SAP.

The median DFS along with corresponding 95% CI will be estimated for each arm using Kaplan-Meier (KM) methods. The hazard ratio (Arm A/Arm B) will be estimated by proportional Hazard regression stratified by the factors used in the stratified log-rank test, and with treatment in the model. The DFS rates at 2 years and 5 years will also be estimated for each arm.

The following sensitivity analyses will be performed for DFS:

- DFS defined as in the primary analysis but based on local investigator assessment rather than IRC assessment. The earlier of the tumor scan date and the date of collection of histo-/cytopathology specimen (where applicable) confirming recurrence or secondary malignancy will be used.

- DFS based on IRC review defined as in the primary analysis but without censoring patients who receive further anti-tumor therapy or missed 2 or more consecutive tumor scans prior to recurrence or occurrence of a secondary malignancy or death. In other words, patients receiving further anti-tumor therapy or missing 2 or more consecutive tumor scans before disease recurrence or occurrence of a secondary malignancy or death will be assigned with DFS events at the first date of recurrence or occurrence of a secondary malignancy or death. In the absence of DFS event, DFS time will be censored at the date of last scan prior to the time of analyses. Patients alive who do not have post baseline disease assessment will have their DFS times censored at randomization.

- DFS based on IRC review defined as in the primary analysis but considering start of new anti-tumor therapy prior to recurrence, occurrence of secondary malignancy or death as events at the time of new anti-tumor therapy.

- DFS based on IRC review as defined for the primary analysis but instead assigning the dates for events and censoring at the scheduled scan dates instead of the actual scan dates or the date of collection of histo-/cytopathology specimen. Specifically, events that occur within +/- 4 weeks of a scheduled scan will be considered an event at the scheduled scan. Events outside the 4 week window will be counted as events at the next scheduled scan time and censoring outside the 4 week window would be censored at the previous scheduled scan date. If, however, the event is death, the date of death will be used as the event date unless anti-tumor therapy was received prior to the date of death in which case the subject will be censored at the scheduled scan date prior to the date of anti-tumor therapy or for patients who miss 2 or more consecutive

tumor scans immediately followed by an event will be censored at the date of the last objective tumor assessment prior to the missing/not readable scans.

- A parametric model utilizing techniques for interval-censored data will be used to compare the treatment effect.

9.2.2. Analysis of Secondary Endpoints

OS will be compared between Arm A and Arm B using a stratified log-rank test as described in the primary analysis for DFS. The median OS along with corresponding 95% CI will be estimated by treatment arm using KM methods. The hazard ratio (Arm A/Arm B) will be estimated by Proportional Hazard Regression stratified by the factors used in the stratified log-rank test and with treatment in the model.

9.3. Analysis of Other Endpoints

9.3.1. Patient Disposition

The number of patients enrolled, treated, and evaluated for safety will be summarized. In addition, the number of patients who completed the study and the number of patients who withdrew from the study and reasons for discontinuation will be summarized.

9.3.2. Baseline Characteristics

Demographic characteristics such as age, gender, height, weight, race, prior therapy, prior medication, physical examination, ECOG PS, signs and symptoms, and medical/oncology history will be tabulated.

9.3.3. Study drug Administration/Compliance

Study drug administration will be described in terms of the total number and median number of doses administered (ie, total dose), and reasons for the deviations from planned therapy.

9.4. Safety Analysis

Safety data will be summarized for all patients receiving at least one dose of study drug.

9.4.1. Analysis of Adverse Events

The serious adverse event reporting experience for this study begins from the time that the patient provides informed consent while the adverse event reporting experience for this study begins upon receiving the first dose of study drug and ends 28 days after the last dose of study drug is administered. All AEs (serious and non-serious) reported from the first day of study treatment up to 28 days post study treatment will be considered treatment emergent AEs (TEAEs).

Frequencies of patients experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: A description of the event, duration, whether the AE was serious, intensity,

relationship to study drug, action taken, and clinical outcome. Intensity (severity) of the AEs will be graded according to the CTCAE Version 4.0. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Summary tables will present the number of patients observed with TEAEs and corresponding percentages. Within each table, the AEs will be categorized by MedDRA body system and preferred term. Additional subcategories will be based on event intensity and relationship to study drug.

Individual patient listings will be prepared for all AE data.

9.4.2. Analysis of Clinical Laboratory Data

Listing tables will be prepared for each laboratory measure and will be structured to permit review of the data per patient as they progress on treatment.

Summary tables will be prepared to examine the distribution of laboratory measures over time. Shift tables may be provided to examine the distribution of laboratory toxicities.

9.4.3. Prior/Concomitant Medications and Non Drug Treatments/Procedures

Prior medications, defined as those medications stopped prior to the first day of study treatment, and concomitant medications, defined as medications stopped, ongoing or started on or after the first day of study treatment up to 28 days post the last dose of study treatment, will be summarized, using the WHO-drug coding dictionary. In addition, concomitant non drug treatments/procedures will be summarized using the MedDRA coding dictionary.

9.4.4. Vital Sign and ECOG PS

Descriptive statistics will be provided for ECOG PS at each assessment time.

9.5. Interim Analysis

A single interim analysis (IA) will be performed in the study. O'Brien – Fleming type stopping boundaries based on the Lan-DeMets spending function will be applied. Futility criteria are not used to calculate the nominal alphas (non-binding method) in order to control the overall Type I error.

The interim analysis will take place after the first 184 events (75% of the events as assessed by the IRC) have occurred. If the event occurrence pace is much slower than anticipated, the IA could be performed when less than 184 events observed (<75% of the total required) at sponsor's discretion with the Data Monitoring Committee's (DMC) consensus.

The objectives of the interim analysis will be:

1. To assess safety, including any unexpected toxicity. If the results of the interim analysis indicate serious safety concerns, the Sponsor will consult with HRAs regarding stopping the clinical trial.

2. To allow for early stopping of the trial due to futility. If the conditional power is low, the sponsor may choose to stop following up patients. Conditional power calculations will be performed using SAS Version 9.2. Criteria for futility will be provided in SAP.

3. If the results of the interim analysis demonstrate statistically significant differences between the 2 treatment arms for DFS, the sponsor, in consultation with HRAs, will disseminate the results of the trial, and the interim analysis may be considered the final analysis for DFS. The nominal level of significance for the interim analysis of DFS determined using the Lans-DeMets procedure with an O'Brien-Fleming type stopping rule will be 0.0194 (if the interim analysis is performed at 184 events).

The following table summarizes the nominal significance level (2-sided) at each analysis when 75% and 100% of events are observed at the interim analysis and the final analysis.

Fraction of total events	Nominal α level
75%	0.0194
100%	0.0442

The actual nominal α levels for the interim analysis and for the final analysis will depend on the fraction of total events occurred at the time of interim analysis.

At the interim analysis statistical hypothesis tests will be performed only for the primary efficacy parameter, DFS (based on the IRC tumor assessments). The stratified log-rank statistic will be calculated. The DFS curve and OS curve estimated by the method of Kaplan-Meier will be summarized for each treatment group. The interim safety report will review all aspects of the data collected for each patient. Other important additional factors that reflect the integrity of the protocol will be addressed in the interim report.

As per sponsor policy with respect to interim analyses of ongoing mortality studies, distribution of the analyses will be limited to appropriate individuals within the entire organization. Results will be presented at the treatment group level only. The results will not be shared with all the study team members or investigators nor broken down by center.

9.6. Data Monitoring Committee

A Data Monitoring Committee (DMC) will be formed to assure patient safety in this clinical trial. The DMC will include a panel of experts recruited from outside of the institutions involved in this study. The DMC will have access to unblinded patient treatment assignment information. The DMC members will also have additional responsibility as they will be involved in the conduct and interpretation of data analyses for efficacy in addition to their primary responsibility for patient safety. The committee will review tabulated aggregate toxicity and endpoint data. The committee will submit written recommendations on the progress of the study to the Sponsor.

Further procedural matters and meeting schedule will be defined by mutual agreement of DMC members in accordance with sponsor guidelines.

9.7. Independent Review Committee (IRC)

The radiographic images and/or available local histo-/cytopathology reports (for patients who have site confirmation of recurrence or occurrence of secondary malignancy in the absence of IRC imaging confirmation) will be evaluated by an IRC to assess tumor status and to confirm recurrence or occurrence of a secondary malignancy. The radiographic images and/or histo-/cytopathology reports documenting efficacy endpoints must be made available to allow the independent review. The core laboratory will work with each clinical site to institute an acquisition protocol and other processes that will allow electronic transfer, where possible, of appropriate information used for tumor assessments. Two independent reviewers will read scans. Differences between the two independent reviewers should be resolved by a third reviewer (adjudicator) for final determination. In addition, an independent clinical oncologist will assess available local histo-/cytopathology reports for evidence of malignancy for patients for which there is site confirmation of recurrence or occurrence of secondary malignancy in the absence of IRC imaging confirmation. For primary statistical analysis, the results of the independent review will be used.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During trial conduct, Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and GCPs are being followed. The monitors will review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow sponsor monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The trial site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of sponsor and should not be made available in any form to third parties, except for authorized representatives of sponsor or appropriate regulatory authorities, without written permission from sponsor.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Patient source documents are the investigator's patient records maintained at the trial site. In most cases, the source documents will be the

hospital's or the investigator's chart. In cases where the source documents are the hospital or the investigator's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, Sponsor and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or sponsor, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed ICD, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the trial, Sponsor should be prospectively notified. The trial records must be transferred to an acceptable designee, such as another investigator, another institution, or to sponsor. The investigator must obtain sponsor's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the trial protocol, protocol amendments, ICD, and other relevant documents, eg, advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to sponsor.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and sponsor in writing within 5 working days after the implementation.

12.2. Ethical Conduct of the Trial

The trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, Sponsor will maintain high standards of confidentiality and protection of patient personal data.

The ICD must be agreed to by sponsor and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The investigator must ensure that each trial patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written ICD each patient or the patient's legally acceptable representative before any trial-specific activity is performed. The ICD used in this trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and sponsor before use. The investigator will retain the original of each patient's signed ICD.

13. DEFINITION OF END OF TRIAL

End of Trial in all participating countries is defined as collection of the final data point in the study. Because this clinical trial includes a survival endpoint, the last data point is anticipated to be the last survival follow-up (ie, date last known alive or of death) prior to the cutoff date for database lock for the final Clinical Study Report.

If the trial is terminated upon recommendation by the DMC according to prospectively-defined criteria, End of Trial is defined as the date upon which sponsor received notification of the decision of the DMC.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, DMC, or at the discretion of sponsor. In addition, Sponsor retains the right to discontinue development of axitinib, at any time.

If a trial is prematurely terminated or discontinued, Sponsor will promptly notify the participating investigators. After notification, the investigators must contact all participating patients within a week of notification. As directed by sponsor, all trial materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF TRIAL RESULTS

Sponsor supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Sponsor’s, and/or the Investigational product owner. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Sponsor’s, and/or the Investigational product owner an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, “publication”) before it is submitted or otherwise disclosed.

The first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 18 months of completion or

termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study patients, and the CSA will control as to all other issues.

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APPENDICES

Appendix 1. Required Laboratory Tests

	Conventional Units	Conversion Factor	SI Units
Hematology			
Hemoglobin (Hgb)	g/dL	x 10	g/L
Platelet count (Plt)	$10^3/mm^3$	x 10^9	$10x^{12}/L$
White blood count (WBC)	$10^3/mm^3$	x 10^6	$10^9/L$
White blood cell differential			
Neutrophil	%	x 0.01	fraction
Lymphocytes	%	x 0.01	fraction
Chemistry			
Total bilirubin	mg/dL	x 17.1	µmol/L
Alanine transaminase (ALT)	U/L	N/A	U/L
Aspartate transaminase (AST)	U/L	N/A	U/L
Alkaline phosphatase	U/L	N/A	U/L
Lactic dehydrogenase (LDH)	U/L	x 0.016667	µkat/L
Albumin	g/dL	x 10	g/L
Total protein	g/dL	x 10	g/L
Sodium	MEq/L	x 1.0	mmol/L
Potassium	MEq/L	x 1.0	mmol/L
Chloride	MEq/L	x 1.0	mmol/L
Calcium	mg/dL	0.25	mmol/L
Phosphate	mg/dL	x 0.323	mmol/L
Blood urea nitrogen (BUN)/Urea	mg/dL	x 0.357	mmol/L
Creatinine	mg/dL	x 88.4	µmol/L
Glucose	mg/dL	x 0.055	mmol/L
PT/INR	N/A	N/A	N/A
Thyroid Function Tests			
Thyroid stimulating hormone (TSH)	µU/mL	x 1.0	mIU/L
Free T3	pg/dL		
Free T4	ng/dL		
Urinalysis			
Urine Protein	N/A		

Appendix 2. ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 3. National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (Version 4.0) has been placed in the Study Reference Binder for this protocol. Alternatively, the NCI CTCAE may be reviewed on-line at the following NCI website:

http://ctep.cancer.gov/reporting/ctc.html

Appendix 4. Nephrectomy Procedure

Radical nephrectomy procedure performed either by open or by laparoscopic technique should include: early ligature of the renal vessels and en bloc removal of the intact specimen including tumoral kidney and surrounding perinephritic fat.

Partial nephrectomy can be allowed provided all inclusion criteria are met and surgical margins are obtained.

Adrenal gland removal should be performed in case of large upper pole tumor or in case of abnormal adrenal imaging on preoperative CT. In other cases, routine adrenal gland excision is not mandatory and should be performed according to surgeon preferences.

Lymph node dissection (LND) should be performed in case of suspicion of nodal invasion either on preoperative CT imaging or at intra-operative finding. In other cases, LND will be performed according to surgeon preferences.

In all cases, there must be no evidence of residual macroscopic disease on post-operative CT.

Appendix 5. Abbreviations and Definitions of Terms

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ANC	Absolute Neutrophil Count
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CRF	Case Report Form
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events (US-NCI)
CYP3A4/5	Cytochrome P450 enzyme-3A4/5
dBP	diastolic Blood Pressure
DFS	Disease Free Survival
DMC	Data Monitoring Commitee
ECG	Electrocardiogram
ECOG	Eastern Collaborative Oncology Group
EIU	Exposure in Utero
EQ-5D	European Quality of Life Questionnaire in 5 functional domains
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HRA	Health Regulatory Authority
ICD	Informed Consent Document
ICH	International Conference Harmonisation
IEC	Independent Ethics Committee
IFN-α	Interferon-alfa
IL-2	Interleukin-2
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Commitee
IUD	Intrauterine Device
KM	Kaplan Meyer
LDH	Lactic Dehydrogenase
LND	Lymph Node Dissection
MedDRA	Medical Dictionary for Regulatory Activities
mRCC	Metastatic Renal Carcinoma
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall Survival
PFS	Progression Free Survival
PLT	Platelet
PRO	Patient Reported Outcomes
PT	Prothrombin Time
QTc	Corrected Q-T interval
RCC	Renal Cell Carcinoma

sBP	systolic Brood Pressure
TEAE	Treatment Emergent Adverse Event
TNM	Tumor, Nodes, Metastases
TX	Treatment
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
UPC	urine protein: urine creatinine ratio
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cell

PROTOCOL APPROVAL SIGNATURE PAGE

Compound:	AG-013736
Compound Name:	Axitinib
Protocol Number:	AP311736
Phase:	III
Version and Date	version - 10 March 21, 2017

Rolf Linke
Chief Medical Officer
SFJ Pharmaceuticals

21. March 2017

Rolf Linke Date