CASE WESTERN RESERVE UNIVERSITY | CASE COMPREHENSIVE CANCER CENTER

NCI Comprehensive Cancer Center
A Cancer Center Designated by the National Cancer Institute

STUDY NUMBER: CASE 7815

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Version Number: 10

STUDY TITLE: A PHASE II STUDY OF THE EFFICACY AND SAFETY OF AXITINIB GIVEN ON AN INDIVIDUALIZED SCHEDULE FOR METASTATIC RENAL CELL CANCER AFTER TREATMENT WITH PD-1 OR PD-L1 INHIBITORS

PRINCIPAL INVESTIGATOR: Moshe C. Ornstein MD MA
Cleveland Clinic Taussig Cancer Center
9500 Euclid Avenue, CA-60
Cleveland, Ohio 44195
[redacted]

CO- INVESTIGATORS: Brian I Rini MD
Jorge Garcia, MD
Tim Gilligan, MD
Monty Pal, MD / City of Hope
Amir Mortazavi, MD / OSU
Kimryn Rathmell MD / Vanderbilt

STATISTICIAN:
[redacted]

RESEARCH NURSE: [redacted]

STUDY COORDINATOR: [redacted]

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SUPPORT/FUNDING: Pfizer

SUPPLIED AGENT(S): Axitinib, Pfizer

SUMMARY OF CHANGES

Protocol Date	Section	Change
13JUL2015		Initial Submission to PRMC
16SEP15		PRMC Approved Version
23OCT2015	13.1	Initial IRB approval; added, minor formatting and editing
24NOV2015	2.1	Reworded the primary objective to clarify that the objective is to determine whether this individualized dosing schema will lead to improved PFS.
	3.1	The inclusion criteria have been modified as follows: 1. To highlight that anti-PD-1/PD-LI therapy must be the most recent therapy prior to enrollment on this study. 2. To highlight that **only one prior VEGF directed therapy** is permitted. 3. To clarify that prior VEGF directed monotherapy (i.e. not in combination with anti-PD-1/PD-LI therapy) is also permitted.
	3.2	1. Added an exclusion criterion to emphasize that **more than one** VEGF-based therapy given either as monotherapy or in combination with anti-PD-1/PD-LI therapy is not permitted. 2. Clarified that patients with controlled atrial fibrillation would not be excluded. 3. Removed exclusion criteria that would exclude patients who used CYP3A4 inhibitors and inducers within 7 and 12 days of the study, respectively. This issue is clarified in section 6.4.
	4.0	The study calendar had a variety of formatting issues when changes were tracked. Therefore a new calendar was inserted. The following changes were made in the calendar/footnotes: 1. Added row to state that ECOG/KPS will be collected on days a physical exam occurs.

		2. Removed clinic visit from C1D14 assessment of toxicity. This will be done by phone call instead. 3. Clarified timing of imaging (footnote 5). 4. LDH will be drawn at baseline only (footnote 7). 5. Clarified need / criteria for pregnancy test (footnote 8). 6. Highlighted that protocol treatment should begin with three days of registration and not seven days.
	6.4	Clarified which classes of drugs will be collected as concomitant medications during screening period and throughout study. 1. Cardiac medications 2. CYP3A4 meds (including list) 3. Steroids (including dose) 4. Anti-diarrhea medications
	6.4.1	Clarified that the use CYP3A4 inhibitors and inducers in period immediately preceding study would not lead to exclusion but is not recommended. Also highlighted that the use of these meds is permitted during the study though not recommended.
	7.2	1. Clarified number of 5mg and 1mg pills that will be given to patients at beginning of each cycle. 2. Provided name and fax number for diary sheets to be sent at the end of each cycle.
	10	The statistics section has been revised and condensed with the following main changes: 1. Primary statistical analysis has been changed to highlight its direct relationship to the primary objective. 2. Patient sample size has been further clarified 3. More information has been included with regards to the rationale for expected study duration. 4. Toxicity criteria for study discontinuation have been added.
25JAN2016	1	Administrative changes to Co-Investigator section on page 1
14DEC2016		Administrative changes to Co-Investigator section on page 1 Updated protocol date
	3.1	Inclusion-adding 2 week wash out and updated the Serum Creatinine to be less than or equal to 2.0 x ULN This is to align with our labs normal ranges page 7 was also updated to reflect this change
	3.2	Exclusion-CNS-Mets updated to 1 month stable instead of 3-this is to align the protocol with parameters used in clinical practice. Page 7 has also been updated
	3.3	Language has been updated
	7.2	Updated 1mg supply to 14-Day (#28)
	9.2	Language updated to be after first dose of study drug

	9.4	Relationship language has been for alternate etiology for unrelated events need to be provided
	15.6	Removed
	15.7	Removed
	15.8	Removed
20FEB2017	Page 2	Administrative changes adding Research Nurse phone number
	Synopsis & 3.1/3.2	Eliminate the restriction of 'only ONE prior VEGF-based therapy (Bevacizumab or VEGF TKI) is permitted. Both inclusion & exclusion criteria. Rationale: Allowing 2 prior VEGF-based therapies won't impact the study objectives, and is consistent with clinical practice for Axitinib.
	Synopsis & 3.2	Eliminate the QTc interval exclusion criteria. Rationale: No QTc restriction for Axitinib in clinical practice.
05JAN2018	Cover Page	Change PI. Add version number. Removal of Co-I Petros Grivas
	Synopsis & 3.1	Remove inclusion criteria of neoadjuvant or adjuvant therapy
	4	Changed bone scan frequency after cycle 7 day 1 to every 16 weeks per MD discretion.
	4	Changed CT scans to "following Cycle 11 Day 1 assessment, CT scans to be done every 12 weeks."
	5	Changed "drug-related" to "axitinib-related" in calendar footnote "a".
	7.2	Diary sheets will now be faxed to Keralee Morey (Fax: 216-636-5675) instead of Laura Wood
	7.2	Changed method of diary sheet submission from fax only to "electronic/email or fax"
	10	Sample size was decreased to 38 patients based on new data regarding efficacy of axitinib in this setting. Although the statistical analysis remains the same, the number of needed patients has changed.
18Jul2018	3.3	Updated study coordinator to Jackie Tomer
	7.2	Updated contact information for diary cards
	9.4	Updated SAE reporting to Jackie Tomer
08Oct2018	Cover page	Changed statistician to Brian P. Hobbs PhD. Updated OSU PI
	4	Calendar was updated to resolve a discrepancy in imaging frequency between the calendar of footnotes. Also added

		information on scan frequency for patients continuing axitinib post-PD.
	6.3	PI was changed to Moshe Ornstein MD
	6.5	This section was added to provide information regarding duration of follow-up
	8.2	Imaging text was changed to reflect the calendar clarification

SYNOPSIS

Study Title:	A Phase II Study of the Efficacy and Safety of Axitinib Given on an Individualized Schedule for Metastatic Renal Cell Cancer after Treatment with PD-1 or PD-L1 Inhibitors
Primary Objectives:	To determine whether axitinib given on an individualized dose/schedule for metastatic renal cell carcinoma following immunotherapy with PD-1 or PD-L1 Inhibitors leads to improved PFS
Secondary Objectives:	To characterize the objective response rates in patients given axitinib on an individualized dose/schedule To evaluate the tolerability and safety of an alternative method of axitinib titration. To characterize the anti-tumor effect, as measured by change in tumor burden per RECIST 1.1, of axitinib titration performed after initial RECIST PD on axitinib
Study Design:	A Phase II study, single arm study, open-label, safety and efficacy study.
Duration:	Approximately 3 years, including 18-24 months of recruitment, minimum 4 months of treatment and a minimum of 1 year of follow-up
Planned Total Sample Size:	38 evaluable patients will be enrolled in this study.

Inclusion/Exclusion Criteria:	**Inclusions:** Histologically confirmed, locally recurrent or metastatic clear cell renal cell carcinoma Has received one prior systemic therapy regimen for mRCC directed against PD-1 and/or PD-L1 which must have been the most recent regimen o Prior high-dose interleukin-2 therapy is permitted in addition to anti-PD(L)1 therapy, but is not required o Prior bevacizumab or VEGF TKI is permitted either in combination with anti-PD(L)1 therapy OR as monotherapy when given PRIOR to anti-PD(L)1 therapy- o o Prior treatment with combined ipilimumab and nivolumab is permitted o Prior axitinib in any setting is not permitted A minimum of two weeks since last dose of most recent RCC therapy assuming resolution of clinically significant treatment-related toxicities to grade 1, baseline, or controlled with supportive medications Evidence of measurable disease per RECIST 1.1. Male or female, age ≥ 18 years Karnofsky performance status ≥ 70 %. Adequate organ function as defined by: o Absolute neutrophil count (ANC) ≥1,000/μL o Platelets ≥100,000/μL o Hemoglobin ≥9.0 g/dL o Serum calcium ≤12.0 mg/dL o Serum Creatinine ≤2.0 x ULN o Total serum bilirubin ≤1.5 x ULN o SGOT≤2.5 x ULN and SGPT ≤2.5x ULN Signed informed consent and willingness/ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

	Exclusion: Non-clear cell RCC Major surgery within 4 weeks of starting the study treatment. Radiation therapy within 2 weeks of starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated. NCI CTCAE Version 4.03 grade 3 hemorrhage within 4 weeks of starting the study treatment. Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack. Ongoing cardiac dysrhythmias of NCI CTCAE Version 4.03 grade ≥2. Controlled atrial fibrillation is permitted. Uncontrolled hypertension (>160/100 mm Hg despite optimal medical therapy) Concurrent treatment on another clinical trial. Supportive care, non-treatment trials, and imaging trials are allowed.

Exclusion criteria (cont.)	Pregnancy or breastfeeding. Female subjects must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum) prior to enrollment. Male subjects must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study. Uncontrolled CNS metastases. Patients are considered to have controlled CNS metastases (and thus eligible) if they have completed local therapy (XRT and/or surgery) and are off steroids with clinical and radiographic stability 1month from the end of CNS-directed therapy.
Test Drug Administration:	The intent is to maximize dose intensity of axitinib based on individual tolerability using the dose modification criteria described in Section 5. Dose changes are done if selected toxicity (oral mucositis, diarrhea, fatigue, hand-foot syndrome) is $\leq$ grade-2. There will be no mandated dosing or schedule changes for hypertension, hypothyroidism, skin color changes, heartburn etc. Patients will continue therapy until progression according to RECIST criteria version 1.1 or investigator discretion of clinical benefit. Patients may undergo dose escalation following disease progression at the discretion of the provider.

Treatment and Post-Treatment Assessments:	One cycle is defined as 28 days. <u>During the first cycle:</u> • History and Physical exam at beginning of each cycle • CBC with differential • Complete Metabolic Panel (CMP) • Thyroid function tests • Telephone encounter during first week to assess toxicity • Phone call after two weeks to assess toxicity <u>During Subsequent Cycles:</u> • History and Physical exam at beginning of each cycle • CBC with differential at beginning of each cycle • CMP at beginning of each cycle • Telephone call or clinic visit 7 & 14 days after each dose change • Clinic visits or telephone calls as needed to assess toxicity <u>Every two cycles:</u> • Restaging of involved areas • Thyroid function tests .
Response:	Response will be assessed as per RECIST version 1.1
Safety Variables & Analysis:	Adverse Events will be assessed as per CTCAE version 4.03

ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Events
AHFS	American Hospital Formulary Service
ANC	Absolute Neutrophil Count
ASHP	American Society of Hospital Pharmacists
AUC	Area Under the Curve
BID	Twice Daily
BP	Blood Pressure
CBC	Complete Blood Count
CCCC	Case Comprehensive Cancer Center
CCF	Cleveland Clinic Foundation
CITI	Collaborative Institutional Training Initiative
C_{max}	Maximum Plasma Concentration
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety and Toxicity Committee
EC	Ethics Committee
EKG	Electocardiogram
FDA	Food and Drug Administration
HR	Hazard Ratio
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LAR	Legally Acceptable Representative
MD	Medical Doctor
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magentic Resonance Imaging
NCI	National Cancer Institute
OS	Overall Survival
PD	Progressive Disease
PD(L)-1	Programmed Cell Death Ligand 1
PD-1	Programmed Cell Death Protein
PFS	Profession Free Survival

PI	Principal Investigator
PK	Pharmacokinetics
PR	Partical Response
PRMC	Protocol Review and Monitoring Committee
QD	Every Day
QOL	Quality of Life
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Events
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
TKI	Tyrosine Kinas Inhibitor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VEGFR	Vascular Endothelial Growth Factor
XRT	Radiation Therapy

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Background

Axitinib is a tyrosine kinase inhibitor (TKI) of the vascular endothelial growth factor receptor (VEGFR) approved January 2012 for the treatment of metastatic renal cell carcinoma (mRCC).[1, 2] The phase III AXIS trial that led to its approval randomized 723 mRCC patients with progressive disease following treatment with sunitinib, temsirolimus, bevacizumab, or cytokines to receive sorafenib 400mg BID or axitinib at a starting dose of 5mg BID. Dose titration of axitinib to 7mg BID and further to 10mg BID was allowed for patients without grade 2 or higher toxicities or hypertension (BP > 150/90). The primary endpoint was PFS. Median PFS in the axitinib arm was 6.7 months compared to 4.7 months in patients randomized to sorafenib (HR 0.665; 95% CI 0.544-0.812; p<0.0001). The secondary endpoint of objective response rate (ORR) was also significant at 19% for the axitinib arm and 9% for sorafenib (p=0.0001) with a higher median duration of response in patients receiving axitinib compared to sorafenib (11 months vs. 10.6 months). Diarrhea, hypertension, and fatigue were the most common adverse events occurring in greater than 30% of patients.[2]

1.2 Pharmacokinetics of axitinib

The pharmacokinetics of TKIs demonstrate significant inter-individual variability, which may be contribute to the variable clinical response in patients.[3] However, despite variable anti-tumor effects, some general principles about TKI pharmacokinetics have been well-established. Early clinical trials with axitinib demonstrate linear pharmacokinetics in that higher doses of the drug results in proportional increases in plasma level. In a dose-finding phase I trial of thirty-six patients with advanced solid tumors who received axitinib with doses ranging between 5mg BID and 20mg BID, there were dose-proportional increases in mean steady-state concentrations, maximum plasma concentration (C_{max}) and area under the curve (AUC) (Figures 1, 2).[4] These findings were similarly noted in a phase I open-label study of 14 healthy volunteers[5] and have been reproduced in many studies.[6-8]

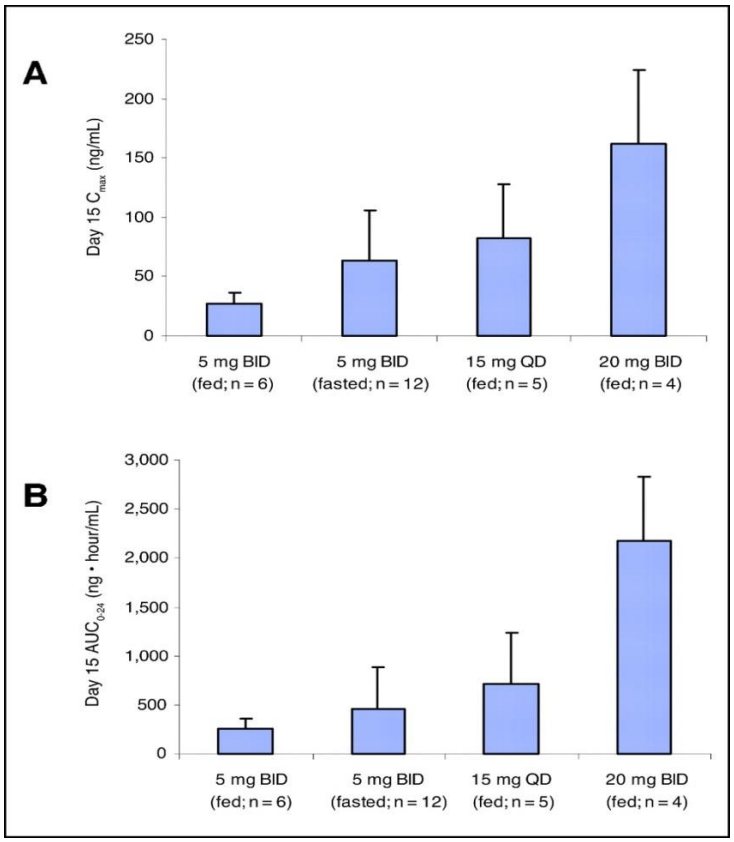


Figure 1. Mean steady-state AG-013736 plasma concentrations on day 15 of dosing. (A) C_{max}, maximum concentration; (B) AUC, area under the curve. QD, every day. [4]

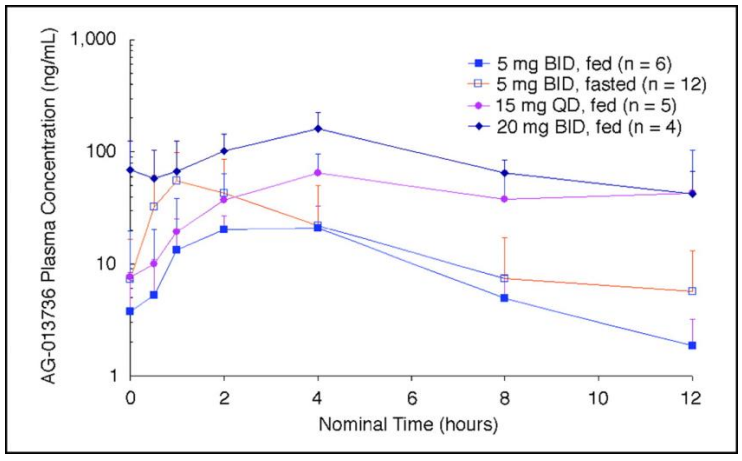


Figure 2. Area under the curve (AUC) and maximum plasma concentration (C_{max}) versus dose: linearity in pharmacokinetics. QD, every day. [4]

A pooled axitinib pharmacokinetic and pharmacodynamic analysis from 17 clinical trials included a total of 590 subjects; 383 were healthy volunteers, 181 mRCC patients, and 26 patients had other solid tumors.[9] These data demonstrated a linear relationship between the dose of axitinib, plasma exposure, and area under the plasma concentration-time curve (AUC). Moreover, the probability of a response to treatment increased with each 100h x ng/mL increase in AUC ($p<.0001$). PFS (13.8 vs. 7.4 months; $p=.003$) and OS (37.4 vs. 15.8 months; $p<.001$) were significantly longer in the high-AUC group (>300 h x ng/mL) than the low-AUC group (<300 h x ng/mL).[9] These data indicate that higher exposure in general is associated with improved clinical outcomes.

1.3 Axitinib Dose Escalation Data

Based on the considerations above, a prospective trial was conducted to determine if dose titration of axitinib led to improved clinical outcomes in patients with mRCC. A phase 2, double-blinded, randomized, international trial enrolled 213 previously untreated mRCC patients to determine if a higher objective response rate would be observed in patients with escalated axitinib doses compared to patients who remained at 5mg BID among all patients eligible for titration.[10] In a 4 week lead-in period prior to randomization, all patients received axitinib 5mg BID. 112 patients with who tolerated the 5mg BID dose for four weeks were subsequently randomized to placebo titration or to have their axitinib titrated to 7mg BID and then, if tolerated, to 10mg BID. Patients in the dose-titration group experienced an increase in the mean axitinib drug exposure from prior to dose titration to 15 days after dose titration (Table 1)[10], demonstrating the linear dose-proportional pharmacokinetics of axitinib dosing.

Table 1. Axitinib pharmacokinetic parameters prior to and after dose titration [10]

	Eligible for dose titration	
	Axitinib titration	**Placebo titration**
Day 15 of lead-in period (prior to titration)		
AUC_{24} ng*h/mL	176 (125-247)	187 (107-327)
C_{max} ng/mL	28.6 (20·5-39.9)	22.5 (15.1-33.7)
Cycle 2 day 15 (after titration)		
AUC_{24} ng*h/mL	259 (150-445)	161 (102-255)
C_{max} ng/mL	31.7 (21.6-46.6)	23.1 (16.4-32.5)

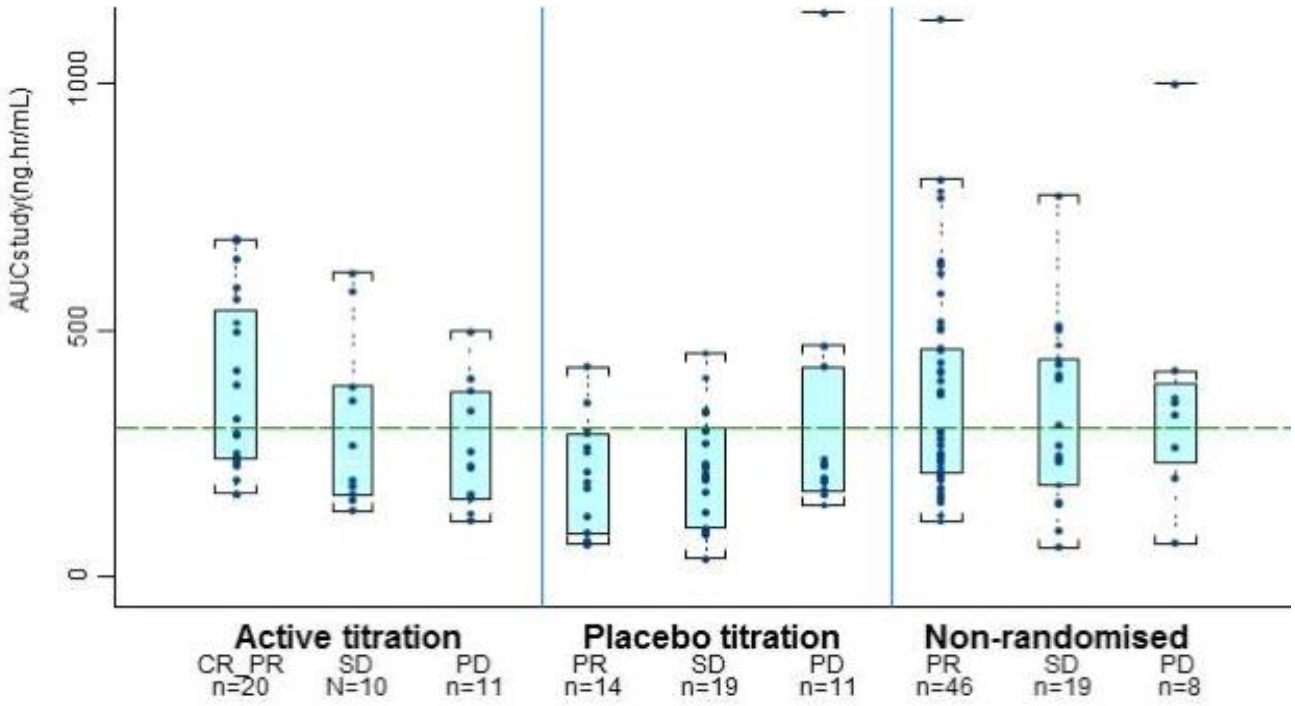
The group of patients randomized to dose titration also had a higher objective response rates (ORR) than the placebo titration group (54% vs. 34%; p = 0.019) (Table 2).

Table 2. Best Observed Response by RECIST [10]

	Total (N=213)	Axitinib titration (n=56)	Placebo titration (n=56)	Non-randomised (n=91)
Complete response	1 (<1%)	1 (2%)	0	0
Partial response	102 (48%)	29 (52%)	19 (34%)	54 (59%)
Stable disease	60 (28%)	13 (23%)	24 (43%)	23 (25%)
Progressive disease	38 (18%)	13 (23%)	11 (20%)	11 (12%)
Not assessed	9 (4%)	0	1 (2%)	2 (2%)
Indeterminate	2 (1%)	0	0	1 (1%)

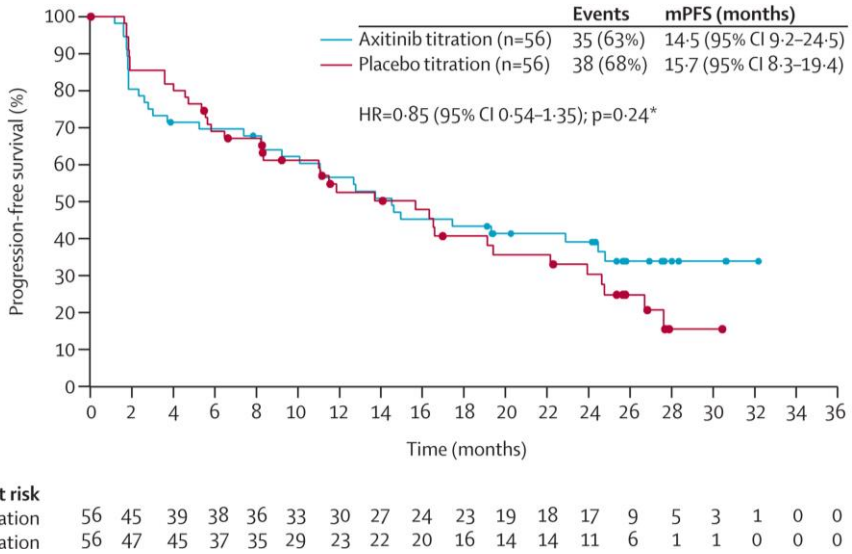
Although the above data demonstrate that axitinib titration will lead to higher axitinib exposure, and, in general, higher exposure will be associated with a higher objective response rate, a number of mitigating factors to applying this in routine clinical practice exist. Firstly, the use of PK measurements to determine dose-titration is imprecise. In this study, there was a 34% response rate in patients eligible for dose titration who were randomized to placebo. Many of these patients had what would be considered 'sub-therapeutic' levels of axitinib yet still demonstrated an objective response (Figure 3). Likewise, many of the patients in the active titration cohort who had stable or progressive disease actually had supra-therapeutic PK levels (Figure 3). These data suggest that although PK levels may reflect objective response on average for an entire cohort of patients, it does not accurately guide dosing for individual patients. Further, several patients who escalated to 7mg BID and higher had to quickly reduce to 5mg BID dosing or lower, suggesting that the current dose titration schema is not suitable for all patients (i.e. the amount of dose increase in the current titration schema represents too big of a dose increase for some patients).

Figure 3. PK levels in three patient cohorts (active titration, placebo titration, and non-randomized) and response of individual patients. Blue dots denote individual patient PK levels. Horizontal green dashed line represent 300h x ng/mL which is considered the therapeutic plasma level of axitinib.



Indeed, although the hazard ratio for PFS favored the titration arm (HR=0.85), this was not statistically significant (Figure 4). Closer examination of the PFS curves reveals and early drop in the titrated arm, in part due to toxicity encountered with titration. This also reveals the tail of the curve favoring dose titration (Figure 4), supporting a hypothesis that a more refined titration schema to allow for sustained titration could lead to enhanced clinical outcome.

Figure 4. Kaplan-Meier Estimates of PFS From First Dose in Randomized Arms – Favorable but non statistically significant PFS in the titration arm (HR = 0.85; p=0.24). Early drop in the titration arm likely related to toxicities in titration arm. Tail of curve demonstrating favorable long-term outcome in the titration arm. [10]



1.4 Rationale for the study

As with many oral targeted drugs, axitinib is characterized by a variable plasma exposure at a given dose among patients and a lack of correlation between plasma levels and efficacy in individual patients. As such, and given rapid absorption and elimination, the clinical development of axitinib incorporated dose titration to allow for higher doses in patients who did not suffer from dose-related toxicities. However, as reviewed above, the current axitinib dosing schema (starting dose of 5mg BID with titration to 7mg BID and then 10mg BID) has several limitations. The goal of this study is to identify an individualized dose-titration algorithm for axitinib that will provide clinicians with a useful tool to optimize clinical outcome in patients with mRCC following treatment with immunotherapy (specifically, checkpoint inhibitors).

Rationale for Proposed Schema: The proposed titration schema contains a number of critical components that differ from the current titration standard. The current package insert titration schema is predicated on the hypothesis of an inherent value to continuous therapy with axitinib even at a lower dose to maintain steady plasma concentration of the drug. As

such, in previous clinical trials, axitinib has been given on a continuous schedule with dose reduction for patients that developed toxicity on continuous therapy. However, rodent data show that intermittent higher dose TKI therapy may be associated with improved efficacy than continuous lower dose therapy.[11] Therefore, in this study patients are treated to toxicity on an individualized dose and schedule and instead of dose-reduction upon grade 2 or greater toxicity, they take an individualized break from the drug and then resume the same dose. The intent, therefore, is not to sustain continuous therapy with a lower dose, but rather to maximize the dose on an intermittent schedule even if it means having a few days off therapy.

It is also well established that because of limited pill sizes available for oral drugs, dose reductions and dose escalations on a fixed schedule cannot be fine-tuned to the same extent as for IV chemotherapy.[12] With the usual dose reductions for axitinib to 3 mg bid and then 2 mg BID patients receive 60% and 40% respectively of the starting dose level and some pts may be under dosed. Conversely with the standard dose escalation to 7 mg BID and then 10 mg BID patients receive 140% and 200% of the starting dose respectively and some patients may be overdosed and end up requiring dose reduction. In our proposed study, most dose escalations and reductions are by a rate of 1mg BID which allows for a more precise titration schema based on tolerance and will likely result in less dose-escalation toxicity given the slower rate of titration.

Rationale for Patient Population: This study will enroll patients with mRCC previously treated with immune checkpoint inhibitors of programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1). Anti-PD-1 and anti-PD-L1 inhibitors have demonstrated efficacy in TKI-refractory and previously untreated mRCC patients[13-16] and clinical trials with these compounds are being offered to patients with mRCC as first line therapeutic options.[17, 18] There are currently no prospective data on the efficacy of axitinib in the post-PD-1/PD-L1 setting, and the available retrospective data are limited to relatively small populations and demonstrate a PFS of approximately 7 months.[19, 20] Recruitment of large number of patients to a first-line individualized axitinib dosing trial would be challenging in the era of checkpoint inhibitors clinical trials, but a trial limited to the post-PD-1/PD-L1 setting would be beneficial

both to identify an improved method of axitinib administration in general and also to prospectively document efficacy after PD-1/PD-L1 inhibition.

Rationale for Allowance of Dose-escalation at Progression: Upon RECIST 1.1 PD, this study recommends dose-escalation in patients without ≥ grade 2 toxicities. This recommendation is based on recently-presented data that suggest a clinical benefit to dose escalation of TKIs upon PD in mRCC. [21] In a retrospective review of 21 patients with mRCC, 89% of whom were treated with axitinib, patients who underwent TKI dose-escalation following PD were assessed for tumor response. 58% of patients had a reduction in tumor burden following dose-escalation and patients remained on dose-escalated therapy post-PD for almost as long as prior to PD (median 6.3 vs 6.8 months, with 28% of patients still on treatment). [21] This suggests a potential clinical benefit to TKI dose-escalation post-PD. These data also suggest that perhaps the patients who developed PD on their initial dose had sub-therapeutic axitinib levels and further underscore the need for a more precise dose-titration schema to maximize the clinical benefit of axitinib.

In summary, the present trial proposes a dose-titration schema of axitinib for patients with mRCC following treatment with immune checkpoint inhibitors. The study aims to identify a fine-tuned titration schema that will maximize dosing while allowing for intermittent individual breaks in hopes of improving overall efficacy. Building on retrospective data, the study will also prospectively evaluate the clinical effect of dose escalation following PD.

2. OBJECTIVES

2.1 Primary objective

- To determine whether axitinib given on an individualized dose/schedule for metastatic renal cell carcinoma following immunotherapy with PD-1 and PD-L1 Inhibitors leads to improved PFS.

2.2 Secondary objectives

- To characterize the objective response rates in patients given axitinib on an individualized dose/schedule
- To evaluate the tolerability and safety of an alternative method of axitinib titration.
- To characterize the anti-tumor effect, as measured by change in tumor burden per RECIST 1.1, of axitinib titration performed after initial RECIST PD on axitinib

3. SUBJECT SELECTION

This trial will be conducted in compliance with this protocol and with oversight by our institution's Institutional Review Board (IRB). Any questions about eligibility criteria must be addressed prior to patient registration.

3.1 Inclusion criteria

Patients will be eligible if they meet <u>all</u> of the following criteria at the time of registration:

- Histologically confirmed, locally recurrent or metastatic clear cell renal cell carcinoma
- Has received one prior systemic therapy regimen for mRCC directed against PD-1 and/or PD-L1 which must have been the most recent regimen
    - Prior high-dose interleukin-2 therapy is permitted in addition to anti-PD(L)1 therapy, but is not required

- Prior bevacizumab or VEGF TKI is permitted either in combination with anti-PD(L)1 therapy OR as monotherapy when given PRIOR to anti-PD(L)1 therapy-
- Prior treatment with combined ipilimumab and nivolumab is permitted
- Prior axitinib in any setting is not permitted

- A minimum of two weeks since last dose of most recent RCC therapy assuming resolution of clinically significant treatment-related toxicities to grade 1, baseline, or controlled with supportive medications
- Evidence of measurable disease per RECIST 1.1.
- Male or female, age ≥ 18 years
- Karnofsky performance status ≥ 70 %.
- Adequate organ function as defined by:
  - Absolute neutrophil count (ANC) ≥1,000/μL
  - Platelets ≥100,000/μL
  - Hemoglobin ≥9.0 g/dL
  - Serum calcium ≤12.0 mg/dL
  - Serum Creatinine ≤2.0 x ULN
  - Total serum bilirubin ≤1.5 x ULN
  - SGOT≤2.5 x ULN and SGPT ≤2.5x ULN

- Signed informed consent and willingness/ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures

3.2 Exclusion criteria

Patients will be ineligible if they meet <u>any</u> of the following criteria at the time of registration:

- Non clear cell RCC
- Major surgery within 4 weeks of starting the study treatment.
- Radiation therapy within 2 weeks of starting the study treatment. Prior palliative radiotherapy to metastatic lesion(s) is permitted, provided there is at least one measurable lesion that has not been irradiated.
- NCI CTCAE Version 4.03 grade 3 hemorrhage within 4 weeks of starting the study treatment (Section 15.4).

- Any of the following within the 6 months prior to study drug administration: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack.
- Ongoing cardiac dysrhythmias of NCI CTCAE Version 4.03 grade ≥2. Controlled atrial fibrillation is permitted.
- Uncontrolled hypertension (>160/100 mm Hg despite optimal medical therapy)
- Concurrent treatment on another clinical trial. Supportive care trials or non-treatment trials, e.g. QOL, and imaging trials, are allowed.
- Pregnancy or breastfeeding. Female subjects must be surgically sterile or be postmenopausal, or must agree to use effective contraception during the period of therapy. All female subjects with reproductive potential must have a negative pregnancy test (serum) prior to enrollment. Male subjects must be surgically sterile or must agree to use effective contraception during the period of therapy. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, and in the judgment of the investigator would make the subject inappropriate for entry into this study.
- Uncontrolled CNS metastases. Patients are considered to have controlled CNS metastases (and thus eligible) if they have completed local therapy (XRT and/or surgery) and are off steroids with clinical and radiographic stability 1 month from the end of CNS-directed therapy.

3.3 Patient Registration

All patients will be screened by one of the principal investigators or sub-investigators prior to entry into this study. An explanation of the study and discussion of expected side effects and full disclosure of the “informed consent” document will take place. Eligible and consented patients will be registered into the study. No eligibility exceptions will be made.

To enter eligible patients on study, investigators register patients by contacting the Cleveland Clinic Lead Study Coordinator. In the event that the Lead Study Coordinator cannot be reached, the Database Manager may be contacted to register a patient. Contact information for these individuals is listed below. All patients will be registered in ONCORE. Overture will act as the data management system. Please refer to the calendar for collection details.

Title	**Name**	**Phone**	**E-mail**
Lead Study Coordinator	Jackie Tomer	216-444-9814	tomerj2@ccf.org
Database Mgr	Matthew Rump	(216) 444-9301	rumpm@ccf.org

4. STUDY CALENDAR

Required Investigations	Baseline (within 4 weeks prior to C1D1)	First Cycle (28 days)		Day 7 and 14 after each dose change (+/- 2 working days)	Each Cycle Day 1[3,5] (28 days +/- 3 working days)	Safety assessment[6] (Within 30 days after off treatment +/- 3 days)
		Day 7[1] (+/- 2 working days)	Day 14[1] (+/- 2 working days)			
History and Physical Exam	X				X[9]	
KPS and ECOG performance status	X				X	
Informed consent	X					
Assessment of Toxicity		X (phone call)	X (phone call)	X (phone call and/or clinic visit)	X	Assess for resolution of treatment-related toxicities within 30 days of last dose
CBC w/ differential, CMP, and LDH[7]	X				X	as clinically indicated
TSH, T3, T4	X				X[4]	as clinically indicated
Pregnancy Test[8]	X					
EKG	X					
Radiographic Assessment[2]	X				X[5]	
Patient diary (BP/dosing)	X----------X					

1 No dose escalation prior to day 14 of cycle 1

2 CTs (head, chest, abdomen, pelvis; with oral and IV contrast if possible) and bone scan required at baseline and must be done within 28 days of registration. MRI is allowed instead of CT head at baseline.. CT head will be done after baseline as clinically indicated. Follow-up scans are based on C1D1 date regardless of the date of baseline scans.

3 Beginning at C5D1 this column can be extended to every 2 cycles per provider discretion. Following C13D1 visit, this can be extended to every 12 weeks (i.e., 3 cycles)

4 Tests to be done at imaging timepoints points

5 After baseline, bone scan only if indicative of metastatic disease at baseline or if clinical signs/symptoms develop. CT Chest-Abdomen-Pelvis will be done every 8 weeks based on C1D1 date regardless of the date of baseline scans. Following Cycle 13 Day 1 assessment, CT scans to be done every 12 weeks. [Note: patients continuing axitinib post-PD will have CT c/a/p every 8 weeks and bone scans as needed per MD discretion]
Following Cycle 7 Day 1 disease assessment, bone scan to be done every 16 weeks per MD discretion (and every 24 weeks after C13 per MD discretion)

6 Treatment-related AE reporting ends at the time new treatment is started (see section9.6). After C13D1, all SAEs will be documented, AEs will be followed per SOC but not necessary to document for study-related purposes.

7 LDH at baseline only

8 Serum pregnancy test for women of childbearing potential. No childbearing potential defined as > 12 months of non-therapy-induced amenorrhea or surgically sterile.

9 Targeted physical exam per MD discretion when patient is in for a clinic visit
Protocol treatment should begin within 3 working days of patient registration.

5. DOSE-TITRATION SCHEMA

Dose Level	Dose	If grade 2 or greater toxicity during days 1-7[a]	If grade 2 or greater toxicity during days 8-14 [a]	If no grade 2 or greater toxicity after 14 days [a]
Dose reduction level 3	2 mg BID	Discuss with study sponsor	Hold axitinib if needed (e.g. 3 days) then resume at 2 mg BID with breaks as needed[c]	Stay on 2mg BID[c]
Dose reduction level 2	3 mg BID	Dose reduce to 2mg BID[b] (can hold axitinib prior to restarting per MD discretion)	Hold axitinib if needed (e.g. 3 days) then resume at 3 mg BID with breaks as needed[c]	Stay on 3mg BID[c]
Dose reduction level 1	4 mg BID	Dose reduce to 3mg BID[b] (can hold axitinib prior to restarting per MD discretion)	Hold axitinib if needed (e.g. 3 days) then resume at 4 mg BID with breaks as needed[c]	Stay on 4mg BID[c]
Starting dose level	**5 mg BID**	**Dose reduce to 4mg BID**[b] (can hold axitinib prior to restarting per MD discretion)	**Hold axitinib if needed (e.g. 3 days) then resume at 5 mg BID with breaks as needed**[c]	**Dose escalate to 6 mg BID**
Dose escalation level 1	6 mg BID	Dose reduce to 5mg BID[b] (can hold axitinib prior to restarting per MD discretion)	Hold axitinib if needed (e.g. 3 days) then resume at 6 mg BID with breaks as needed[c]	Dose escalate to 7 mg BID
Dose escalation level 2	7 mg BID	Dose reduce to 6mg BID[b] (can hold axitinib prior to restarting per MD discretion)	Hold axitinib if needed (e.g. 3 days) then resume at 7 mg BID with breaks as needed[c]	Dose escalate to 8 mg BID
Dose escalation level 3	8 mg BID	Dose reduce to 7mg BID[b] (can hold axitinib prior to restarting per MD discretion)	Hold axitinib if needed (e.g. 3 days) then resume at 8 mg BID with breaks as needed[c]	Dose escalate to 10 mg BID[d]
Dose escalation level 4	10 mg BID	Dose reduce to 8mg BID[b] (can hold axitinib prior to restarting per MD discretion)	Hold axitinib if needed (e.g. 3 days) then resume at 10 mg BID with breaks as needed[c]	Discuss dose escalation with sponsor

[a] Dosing modifications based only on the following grade 2 toxicities: oral mucositis, diarrhea, hand-foot syndrome, fatigue. Dose modifications for other axitinib-related AEs can be considered per study principal investigator.CTC v4 definitions of grade 2 toxicities:

Oral mucositis: Moderate pain; not interfering with oral intake; modified diet indicated

Diarrhea: Increase of 4 - 6 stools per day over baseline

HFS: Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL

Fatigue: Fatigue not relieved by rest; limiting instrumental ADL

[b] After dose reduction, re-escalation as tolerated may be considered per provider discretion

[c] Give break if needed (e.g. 3 days) when grade 2 or greater mucositis, diarrhea, HFS or fatigue develops. If patient consistently develops grade 2 or greater toxicity within 7 days on therapy after a break, consider dose reducing by one level

[d] Dose escalation to 9mg BID can be considered per provider discretion

6. TREATMENT PLAN

This prospective single arm study will evaluate the efficacy and safety of axitinib given on an individualized dosing schedule in subjects with metastatic clear cell RCC who have been treated with PD-1 and PD-L1 inhibitors. All subjects will be followed for Progression Free Survival (PFS), including patients who discontinue axitinib for toxicity.

6.1 Treatment schedule

The intent is to maximize sustained dose intensity of axitinib based on individual tolerability using the dose modification criteria described in Section 5. Dose and schedule changes are done if specific toxicity (oral mucositis, diarrhea, hand-foot syndrome, fatigue) is ≥ grade 2. Patients will initially continue therapy until progression according to RECIST criteria version 1.1 (Section 15.1). At progressive disease dose escalation above current dose is allowed based on investigator discretion of clinical benefit. However, axitinib should be discontinued if a second RECIST PD following dose escalation, patient intolerability, or at provider discretion.

6.2 Subject compliance and dropout

Patients must strictly follow the dosing schedule during each course as described by their treating investigator. Compliance to study medication and blood pressure records will be ascertained by use of patient diaries and pill count (Section 15.5). Patients will record the date, time and number of pills consumed in the diary on a daily basis. The patient diary should be reviewed with the patient for completion and to address any discrepancies or absent data. The principal investigator or the designee will account for the number of capsules dispensed against those returned by the subject. Any deviations and missed doses will be recorded in the CRF and drug accountability logs for verification with the reasons.

The investigator/designee will try to ensure complete compliance with the dosing schedule by providing timely instructions to the subjects. Patients withdrawn prior to completion of first course because of non-compliance not related to study drug related toxicity will be replaced. **Completed diary sheets must be submitted to CCF.**

6.3 Premature withdrawal/ discontinuation criteria

Patients may withdraw from the trial at any time, for any reason, at their own request. Patients may be withdrawn at any time at the discretion of the investigator or sponsor for concurrent illness, safety, behavioral, or other 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 and reason for withdrawal, if possible. The investigator should request the patient return all unused investigational product(s), request the patient to return for a final visit, if applicable and follow-up with the subject regarding any unresolved adverse events.

If the subject 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. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Patients will be withdrawn from treatment in the case of:

• Disease progression per RECIST v1.1. **Patients with initial disease progression are permitted and encouraged to stay on therapy with further axitinib upward dose titration (following the dose titration schema in Section 5) at MD discretion of clinical benefit until a second RECIST v1.1 PD.** Principal Investigator (Moshe Ornstein MD) & Cleveland Clinic Data Manager must be notified by email when a patient with disease progression will be continuing on study for clinical benefit.

• Unacceptable toxicity

• Need for anti-cancer therapy not specified in the protocol. Surgery to remove a metastasis or palliative radiotherapy is permitted after discussion with the Principal Investigator (Moshe Ornstein, MD).

• Patient noncompliance

• Patient lost to follow-up

• Patient choice to withdraw from treatment (follow-up permitted by patient)

• Patient choice to withdrawal consent to study (cessation of follow-up)

6.4 Concomitant Medications

The following medications/classes taken during the 15 days prior to Cycle 1 Day 1 and through Cycle 13 Day 1 must be recorded on the CRF.

a. All cardiac medications

b. CYP3A4 meds (specifically omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, dexamethasone, diltiazem, phenytoin, rifampin, St. Johns wort, carbamazepine, phenobarbatol, amobarbitol, primidone, rifabutin, felbamate, verapamil, grapefruit juice, ketoconazole, itraconazole, erthyromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, amprenavir, delavirdine and nefazodone)

c. Steroids (include dose)

d. Anti-diarrheals

6.4.1 Inhibitors and Inducers of CYP3A4

Axitinib is primarily metabolized in the liver by CYP3A4/5. [22] There was a 1.5- and 2-fold in C max and AUC∞, respectively when axitinib was co-administered with ketoconazole, a potent inhibitor of CYP3A4. Similarly, the C max and AUC∞ decreased 71% and 79%, respectively when co-administration of rifampin, a strong CYP3A4/5 inducer. Therefore, co-administration with potent inhibitors (ketoconazole, itraconazole, clarithromycin, diltiazem, delavirdine, indinavir, saquinavir, ritonavir, atazanavir, nelfinavir) and strong inducers (rifampin, rifabutin, carbamazepine, phenobarbital, phenytoin, St. John's wort, efavirenz, tipranavir) of CYP3A4 may result in significant increases/decreases in exposure of axitinib and may alter the safety/efficacy of the drug.

During the study, concurrent administration of potent CYP3A4 inhibitors and inducers (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole, dexamethasone, diltiazem, phenytoin, rifampin, St. Johns wort, carbamazepine, phenobarbatol, amobarbitol, primidone, rifabutin, felbamate, verapamil, grapefruit juice, ketoconazole, itraconazole, erthyromycin, clarithromycin, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, amprenavir, delavirdine and nefazodone) are not recommended.

Alternative therapies should be used when available.

6.4.2 Anticoagulants

The use of Coumarin-derivative anticoagulants such as warfarin (Coumadin) is not recommended.

6.4.3 Other Anticancer or Experimental Therapy

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

6.4.4 Antiemetic and Antidiarrheal Therapy

Supportive care may include premedication with antiemetics to limit treatment-related nausea and vomiting. Patients may receive prophylaxis of treatment-induced diarrhea.

6.4.5 Hematopoietic Growth Factors

Prophylactic use of hematopoietic growth factors to support neutrophil or platelet counts is not permitted during this study. Patients who enter the study on stable doses of erythropoietin or darbepoietin may continue this treatment, and patients may start either drug during the study at the discretion of the investigator. Patients with neutropenic fever or infection should be treated promptly and may receive therapeutic colony-stimulating factors if appropriate.

6.4.6 Other Concomitant Medications

Anti-inflammatory drugs should be avoided to preserve renal function but narcotic analgesics may be offered as needed. Packed red blood cell and platelet transfusions should be administered as clinically indicated.

Patients on this trial may be supported with appropriate hormone replacement therapy in the event they develop adrenal insufficiency in the absence of disease progression or unacceptable treatment-associated toxicity. Patients may receive bisphosphonates or denosumab for treatment of their bone metastases or hypercalcemia.

6.4.7 Concomitant Radiotherapy or Surgery

Palliative radiotherapy to specific sites of disease is permitted if considered medically necessary by the treating physician. Patients requiring radiotherapy will be considered to have disease progression, but may continue on axitinib if felt to be of clinical benefit per MD discretion. Axitinib treatment can continue during simple local radiation to metastatic bone lesions or briefly held at MD discretion. Axitinib should be held during radiotherapy that involves brain and spinal cord. The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate CRFs.

6.**5 Duration of follow-up**

Patients will be followed until they are removed from the clinical trial either due to progressive disease (PD) or other reasons as outlined in section 6.3. A subsequent safety assessment within 30 days (+/- 3 days) will be conducted as per study calendar in section 4. Duration of follow up of AEs and SAEs is listed in section 9.6.

Patients on therapy for more at least 12 months will only be followed for SAEs, imaging, tumor measurements, off-study date, and survival status.

7 INVESTIGATIONAL MEDICINAL PRODUCT

Study agent

Axitinib (AG013736; Inlyta) is a small molecule with the molecular formula $C_{22}H_{18}N_4OS$. It has a molecular mass of 386.469 g/mol. The chemical name of axitinib is *N*-Methyl-2-[[3-[(*E*)-2-pyridin-2-ylethenyl]-1*H*-indazol-6-yl]sulfanyl]benzamide

7.1 Drug supply

Axitinib will be supplied as 5mg and 1mg tabs by Pfizer, Inc.

7.2 Characterization of the Investigational medicinal product

Axitinib is available in red film-coated tablet form in 1mg and 5mg formulations. Patients will initially be given a 28-day supply of 5mg tablets (#56) and a 14-day supply of 1mg tablets (#28) to allow for easy dose titration or reduction during the initial cycle. For subsequent cycles, a sufficient quantity of 5mg and 1 mg tablets will be dispensed to allow for dose titration based on section 5.

Axitinib will be administered orally BID at approximately the same time in the morning and evening on a continuous dosing schedule, ie, without a break in dosing in the absence of drug-related toxicity. Axitinib tablets are to be taken approximately 12 hours apart and may be administered without regard to meals. Tablets must not be crushed, split, or dissolved, and patients should be instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing. A diary sheet will be provided to the patients to provide guidance for the correct use of axitinib (Section 15.5).

Patients must be instructed that if they miss a dose or vomit any time after taking a dose, they must not "make it up" with an extra dose, but instead resume subsequent doses as prescribed. Any missed dose may be taken late, up to 3 hours before the next scheduled dose of that day, otherwise, it should be skipped and dosing resumed with subsequent doses as prescribed. Patient must be instructed to record all doses (missed or vomited doses or extra doses) in a dosing diary supplied by the site. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

****ALL drug diary sheets must be submitted electronically (email) or faxed to Jackie Tomer (email: tomerj2@ccf.org; FAX: 216-636-6577 at the completion of each cycle of treatment.**

7.3 Packaging, labeling and dispatch of the Investigational medicinal product

Axitinib will be dispensed 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.

7.4 Stability and Storage

Axitinib must be stored at controlled room temperature of 20°C to 25°C (68°F to 77°F).

7.5 Accountability and Destruction of Investigational medicinal product

The Principal Investigator (or an authorized designee) at must maintain a careful record of the inventory of the Investigational medicinal product received using the Drug Accountability Form. The study drug will be destroyed as per site's destruction policies and documentation of study drug destruction will be provided to Cleveland Clinic.

7.6 Drug Administration

Study drug accountability records will be maintained at the site pharmacy and will be available for review by the study monitor during each monitoring visit and at the close out visit. All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

Patient returned medication should be retained on site for monitor verification prior to destruction as per the institution's policy.

8. MEASUREMENT OF DRUG EFFECT

8.1 Safety assessment

The adverse effects of the drug will be assessed starting at Cycle 1 Day 1 including adverse events, vital signs and by clinically significant changes in the laboratory evaluations and EKGs. Treatment-related AEs will be assess for 30 days following discontinuation of study drug therapy or until initiation of subsequent treatment, however documentation for study related purposes is only required through C13D1.

Adverse events (AE) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.03 for adverse event reporting.

8.2 Efficacy assessments

Patients must have measurable disease at screening and will be evaluated for response on the basis of RECIST criteria version 1.1 (Section 15.1). Tumor measurements using physical examination, spiral CT scan and/or MRI or other appropriate techniques deemed suitable by the investigator will be performed at screening within 28 days of patient registration and repeated every 8 weeks until disease progression. After baseline, bone scan only if indicative of metastatic disease at baseline or if clinical signs/symptoms develop. CT Chest-Abdomen-Pelvis will be done every 8 weeks based on C1D1 date regardless of the date of baseline scans. Following Cycle 13 Day 1 assessment, CT scans to be done every 12 weeks. Disease assessment with CT chest-abdomen-pelvis will continue every 8 weeks for patients continuing on treatment following disease progression (bone scans to be done per MD discretion). Scans can be done more frequently per MD discretion; these scans will be submitted on an unscheduled disease assessment CRF.

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9. SAFETY AND REPORTING REQUIREMENTS

9.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product during the course of a study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A laboratory test abnormality considered clinically relevant (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the Investigator should be reported as an adverse event.

9.2 Adverse Event Documentation

Adverse events will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.03 for adverse event reporting (Section 15.4).

All treatment-related adverse events (AE) and serious adverse events (SAEs) will be followed from the time first dose of study drug is administered and documented until resolution. Following C13D1, documentation is not needed for study related purposes.

Treatment-unrelated SAEs and all AEs will be followed from the time the first dose of study drug is administered and documented for 30 days, until resolution, or until a new therapy is started (whichever comes first).

All AEs must be recorded on case report forms (CRFs) through C13D1. Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

9.3 Serious Adverse Event

A Serious Adverse Event or Reaction is any AE occurring at any dose that:

• Results in death

• Is life-threatening

• Requires inpatient hospitalization or prolongation of existing hospitalization

• Results in persistent or significant disability/incapacity

• Is a congenital anomaly / birth defect

• Is an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not

result in hospitalization). Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the sponsor may be of interest for the overall conduct of the study.

Life-threatening: The term “life-threatening” in the definition of “serious” refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study or for prophylactic insertion of a gastric feeding tube).

OR

The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of ‘medically important’ and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.

Any death (regardless of cause) that occurs from the time of administration of the first dose of study therapy until 28 days after the final administration of the study drug, and any death occurring after this time that is judged at least possibly related to prior treatment with the study drug, will be promptly reported.

Adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03 (section 15.4).

9.4 Reporting Serious Adverse Events

All serious adverse events (SAE) and other adverse events must be recorded on case report forms.

SAEs should be reported to Pfizer using the Pfizer SAE form and cover page. SAE's should also be reported internally to individual institutions IRB per local IRB reporting policies and reported to the lead study coordinator by -email to Jackie Tomer at tomerj2@ccf.org or fax to 216-636-5677.

Serious adverse events should be documented and recorded at each visit using NCI CTCAE version 4.03 (section 15.4).

Drug-related SAEs from the time the first dose of study drug is administered will be followed and reported until resolution.

Drug-unrelated SAEs from the time the first dose of study drug is administered continue to be followed and documented for 30 days following discontinuation of study drug administration, initiation of subsequent treatment, or resolution (whichever comes first).

9.5 Procedure for Expedited Reporting

Responsibility for Reporting Serious Adverse Events to Pfizer

Each participating site will be responsible for submitting SAE (Initial and/or Follow-up reports) to Pfizer using the Pfizer's SAE cover form. The initial SAE form must be faxed to Pfizer and Cleveland Clinic within 24 hrs after the site is made aware of the SAE.

Reporting Serious Adverse Events to Local Research Ethics Boards

Cleveland Clinic will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities as reported to Pfizer. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their institutional review boards (IRBs) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to IRBs must be kept on file at each participating site.

Documentation can be any of the following:

• letter from the IRB acknowledging receipt

• stamp from the IRB, signed and dated by IRB chair, acknowledging receipt

• letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a center should also be reported to local IRBs.

9.6 Follow up of Adverse Events and Serious Adverse Events

Drug-related SAEs will be followed until resolution.

Drug-unrelated SAEs will be followed for 30 days following discontinuation of study drug administration, initiation of subsequent treatment, or resolution (whichever comes first).

9.7 Relationship

For all AEs, relationship to study drug will be reported on the appropriate AE CRF page. The PI must judge whether the study drug caused or contributed to the AE in which case it is considered to be an ADR, and report it as either:

Related (definitely, probably or possibly): there is a reasonable possibility that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:

- There is a plausible time sequence between onset of the AE and study drug administration;

- There is a plausible biological mechanism through which study drug may have caused or contributed to the AE;

Not related: It is highly unlikely or impossible that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related: an alternate etiology needs to be provided for the adverse event.

- another cause of the AE is evident and most plausible;
- the temporal sequence is inconsistent between the onset of the AE and study drug administration; a causal relationship is considered biologically implausible.

10. STATISTICAL ANALYSIS

10.1 Study design and justification for sample size

Study design: This is a single-arm, single-stage phase II study investigating the use of an individualized dosing regimen of axitinib in patients with metastatic renal cell carcinoma. The primary outcome for this study is progression-free survival (PFS), defined as the interval between the date a patient first receives axitinib and the date of death or confirmed progression according to RECIST criteria. Any patient alive and without known progression at the time of analysis will be censored as of the last date the patient can be confirmed to be progression-free. Secondary endpoints include overall survival, RECIST-based response, and adverse events defined and graded according to NCI CTCAE Version 4.03 criteria.

Sample size: 38 evaluable patients.

Justification for sample size: Based on prior studies patients treated with axitinib following anti PD-1 therapy for mRCC have a PFS of approximately 6.5 months.[19, 20] The hypothesis of this study is that with appropriate dose titration based on toxicities patients will reach a more optimal drug dose to increase benefit while minimizing risk. As such, we anticipate an approximately 45% increase in median PFS from 6.5 months to 9.5 months, which is felt to represent a clinically-meaningful improvement. Assuming accrual is fairly

uniform and will take approximately 18-24 months, there will be a minimum of 12 additional months of follow-up once the last patient has entered, and that PFS follows an exponential distribution (which is reasonable based on what has been seen historically in advanced RCC), 38 eligible and evaluable patients will be needed to test the above hypothesis with ≥80% power (based on a 1-sided MLE test with 10% type I error). Allowing for ineligible/unevaluable a total of 40 patients will be accrued.

A 20% rate of discontinuation due to toxicity will be considered unacceptable. If at any time >2/10, >4/20, or >6/30 patients need to be discontinued due to toxicity, consideration will be given to stopping the study. With these guidelines the likelihood of a boundary being crossed in the first 10 patients is 7% if the underlying risk is 10%, 32% if it is 20%, and 62% if the risk is 30%. The overall likelihoods of a boundary being crossed at some point are 10%, 53%, and 89%, respectively.

10.2 Study population

The study population will consist of all patients who are registered and receive at least one dose of axitinib. All efficacy and safety analyses will be conducted using the study population. Any patient who is registered on to this trial but never receives study treatment will be described, including the reason(s) for non-participation.

10.3 Statistical Anylysis

Data analysis will primarily be descriptive in nature, although as discussed above the underlying hypothesis that axitinib titration can improve PFS will be tested using a MLE test. Categorical data, such as adverse events and response rate, will be summarized using proportions and frequencies. Continuous endpoints, such as dose information will be summarized using medians and ranges, and PFS and overall survival will be summarized using the Kaplan-Meier method.

11. ETHICS

11.1 Informed Consent

Subject / Legally acceptable representative (LAR) (as applicable) consent must be obtained according to institutional review board (IRB) and/or ethics committee (EC) requirements prior to any study-specific screening procedures. Sample English consent forms for the trial will

be provided. A copy of the initial IRB/EC full board approval and approved consent form must be sent to Cleveland Clinic. The subject/LAR must sign consent prior to registration.

11.2 Institutional Review Board Approval

Initial approval: Full approval of the protocol and consent form by the appropriate IRB/EC must be obtained prior to commencement of the clinical trial.

Continuing approval: Annual (or as required by the IRB/EC re-approval may be required for as long as subjects are being followed on protocol. It will be investigator's responsibility to apply for and obtain the re-approval.

Amendment: All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the IRB/EC and health authorities. Amendments will be reviewed and approved by applicable regulatory authorities prior to central implementation of the amendment, and by IRB/ECs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or when the change(s) involves only logistical or administrative aspects of the trial.

Serious Adverse Events, Safety Updates and Investigator Brochure Updates: During the course of the study serious adverse events, safety updates or investigator brochure updates may be sent to you for reporting to your IRB/EC. If/when this occurs documentation of IRB/EC submission of this information must be forwarded to Cleveland Clinic.

12. DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

12.1 Documentation of subject's participation

A statement acknowledging the participation of a subject in this clinical trial must be documented in the subject's medical records.

12.2 Regulatory Requirements

The following are required from all investigators:

• Completion of CITI - Collaborative Institutional Training Initiative

• Completion of necessary IRB/EC training.

12.3 Subject Confidentiality

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by his/her initials. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts, tests will be made available to Pfizer, the Cleveland Clinic Taussig Cancer Institute, the IRB, and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital. A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

12.4 Confidentiality of the study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the IRB. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

12.5 Registration of Clinical Trial

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible

for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

12.6 Data reporting

The data will be collected on eCRFs in Overture and analyzed after entry into a study database.

12.7 Case Report Forms

The eCRFs for the study will be provided by Database Manager for Cleveland Clinic .

12.8 Maintenance of study records

To enable evaluations and/or audits from Regulatory Authorities, the Sponsor, and the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition. The Investigator should retain these records after study close-out as required by United States regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

13. QUALITY ASSURANCE AND QUALITY CONTROL

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.

13.1 On site Monitoring / Auditing

13.1 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the Center to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded,

analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements.

13.2 Data Safety and Monitoring Plan

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI regulations.

14. ADMINISTRATIVE PROCEDURES

14.1 Amendments to the protocol

Modifications of the signed protocol are only possible by approved protocol amendments authorized by the Sponsor. All protocol amendments will be approved by the IRB prior to implementation. The Investigator must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial subject or when the change(s) involves only logistical or administrative aspects of the trial.

14.2 Protocol deviations and Violations

All violations or deviations are to be reported to the site's IRB. All IRB correspondence is to be forwarded to Cleveland Clinic The site must notify Cleveland Clinic immediately of any protocol violations.

14.3 Premature discontinuation of the study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The IRB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. APPENDICES

15.1 RECIST 1.1 Criteria

The determination of antitumor efficacy during this study will be based on objective tumor assessments made according to the RECIST system of unidimensional evaluation.

Measurability of Tumor Lesions

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or non-measurable by the RECIST criteria as described below.

Measurable:

Tumor lesion: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm);
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

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

Non-Measurable: All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

NOTE: If measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total representative of all involved organs should be identified as **target lesions** and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesion with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter for all target lesions will be calculated and recorded as the baseline sum longest

diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment. All measurements should be performed using a caliper or ruler and should be recorded in metric notation in centimeters.

All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent."

Techniques for Assessing Measurable Disease

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical (physical) examination when both methods have been used to assess the antitumor effect of a treatment.

Definitions of Tumor Response

Target Lesions

Complete response (CR) is defined as the disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial response (PR) is defined as a ≥30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum longest dimensions.

Progressive disease (PD) is defined as a ≥20% increase in the sum of the longest dimensions of the target lesions taking as a reference the smallest sum of the longest dimensions recorded since the treatment started, or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable disease (SD) is defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as a reference the smallest sum of the longest dimensions since the treatment started.

Non-Target Lesions

Complete response (CR) is defined as the disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD is defined as a persistence of ≥1 non-target lesions.

Progressive disease (PD) is defined as unequivocal progression of existing non-target lesions, or the appearance of ≥1 new lesion.

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

Confirmation of Tumor Response

To be assigned a status of PR or CR, changes in tumor measurements in patients with responding tumors must be confirmed by repeat studies that should be performed ≥4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

Determination of Tumor Response by the RECIST Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. Determination of tumor response at each assessment is summarized in the following table.

Response Evaluation Criteria in Solid Tumors

Target Lesions[1]	Non-Target Lesions[2]	New Lesions[3]	Tumor Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any response	Yes or No	PD
Any response	PD	Yes or No	PD
Any response	Any response	Yes	PD

[1] Measurable lesions only.
[2] May include measurable lesions not followed as target lesions or non-measurable lesions.
[3] Measurable or non-measurable lesions.

15.2 ECOG PERFORMANCE STATUS SCALE

Performance Status	Definition
0	Fully active; no performance restrictions; can carry out all pre-disease activities
1	Restricted in strenuous activity. Fully ambulatory and able to carry out light work (light house work, office work, etc.)
2	Ambulatory and capable of all self-care but unable to perform any work activities. Up and ambulatory > 50% of the day.
3	Capable of only limited self-care; confined to bed/chair > 50% of the day
4	Completely disabled, cannot carry out self-care, totally confined to bed/chair
5	Dead

15.3 KARNOFSKY PERFORMANCE STATUS SCALE

Definition	Degree of Functional Capacity Criteria	Score
Able to carry on normal activity and to work; no special care needed	Normal, no complaints, no evidence of disease	100
	Able to carry on normal activity, minor signs or symptoms of disease	90
	Normal activity with effort, some signs or symptoms of disease	80
Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed	Cares for self, unable to carry on normal activity or to do active work	70
	Requires occasional assistance, but is able to care for most needs	60
	Requires considerable assistance and frequent medical care	50
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly	Disabled, requires special care and assistance	40
	Severely disabled, hospitalization is indicated although death is not imminent	30
	Hospitalization is necessary, very sick, active supportive treatment necessary	20
	Moribund, fatal processes progressing rapidly	10
	Dead	0

15.4 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

The NCI CTCAE (version 4.03, dated 14 June 2010) has been placed in the Study Reference Binder for this protocol. Alternatively, the NCI CTCAE may be reviewed online at the following NCI website:

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

15.5 BLOOD PRESSURE MEASUREMENT / STUDY DRUG DOSING

Name____ Patient # ___________________________ Study ID # _____________ Cycle # _______ Page # _____

Phase II Study of Axitinib Given on an Individualized Schedule for Metastatic RCC after Treatment with PD-1 or PD-L1 Inhibitors

BLOOD PRESSURE MEASUREMENT / STUDY DRUG DOSING

Instructions: While on Axitinib, measure and record your blood pressure **once a day, before your evening dose of Axitinib**.

If Axitinib is interrupted, please continue to measure and record your blood pressure once per day.

Please bring this completed diary with you to each clinic visit.

*If your systolic blood pressure (the top number) is above 150 **OR** if your diastolic blood pressure (the bottom number) is above 90, call ______________________________ at ______________________ for further instruction.

Blood Pressure Measurements						Axitinib Dosing	Side effects and medications you took to treat the side effects
Date	Time	Systolic (top number)	Diastolic (bottom number)	Was your systolic blood pressure above 150 or diastolic blood pressure above 90? *If yes, see above.		Write each dose below (3mg, 4mg, 5mg, 6mg, 7mg, 8mg, 10mg)	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	
	a.m.					AM dose: ______ mg	
	p.m.			☐Yes	☐No	PM dose: ______ mg	

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