SWOG CANCER RESEARCH NETWORK

Version Date: September 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Veronica Garcia, M.S., Protocol Coordinator II (E-mail: vgarcia@swog.org)

RE: **S1500**, "A Randomized, Phase II Efficacy Assessment of Multiple MET Kinase Inhibitors (Cabozantinib [NSC #761968], Crizotinib [NSC #749005], Savolitinib [NSC #785348], and Sunitinib [NSC #736511]) in Metastatic Papillary Renal Carcinoma (PAPMET)" Study Chairs: Drs. S. K. Pal and P. N. Lara, Jr.

REVISION #14

Study Chair: Sumanta K. Pal, M.D.
Phone number: 626/256-4673
E-mail: S1500question@swog.org

Protocol Changes
(√) Other: Addition of Translational Medicine Sub-study

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice

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REVISION #14

The above-referenced study has been updated as follows:

1. The Version date of the protocol and model consent were updated. No other changes were made to the model consent form.

2. Title Page: Dr. Brian Shuch's contact information was updated on the title page.

3. The Table of Contents was updated.

4. Section 1.3: Two translational medicine objectives were added to include the objectives of the "Identification and Characterization of Oncometabolite-Induced DNA Repair Defects in Sporadic Papillary Kidney Cancer" TM sub-study.

5. Appendix 18.0: The appendix was updated to include the TM study "Identification and Characterization of Oncometabolite-Induced DNA Repair Defects in Sporadic Papillary Kidney Cancer" as Appendix 18.4. Subsequent sections were re-numbered.

6. Appendix 18.4: The TM sub-study "Identification and Characterization of Oncometabolite-Induced DNA Repair Defects in Sporadic Papillary Kidney Cancer" was added.

cc: PROTOCOL AND INFORMATION OFFICE
Naomi Balzer – Haas, M.D. (ECOG/ACRIN)
Mark Stein, M.D. (ECOG/ACRIN)
Daniel J. George, M.D. (Alliance)
Daniel Heng, M.D., M.P.H., F.R.C.P.C (CCTG)

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activation Date 4/5/16

SWOG

A Randomized, Phase II Efficacy Assessment of Multiple MET Kinase Inhibitors (Cabozantinib [NSC #761968], Crizotinib [NSC #749005], Savolitinib [NSC #785348], and Sunitinib [NSC #736511]) in Metastatic Papillary Renal Carcinoma (PAPMET)

NCT#02761057

STUDY CHAIRS:

Principal Investigator:

Sumanta K. Pal, M.D. (Medical Oncology)
City of Hope Medical Center
Department of Medical Oncology
1500 E. Duarte Road
Duarte, CA 91010
Phone: 626/256-4673
FAX: 626/301-8233
E-mail: S1500question@swog.org

Primo N. Lara, Jr., M.D. (Medical Oncology)
UC Davis Cancer Center
4501 X Street
Sacramento, CA 95817
Phone: 916/734-3771
FAX: 916/734-7946
E-mail: S1500question@swog.org

ECOG/ACRIN STUDY CHAIR:
Naomi Balzer- Haas, M.D.
Abramson Cancer Center
3400 Spruce Street
Perelman Center for Advanced Medicine
South Pavilion 7th Floor
Philadelphia, PA 19104
Phone: 215/662-7615
FAX: 215/349-8550
E-mail: Naomi.Haas@uphs.upenn.edu

ALLIANCE STUDY CHAIR:
Daniel J. George, M.D.
Duke University Medical Center
Box 102002
Durham, NC 27710
Phone: 919/668-8650
FAX: 919/660-0178
E-mail: daniel.george@duke.edu

AGENTS:

NCI Supplied Agents (IND # 129330):

Cabozantinib (NSC #761968)
Crizotinib (NSC #749005)
Savolitinib (NSC #785348)
Sunitinib Malate (NSC #736511)

TRANSLATIONAL STUDY CO-CHAIR:

Brian Shuch, M.D. (Urology)
Institute of Urologic Oncology
Wasserman Bldg
300 Stein Plaza, Ste 368
Los Angeles, CA 90095
Phone: 310/206-8183
FAX: 310/794-3512
E-mail: bshuch@mednet.ucla.edu

ECOG/ACRIN TRANSLATIONAL STUDY CO-CHAIR:
Mark Stein, M.D. (Translational Medicine)
Rutgers Cancer Institute of New Jersey
195 Little Albany Street
New Brunswick, NJ 08903-2681
Phone: 732/235-6031
FAX: 732/235-6797
E-mail: mark.stein@rutgers.edu

BIOSTATISTICIANS:
Cathy M. Tangen, Dr.P.H. (Biostatistics)
Melissa Plets, M.S.
SWOG Statistics and Data Management Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/ 667-4623
FAX: 206/667-4408
E-mail: ctangen@fredhutch.org
E-mail: mplets@fredhutch.org

CCTG STUDY CHAMPION:

Daniel Heng, M.D. M.P.H. F.R.C.P.C.
Tom Baker Cancer Centre
ABC45, 1331-29 Street N.W.
Calgary, Alberta, Canada, T2N 4N2
Phone: 403/521-3166
Fax: 403/283-1651
E-mail: daniel.heng@albertahealthservices.ca

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG
CCTG/Canadian Cancer Trials Group

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Via the SWOG website (www.swog.org).

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

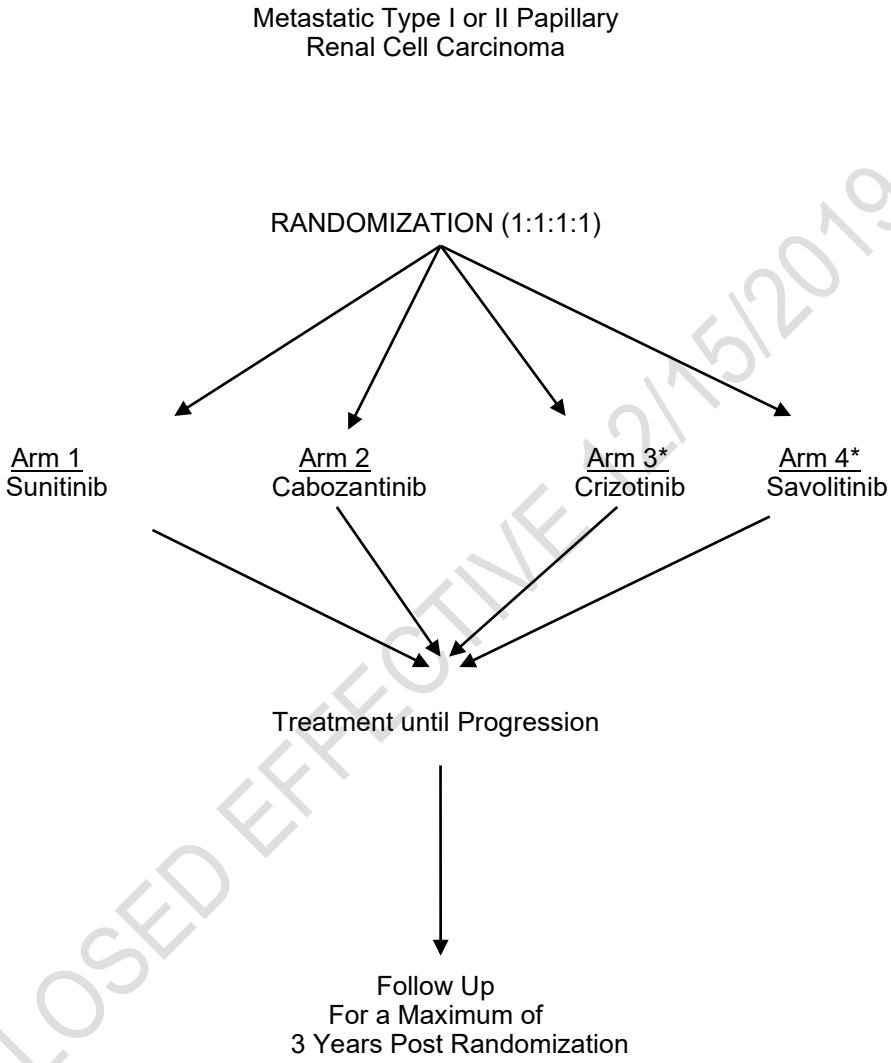
For patient eligibility or data submission questions contact the SWOG Data Operations Center by phone or email:
206/652-2267
guquestion@crab.org

For treatment or toxicity related questions contact the Study Chair by phone or email: (Dr. Sumanta K. Pal at 626/256-4673)

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

SCHEMA



* As of 12/05/18, patients will no longer be randomized to crizotinib or savolitinib based on findings from an interim analysis evaluating futility.

1.0 OBJECTIVES

In the current study, we will explore the hypothesis that inhibitors of MET kinase signaling will delay tumor growth in patients with metastatic papillary renal cell carcinoma (mPRCC) to a greater extent than standard of practice therapies such as the VEGFR inhibitor sunitinib.

1.1 Primary Objective

To compare progression-free survival (PFS) in patients with mPRCC treated with sunitinib to PFS in patients with mPRCC treated with MET kinase inhibitors.

1.2 Secondary Objectives

a. To compare RECIST response rate (RR; defined as the combined rate of confirmed and unconfirmed PR and confirmed and unconfirmed CR) in patients with mPRCC treated with sunitinib to RR in patients treated with putative MET inhibitors.

b. To compare overall survival (OS) in patients with mPRCC treated with sunitinib to OS in patients with mPRCC treated with putative MET inhibitors.

c. To compare the safety profile of sunitinib and putative MET inhibitors in patients with mPRCC.

1.3 Translational Objectives

a. To evaluate the prognostic and predictive value of MET mutations, MET copy number or other markers of MET signaling in patients with mPRCC treated with putative MET inhibitors.

b. To estimate the frequency of high oncometabolite levels in formalin-fixed, paraffin-embedded (FFPE) tissues of patients with advanced papillary renal cell carcinoma by liquid chromatography–mass spectrometry (LC-MS/MS) and estimate progression free survival for those with and without high oncometabolite levels being treated.

c. To correlate the mutational signature suggestive of a homologous recombination defect with high oncometabolite levels in patients with papillary renal cell carcinoma pRCC.

2.0 BACKGROUND

Overview of Papillary Renal Cell Carcinoma

Papillary renal cell carcinoma (pRCC) is the most prevalent form of non-clear cell renal cell carcinoma (RCC); there are between 6,000 – 9,000 cases per year and they represent about 10-15% of all cases of RCC. Males exceed females by approximately three-fold. *(1,2)* Most pRCCs are unilateral but pRCC is the most common multifocal or bilateral renal tumor. *(3)*

PRCC has been subdivided histologically into two distinct classes (type I and type II); as discussed subsequently, there appear also to be molecular features that distinguish them. A familial or hereditary form of pRCC has been described in type I patients that is characterized by development of multiple, bilateral papillary renal tumors and associated with heterozygous germline mutation in the MET proto-oncogene on chromosome 7q31. Somatic mutations in the MET gene have also been identified in up to 13% of papillary renal cell carcinomas. *(4)*

The Role of MET in Papillary Renal Cell Carcinoma

Recently, a great deal of attention has been focused on the status of MET signaling in pRCC. Over a decade ago, Sweeney et al. reported an analysis of MET expression in a series of 51 patients with pRCC. *(5)* Cytoplasmic expression of MET was seen in 80% of the tumors assessed, while membrane expression of MET was seen in 56%. A trend towards poorer survival with increased MET expression was noted in this series. A more recent tissue microarray based study including a total of 330 human RCC specimens suggested that MET expression was highest in papillary and sarcomatoid subtypes of RCC (compared to clear cell, although both clear and non-clear cell RCC expressed higher MET levels than adjacent kidney parenchyma) and, similarly, that increased MET expression was associated with poorer survival. *(6)*

In what is perhaps the most detailed assessment of MET aberrations to date, Albiges et al. assessed a series of 220 frozen tissues derived from patients with sporadic pRCC in the French RCC Network. *(7)* Gene expression was assessed in 98 of these specimens, and ultimately suggested high MET expression level across all patients with pRCC. Notably, assessment of copy number pointed to the importance of MET in both type I and type II pRCC; specifically, 81% to patients with type I pRCC had copy number alterations, as compared to 46% in type II pRCC. Somatic mutations of the MET gene were identified in 11/51 (21.6%) of type I pRCC samples examined.

A preliminary report from the TCGA Kidney Renal Papillary Working Group described the comprehensive molecular characterization of 161 primary pRCC (75 type I, 60 type II and 26 unclassified). In addition to MET somatic (9.3%) and germline (1.9%) mutations, two in-frame translocations involving the MET gene (fusion partners BAIAP2L1 and C8orf34) were described. An alternate MET RNA splicing isoform that codes for a shortened stable form of MET protein was also observed. This new splice variant may represent a mechanism of ligand-independent MET activation. These MET alterations were mutually exclusive and occurred predominantly in Type I pRCC tumor samples. The previously recognized correlation between increased MET copy number and elevated MET expression was confirmed. The study highlighted the diverse alterations leading to MET activation in pRCC and raised the question of molecular genotype and response to MET inhibitors.

Current Treatment Standards for Advanced Papillary Renal Cell Carcinoma

There is no FDA-approved standard of care for the treatment of either subtype of mPRCC. Several efforts have been made to characterize the activity of vascular endothelial growth factor (VEGF)-directed therapies in this setting (Table 1). A single-institution retrospective analysis suggested a low response rate (RR) with sunitinib, but an appreciable progression-free survival (PFS) of 11.9 months. *(8)* Subsequent prospective studies have suggested a more modest PFS in association with sunitinib – for instance, Ravaud et al. reported a PFS of 6.6 months and 5.5 months in a series of 61 patients with type I and type II mPRCC, respectively. *(9)* Tannir et al. examined a smaller series of mPRCC patients (n=27), with a sobering PFS of 2.7 months. *(10)*

Table 1. Studies evaluating sunitinib in mPRCC.

Agent	N	Source	Key Descriptors/Findings
Sunitinib	53	Choueiri et al. (J Clin Oncol 2008)	• Retrospective analysis • Histology: Papillary/Chromophobe • 41 pts with papillary • Median PFS of 7.6 mos in papillary • RR of 5% in papillary

Sunitinib	57	Tannir et al. (Eur Urol 2012)	• Histology: Non-clear cell • 27 pts with papillary • Median PFS 1.6 mos in papillary • RR 0% in papillary
Sunitinib	61	Ravaud et al. (Ann Oncol 2012) (SUPAP)	• Histology: Papillary • RR 13%/11% in Type 1/2 • PFS 6.6/5.5 mos in Type 1/2

Approximately 20% of patients enrolled on the pivotal Phase III assessment of temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, did possess non-clear cell histology. *(11)*

Consistent with findings for the overall study population, subset analyses from this study suggested that patients with non-clear cell histology derived greater benefit with respect to OS. *(12)* Other than this, scant prospective data are available to document the activity of mTOR inhibitors in mPRCC. One Phase II study reported by Koh et al. included 29 patients, with an associated RR and PFS of 7% and 5.2 months, respectively. *(13)*

Some comparative data can be gained from the RECORD-3 trial, which compared the sequence of sunitinib and everolimus and vice versa. *(14)* Among patients with non-clear cell disease (n=64), first-line PFS with sunitinib in non-clear cell patients appeared to be slightly higher (7.23 months versus 5.09 months; HR 1.54, 95%CI 0.86-2.75). In the recently reported ESPN study, a heterogeneous mix of patients with non-clear cell disease was randomized to receive either sunitinib or everolimus. *(15)* In this study, median PFS with 1st-line sunitinib was 6.1 months as compared to 4.1 months with everolimus (P=0.25).

Given these data, moving forward, sunitinib is considered the preferred comparator in studies assessing novel targeted agents in pRCC. It is for this reason that we have proposed a randomized, Phase II design, with individual comparisons of experimental agents to sunitinib.

<u>A Potential Role for MET Inhibitors in Papillary Renal Cell Carcinoma</u>

As noted, there is no standard of care for treating mPRCC – the bulk of data accumulated thus far is from retrospective analyses or from small prospective Phase II trials evaluating either VEGF/VEGFR-directed therapies or mTOR inhibitors. Because of the discouraging results noted in many of these efforts, investigators have been pursuing therapeutic avenues that better reflect the biology of the disease. For instance, targeting MET signaling in type I mPRCC is a rational strategy based on increased MET expression and frequently observed aberrations in MET. In one series of 51 patients with pRCC, cytoplasmic and membrane expression of MET was noted in 80% and 56% of specimens, respectively, and was associated with poor prognosis. *(16)* In a larger series of RCC patients (n=330), MET expression was significantly higher in patients with pRCC, and was again associated with poorer survival. *(17)*

There are multiple MET inhibitors currently in clinical development by different pharmaceutical companies and it is not clear which of these is the most efficacious. The current trial would explore type I (MET-specific) and type II (multi-kinase) small molecule MET inhibitors that are at varying stages of clinical development. While the approach of separate Phase II evaluations could be considered, having a randomized Phase II trial incorporating the full spectrum of therapies with a common comparator arm would allow for more efficient evaluation of these agents. Careful inferences could be made about comparative efficacy and toxicity and facilitate selection of appropriate agents for subsequent monotherapy Phase III testing or combination therapy. Given the rather small proportion of patients with mPRCC (roughly 10-15% of the mRCC population), the “umbrella” platform design proposed herein is considered to be optimal.

Choueiri et al. recently reported a Phase II assessment of the multikinase inhibitor foretinib in patients with pRCC. *(18)* Foretinib has substantial activity against MET, as well as VEGFR, RON, AXL and Tie-2. *(19)* Among 57 evaluable patients, RR was 13.5% and median PFS was 9.3 months. The RR was significantly higher in patients bearing germline mutations in MET (5 of 10, or 50%) as compared to those without (5 of 57, or 9%). Notably, the mutations were relatively infrequent.

Dr. Pal, the Study Chair of the current proposal, was one of several investigators involved with a Phase I study evaluating cabozantinib in metastatic clear cell RCC. *(20)* This dual inhibitor of VEGFR2 and MET displayed significant activity in a heavily-pretreated patient population – amongst 25 patients, 17 patients (64%) had received 2 or more prior lines of therapy. The overall RR was 28%, with a median PFS of 14.7 months. Although this study included patients with clear cell disease, the high activity demonstrated in this experience suggests a potential synergy between targeting VEGF and MET simultaneously. Several other putative MET inhibitors are currently in clinical development; their status in overall clinical development and in pRCC is noted in Table 2.

Table 2. Current status of MET and HGF inhibitors.

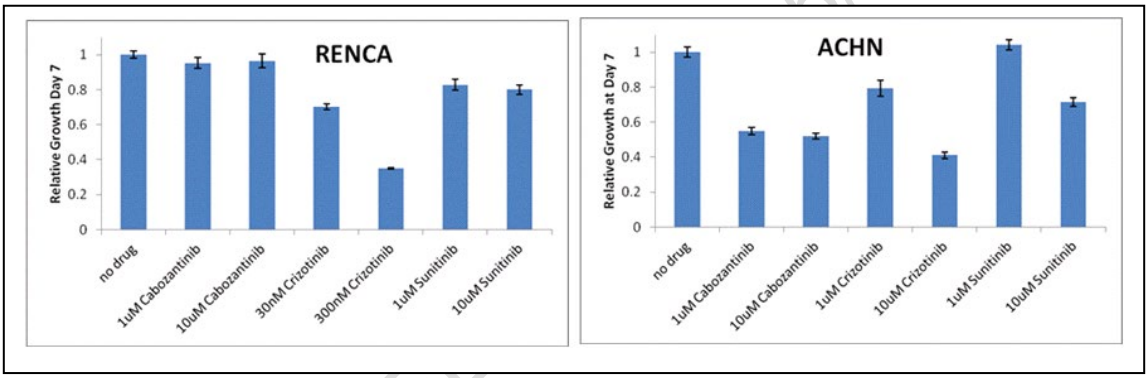
Manufacturer	Compound	Status	Status in pRCC
			•
Amgen	AMG-337	Phase I, II (Gastric)	• No data available
Astra-Zeneca	Savolitinib (HMPL-504)	Phase I/II (PRCC)	• Preclinical in vitro activity- pRCC cell lines, Schuller et al; CCR 2015
Eisai	Golvatinib (E7050)	Phase III (Melanoma) Phase I/II (Hepatocellular)	• No data available
EMD-Serono	EMD1214063	Phase I	• No data available
Exelixis	Cabozantinib (XL184)	Approved (Medullary thyroid cancer) Phase III METEOR trial in RCC	• Activity in ACHN pRCC cell line*
Novartis	INCB28060	Phase I	• No data available
Lilly	LY2801653	Phase I	• No data available
Pfizer	Crizotinib	Phase III (NSCLC)	• Approved for ALK+ NSCLC • Activity in ACHN pRCC cell line* • Multi-histology Phase II (including mPRCC) underway (NCT01524926)
Sanofi-Aventis	SAR155844	Phase I	• No data available
Janssen	J&J38877605	Phase I	• No data available
GSK	Foretinib	Phase II	• Phase II data in pRCC available (Choueiri et al. J Clin Oncol 2010)
Mirati	MGCD265	Phase II	• No data available

Deciphera	Altiranib	Phase I	• No data available
Abbvie	ABT700	Phase I	• No data available
Pieris	PRS110	Preclinical	• No data available
Aveo	Ficlatuzumab	Phase I	• No data available
Amgen	Rilotumumab	Phase III (Gastric)	• No data available
Takeda	TAK-701	Phase I	• No data available

Source: http://www.clinicaltrials.gov **and *Jeremy Jones, PhD (City of Hope).**

As noted, the preponderance of agents have little data to date in pRCC. However, Jeremy Jones, Ph.D. (City of Hope) has performed some preliminary assessments of cytotoxicity in the RENCA (clear cell) and ACHN (papillary) cell line using sunitinib, cabozantinib and crizotinib:

Figure 1 Cytotoxicity with cabozantinib and crizotinib in ACHN and RENCA cell lines.



At physiologic concentrations, it appears that both cabozantinib and crizotinib exhibit significant cytotoxicity in the ACHN cell line. Interestingly, the activity of cabozantinib (which is currently being explored in a Phase III study in clear cell mRCC) appears to be higher in the papillary model examined as compared to the clear cell model (RENCA). Dr. Jones is currently working to develop xenografts bearing ACHN tumors for further examination of these compounds.

Schuller and colleagues reported on the anti-tumor efficacy and pharmacodynamics of a type I (specific) MET inhibitor Savolitinib against two patient xenograft derived pRCC cell line models with MET amplification. Savolitinib induced tumor regressions in vivo in both cell lines at clinically relevant concentrations. The investigators also demonstrated inhibition of MET activation (pMET) and activation of apoptotic signaling in tumors that regressed. Savolitinib was superior to sunitinib, which had limited anti-tumor activity in these two pRCC models.

As these experiments demonstrate, MET inhibition holds promise as a therapeutic strategy for mPRCC. Furthermore, there is no shortage of MET inhibitors available for clinical examination. As previously noted, an independent examination of these MET inhibitors in pRCC would be highly inefficient, requiring high number of patients derived from a relatively small population. Furthermore, if multiple agents showed activity, it would be challenging to decide upon the optimal treatment without randomized data – again requiring substantial numbers of patients and extensive resources.

Inclusion of Women and Minorities

This study was designed to include women and minorities but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	2	0	0	2
Asian	2	2	0	1	5
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	7	14	2	2	25
White	46	86	5	11	148
More Than One Race	0	0	0	0	0
Total	55	104	7	14	180

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study cabozantinib, crizotinib, savolitinib and sunitinib are considered investigational and are being provided under an IND held by the National Cancer Institute. Investigator Brochure Availability: The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email (ibcoordinator@mail.nih.gov).

3.1 Cabozantinib s-malate (XL-184, EXEL-7184, EXEL-02977184, Cometriq®) (NSC #761968) (IND #129330)

a. PHARMACOLOGY

Mechanism of Action: XL-184 (cabozantinib) inhibits several receptor tyrosine kinases (RTKs). Activated RTKs stimulate various intracellular signaling pathways that lead to cell survival and/or proliferation, tumor growth, angiogenesis and metastasis. Cabozantinib inhibits the following RTKs; RET; met proto-oncogene encoding hepatocyte growth factor (c-MET); vascular endothelial growth factor receptors (VEGFR)-1, VEGFR-2, and VEGFR-3; stem cell factor receptor (c-Kit); tropomyosin receptor kinase B (trkB); fms-like tyrosine kinase 3 (Flt-3); AXL; ROS1, RON and TIE-2.

b. PHARMACOKINETICS

1. Absorption: Following oral administration, the median time to peak plasma concentrations (Tmax) ranged from 2 to 5 hours post-dose. Area

under the concentration-time curve (AUC) indicated that daily administration of 140 mg cabozantinib for 19 days resulted in 4-fold to 5-fold mean cabozantinib accumulation compared to single-dose administration. Steady-state concentrations of the drug were achieved in 15 days. In healthy individuals, administration of a single 140 mg oral dose of the drug followed by a high-fat meal increased the peak plasma concentration and AUC of cabozantinib by 41 and 57%, respectively, compared to fasted conditions.

2. Distribution: Cabozantinib is highly bound to plasma proteins (≥99.7%). The oral volume of distribution (V/F) is approximately 349 L.

3. Metabolism: Cabozantinib is metabolized in the liver by cytochrome P-450 (CYP) isoenzyme 3A4. In vitro studies showed that cabozantinib malate is a substrate of CYP3A4, is an inducer of CYP1A1 mRNA, a mixed-type inhibitor of both CYP2C9 and CYP2C19 and a noncompetitive inhibitor of CYP2C8. However when a single-dose rosiglitazone was coadministered with cabozantinib at steady state, the plasma exposure (Cmax and AUC) of rosiglitazone (a CYP2C8 substrate) was unaffected. Inhibition of CYP2C9 had minimal effects on cabozantinib metabolite formation (i.e., less than a 20% reduction). In vitro studies showed that cabozantinib malate is an inhibitor of P-glycoprotein (P-gp) transport activities and may increase the plasma levels of P-gp substrates. The XL184 N-oxide metabolite forms via CYP3A4 isoenzymes. In vitro studies showed that inhibition of CYP3A4 reduced the formation of the XL184 N-oxide metabolite by more than 80%. Inhibition of CYP isoenzymes 1A2, 2A6, 2B6, 2C8, 2C19, 2D6, and 2E1 had no effect on cabozantinib metabolite formation.

4. Elimination: Healthy individuals were administered a single dose of radiolabeled cabozantinib, approximately 81% of the total administered radioactivity was recovered (54% in feces and 27% in urine) within 48 days. The total body cabozantinib clearance is estimated to be 4.4 L/hr at steady state. The study did not identify clinically relevant differences in cabozantinib clearance based on gender, age, race or the presence of mild to moderate renal impairment (CrCl 30 mL/min or greater). The elimination half-life of cabozantinib is approximately 55 hours.

c. ADVERSE EFFECTS

1. Adverse Effects:
The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 3219 patients. Below is the CAEPR for XL184 (Cabozantinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE

listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4., December 17, 2018[1]

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
INFECTIONS AND INFESTATIONS			
	Infection[5]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lipase increased		***Lipase increased (Gr 4)***

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Platelet count decreased		***Platelet count decreased (Gr 3)***
Weight loss			***Weight loss (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hypophosphatemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Generalized muscle weakness		
	Muscle cramp		
		Osteonecrosis of jaw	
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
		Reversible posterior leukoencephalopathy syndrome	
		Stroke	
		Transient ischemic attacks	
RENAL AND URINARY DISORDERS			
	Hematuria		
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
		Pneumothorax[6]	

Adverse Events with Possible Relationship to XL184 (Cabozantinib) (CTCAE 5.0 Term) [n= 3219]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Respiratory fistula[7]	
	Respiratory hemorrhage[8]		
	Voice alteration		***Voice alteration (Gr 3)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
	Dry skin		***Dry skin (Gr 2)***
	Hair color changes		***Hair color changes (Gr 1)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event[9]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[6]Pneumothorax has been observed at a higher than expected frequency (15-20%) in a study treating patients with relapsed Ewing sarcoma and osteosarcoma all of whom had pulmonary metastases.

[7]Respiratory fistula includes Bronchial fistula, Bronchopleural fistula, Laryngeal fistula, Pharyngeal fistula, Pulmonary fistula, and Tracheal fistula under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Hemoptysis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[9]Thromboembolic event includes pulmonary embolism which may be life-threatening.

Adverse events reported on XL184 (Cabozantinib) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that XL184 (Cabozantinib) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Eosinophilia; Febrile neutropenia; Hemolytic uremic syndrome
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (hypokinetic cardiomyopathy); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Myocarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Vertigo
ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (thyroiditis); Endocrine disorders - Other (thyrotoxicosis); Hyperthyroidism; Hypopituitarism
EYE DISORDERS - Blurred vision; Cataract; Eye disorders - Other (corneal epithelium defect)
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal fissure; Anal mucositis; Anal pain; Anal ulcer; Cheilitis; Colitis; Colonic obstruction; Duodenal ulcer; Dysphagia; Enterocolitis; Esophageal ulcer; Esophagitis; Flatulence; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (pneumoperitoneum); Gastrointestinal pain; Gingival pain; Hemorrhoids; Ileus; Pancreatitis; Periodontal disease; Rectal pain; Rectal ulcer; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema face; Fever; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (implant site inflammation); Hypothermia; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Budd-Chiari syndrome; Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (cholelithiasis); Hepatobiliary disorders - Other (hepatic cirrhosis); Hepatobiliary disorders - Other (hepatic thrombus); Hepatobiliary disorders - Other (hepatitis toxic); Hepatobiliary disorders - Other (hepatorenal syndrome); Portal vein thrombosis

IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Autoimmune disorder

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (post procedural hemorrhage); Injury, poisoning and procedural complications - Other (tendon injury); Wound dehiscence; Wrist fracture

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Investigations - Other (D-dimer); Investigations - Other (urine ketone body present); Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Thyroid stimulating hormone increased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Glucose intolerance; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Buttock pain; Chest wall pain; Flank pain; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle hemorrhage); Myalgia; Neck pain; Osteonecrosis; Osteoporosis; Rhabdomyolysis

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lip and/or oral cavity cancer); Tumor hemorrhage; Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Concentration impairment; Dysarthria; Dysesthesia; Dysphasia; Encephalopathy; Lethargy; Memory impairment; Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (vocal cord paralysis); Peripheral motor neuropathy; Peripheral sensory neuropathy; Presyncope; Seizure; Somnolence; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Depression; Hallucinations; Insomnia; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Glucosuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain; Reproductive system and breast disorders - Other (scrotal ulcer/erythema/edema); Scrotal pain; Vaginal fistula; Vaginal inflammation; Vaginal perforation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Aspiration; Atelectasis; Hoarseness; Hypoxia; Laryngeal edema; Oropharyngeal pain; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and

mediastinal disorders - Other (nasal septum perforation); Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (rales); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Nail changes; Pain of skin; Pruritus; Rash acneiform; Skin and subcutaneous tissue disorders - Other (pain, sloughing of skin and erythema); Skin and subcutaneous tissue disorders - Other (psoriasis); Skin hypopigmentation; Skin ulceration
VASCULAR DISORDERS - Hematoma; Hypotension; Superior vena cava syndrome; Vascular disorders - Other (bleeding varicose vein); Vasculitis

Note: XL184 (Cabozantinib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. Cabozantinib can cause fetal harm if administered to a pregnant woman. In animal reproduction studies, exposure below the recommended human dose were found to be embryolethal and resulted in increased incidences of skeletal and visceral variations and malformations.

   Lactation studies have not yet been performed with cabozantinib malate. It is unknown whether cabozatinib malate or its metabolites are excreted in human milk. The potential benefits of drug treatment against potential risks need to weighed before prescribing this drug during breastfeeding. The manufacturer recommends discontinuing nursing or discontinuing drug, depending upon the importance of the drug to the mother. As many drugs are excreted in human milk and there is a potential for adverse effects in the nursing infant.

3. Drug Interactions:

   CYP450 isozymes: Cabozantinib is a substrate of CYP3A4, potential inhibitor of P-glycoprotein transport activity, substrate of drug transporter MRP2, highly protein bound and may interfere with other agents or patients that have a history of QT prolongation. Due to potential drug interactions, a complete patient medication list including cabozantinib, should be screened prior to initiation of and during treatment with cabozanitinib. See Appendix 18.2.

d. DOSING & ADMINISTRATION

1. See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

1. Cabozantinib is supplied by Exelixis and will be distributed by DCTD/NCI.

2. Cabozantinib is available in 20 mg and 60 mg tablets. The tablets are yellow film-coated containing cabozantinib malate equivalent to 20 mg and 60 mg of cabozantanib. The 20 mg tablets have a round shape and the 60 mg tablets have an oval shape, and they are packaged as 30 per bottle. Inactive ingredients include: microcrystalline cellulose, lactose anhydrous,

hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, and opadry yellow film coating (HPMC 2910/hypromellose 6 cp, titanium dioxide, tracetin, iron oxide yellow).

f. STORAGE, PREPARATION & STABILITY

1. Store intact bottles at controlled room temperature, 20° to 25°C (68° F to 77°F); temperature excursions are permitted between 15°C and 30° (59°F to 86°F) [see USP Controlled Room Temperature].

   If a storage temperature excursion is identified, promptly return XL184 (Cabozantinib) to 20° to 25°C (68° to 77°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. Sites and subjects are advised to dispense cabozantinib in its original container. Cabozantinib tablets can be dispensed in a pill cup with an expiration date not to exceed 24 hours. It can also be repackaged in a HDPE prescription bottle with expiration date not to exceed 7 days. Labeling should be done in accordance to the law and contain the statement "CAUTION: NEW DRUG – LIMITED BY FEDERAL LAW TO INVESTIGATIONAL USE".

3. Stability: Stability testing of the intact bottles is on-going.

3.2 Crizotinib (Xalkori®, PF-02341066) (NSC # 749005) (IND #129330)

a. PHARMACOLOGY

Mechanism of Action: Crizotinib is an inhibitor of receptor tyrosine kinases including ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 (c-ros), and Recepteur d'Origine Nantais (RON). Translocations can affect the ALK gene resulting in the expression of oncogenic fusion proteins. The formation of ALK fusion proteins results in activation and dysregulation of the gene's expression and signaling which can contribute to increased cell proliferation and survival in tumors expressing these proteins. Crizotinib demonstrated concentration-dependent inhibition of ALK, ROS1, and c-Met phosphorylation in cell-based assays using tumor cell lines and demonstrated antitumor activity in mice bearing tumor xenografts that expressed EML4- or NPM-ALK fusion proteins or c-Met.

b. PHARMACOKINETICS

1. Absorption: Crizotinib levels peak in 4-6 hours. High-fat meals decrease AUC_{inf} and C_{max} by 14%. Crizotinib may be administered with or without food.

2. Distribution: Approximately 91% protein bound in healthy subjects.

3. Metabolism: Predominantly metabolized by CYP3A4/5. Crizotinib is also a P-glycoprotein substrate.

4. Elimination: Crizotinib is eliminated in both the feces and urine. Single dose crizotinib has a half-life of approximately 42 hours. Multiple dosing results in autoinhibition and decreased mean apparent clearance.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2058 patients. Below is the CAEPR for crizotinib (PF-02341066).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, October 30, 2018[1]

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
CARDIAC DISORDERS			
		Heart failure	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
		Testosterone deficiency	
EYE DISORDERS			
Eye disorders - Other (vision disorders)[2]			***Eye disorders - Other (vision disorders)[2] (Gr 2)***
Periorbital edema			***Periorbital edema (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colonic perforation	

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Esophageal ulcer	
		Esophagitis	
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema face			***Edema face (Gr 2)***
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Generalized edema			***Generalized edema (Gr 2)***
Localized edema			***Localized edema (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (hepatotoxicity)	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
		Blood bilirubin increased	
	Creatinine increased		
		Electrocardiogr	

Adverse Events with Possible Relationship to Crizotinib (PF-02341066) (CTCAE 5.0 Term) [n= 2058]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		am QT corrected interval prolonged	
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		
	Nervous system disorders - Other (neuropathy)[3]		***Nervous system disorders - Other (neuropathy)[3] (Gr 2)***
		Syncope	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal cyst)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash[4]		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

pio@ctep.nci.nih.gov. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Vision disorders may include the following: Chromatopsia, Diplopia, Halo vision, Photophobia, Photopsia, Vision blurred, Visual acuity reduced, Visual brightness, Visual impairment, Vitreous floaters, and Visual perseveration.

[3] Neuropathy may include the following: Acute polyneuropathy, Amyotrophy, Areflexia, Autoimmune neuropathy, Autonomic failure syndrome, Autonomic neuropathy, Axonal neuropathy, Biopsy peripheral nerve abnormal, Burning feet syndrome, Burning sensation, Decreased vibratory sense, Demyelinating polyneuropathy, Dysesthesia, Electromyogram abnormal, Formication, Gait disturbance, Genital hypoesthesia, Guillain-Barre syndrome, Hyperesthesia, Hypoesthesia, Hyporeflexia, Hypotonia, Ischemic neuropathy, Loss of proprioception, Miller Fisher syndrome, Mononeuritis, Mononeuropathy, Mononeuropathy multiplex, Motor dysfunction, Multifocal motor neuropathy, Muscle atrophy, Muscular weakness, Myelopathy, Nerve conduction studies abnormal, Nerve degeneration, Neuralgia, Neuritis, Neuromuscular toxicity, Neuromyopathy, Neuropathy peripheral, Neuropathy vitamin B6 deficiency, Neurotoxicity, Paresthesia, Peripheral motor neuropathy, Peripheral nerve lesion, Peripheral nerve palsy, Peripheral nervous system function test abnormal, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Peroneal muscular atrophy, Peroneal nerve palsy, Phrenic nerve paralysis, Polyneuropathy, Polyneuropathy chronic, Polyneuropathy idiopathic progressive, Radiation neuropathy, Sensorimotor disorder, Sensory disturbance, Sensory loss, Skin burning sensation, Temperature perception test decreased, Tinel's sign, Toxic neuropathy, and Ulnar neuritis.

[4] Treatment-related rash may include erythematous rash, rash maculo-papular, and pruritus.

Adverse events reported on crizotinib (PF-02341066) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that crizotinib (PF-02341066) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (basophilia); Disseminated intravascular coagulation; Eosinophilia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Myocarditis; Pericardial effusion; Supraventricular tachycardia
EYE DISORDERS - Cataract; Optic nerve disorder; Papilledema
GASTROINTESTINAL DISORDERS - Colitis; Dysphagia; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal amyloidosis); Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; General disorders and administration site conditions - Other (failure to thrive); Malaise; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatitis)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder
INFECTIONS AND INFESTATIONS - Abdominal infection; Infections and infestations - Other (peridiverticular abscess); Kidney infection; Lung infection; Sepsis; Skin infection; Urinary tract infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (traumatic lung injury); Spinal fracture; Wound complication
INVESTIGATIONS - Blood lactate dehydrogenase increased; CPK increased; GGT increased; Investigations - Other (monocyte count increased); Investigations - Other (platelet count increased); Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Musculoskeletal and connective tissue disorder - Other (myopathy); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Ischemia cerebrovascular; Pyramidal tract syndrome; Seizure; Stroke
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS - Pregnancy loss
PSYCHIATRIC DISORDERS - Confusion; Delirium; Euphoria
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Renal calculi; Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pneumomediastinum); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hematoma; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

Note: Crizotinib (PF-02341066) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. Crizotinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Advise women of childbearing potential to avoid becoming pregnant while receiving crizotinib. It is not known if crizotinib is excreted in human milk.

3. Drug Interactions: Crizotinib is primarily metabolized by CYP 3A4/5 with minor contributions from CYP2C8, CYP2C19, and CYP2D6. Avoid concomitant use of strong CYP3A inhibitors and inducers. Use of potent CYP3A inducers should be avoided for at least 12 days prior to the first dose of crizotinib. Use of strong CYP3A inhibitors should be avoided for at least 7 days prior to the first dose of crizotinib. Exercise caution with concomitant use of moderate CYP3A inhibitors. Crizotinib moderately inhibits CYP3A4 in a time-dependent fashion. Use caution with patients who receive CYP3A4 substrates with a narrow therapeutic index. Crizotinib is an inhibitor of CYP2B6 in vitro. Use caution with coadministered drugs that are predominantly metabolized by CYP2B6.
Studies demonstrate that crizotinib is a substrate of P-gp and a weak BCRP inhibitor, however the potential to cause drug-drug interactions at therapeutic doses is low. Crizotinib inhibited P-gp, OCT1, and OCT2 in vitro at clinically relevant concentrations. Use caution with coadministration of P-gp, OCT1, and OCT2 substrates.

   Due to potential drug interactions, a complete patient medication list, including crizotinib, should be screened prior to initiation of and during treatment with crizotinib. See Appendix 18.2.

d. DOSING & ADMINISTRATION

   See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

   1. Crizotinib is supplied by Pfizer and will be distributed by DCTD/NCI.

   2. Crizotinib is supplied as 200 mg (size 1, white opaque body and pink opaque cap, with “Pfizer” on the cap and “CRZ 200” on the body) and 250 mg (size 0, pink opaque body and cap, with “Pfizer” on the cap and “CRZ 250 on the body) hard gelatin capsules. Each bottle contains 60 capsules.

      Excipients include colloidal silicon dioxide, microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, and hard gelatin capsule shells as inactive ingredients. The pink opaque capsule shell components contain gelatin, titanium dioxide, and red iron oxide. The white opaque capsule shell components contain gelatin, and titanium dioxide. The printing ink contains shellac, propylene glycol, strong ammonia solution, potassium hydroxide, and black iron oxide.

f. STORAGE, PREPARATION & STABILITY

   1. Store at room temperature 20° to 25° C (68°F - 77°F), excursions permitted between 15 to 30°C (59 to 85°F).

      If a storage temperature excursion is identified, promptly return crizotinib to between 15 and 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

   2. Stability: Shelf life is consistent with commercially-labeled product.

3.3 Savolitinib (AZD6094, Volitinib) (NSC #785348) (IND #129330)

a. PHARMACOLOGY

Mechanism of Action: AZD6094 is a potent and selective small molecule cMet kinase inhibitor, with IC50 of 3 to 5 nM for cMet kinase inhibition at enzyme and anti-tumour cell levels. Consistent with its potent enzyme and cell activity, AZD6094 was found to inhibit cell growth in vitro against tumours with cMet amplification in the absence of HGF-stimulation with IC50s generally below 10 nM. It also potently inhibited HGF-stimulated cell proliferation against tumours with cMet overexpression or carrying a HGF/cMet autocrine loop. In human xenograft mice models, AZD6094 demonstrated excellent anti-tumour activity against cMet gene amplified gastric and lung tumours following once daily treatment. In tumours with both cMet and epidermal growth factor receptor (EGFR) overexpression, it was found that combination of AZD6094 with erlotinib, an EGFR inhibitor, was more effective than either agent alone.

b. PHARMACOKINETICS

Preliminary pharmacokinetic (PK) data are included from Study D5081C00001.

Preliminary single and multiple dose PK data are available following dosing with 100 mg, 20 0mg, 400 mg, 600 mg and 800 mg. Following administration of single doses, exposure was typified by absorption with a Tmax of approximately 1.0-2.7 hours followed by an elimination phase. The terminal half-life (t1/2) ranged from 3.6-6.8 hours, consistent with achieving steady state by Day 3 of treatment. The dose-normalized exposure (Cmax and AUC) of AZD6094 after single doses, indicated that exposure may not be dose-proportional over the range of 100 to 800 mg but the moderate variability observed may have influenced this conclusion. The oral clearance (CL/F) ranged from 27-48 L/h and volume of distribution (Vz/F) ranged from 219-322 L.

Following multiple doses, Tmax occurred at a range of 1.3-2.7 hours, which is similar to that observed after a single dose followed by elimination which was generally consistent with the early elimination after single doses. There appeared to be no trend for accumulation of AZD6094; RAC values were approximately 1, and consistent with a relatively short t1/2. Overall the multiple dose PK was consistent with the single dose data. The AUCss exposure on Day 21 indicated that exposure may not be dose-proportional over the range of 100 to 800 mg but the moderate variability observed may have influenced this conclusion.

The main metabolites M2 and M3 were rapidly formed following oral administration of the parent drug resulting in a Tmax range from 1.2-3.8hr. The relationship between dose and Cmax and AUC displayed nonlinear traits, which was supportive of observations made with the parent compound. Plasma profiles after multiple dosing were similar for each individual after single and multiple dosing, such that subjects with low M2 or M3 levels on day 1 also showed low levels at steady state. The mean T1/2 for M2 and M3 was in a similar range and was variable within cohorts, ranging from 5.5 –16.1hr.

c. ADVERSE EFFECTS

1. The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a

separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 259 patients.* Below is the CAEPR for AZD6094 (savolitinib; volitinib).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, April 2, 2020[1]

Adverse Events with Possible Relationship to Savolitinib (AZD6094) (CTCAE 5.0 Term) [n= 381]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Edema limbs			***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatotoxicity)[2]		
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		

Adverse Events with Possible Relationship to Savolitinib (AZD6094) (CTCAE 5.0 Term) [n= 381]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Creatinine increased		
		Electrocardiogram QT corrected interval prolonged	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Stevens-Johnson syndrome	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Hepatoxicity may manifest as increased liver enzymes (e.g., Alanine aminotransferase increased, Aspartate aminotransferase increased, Alkaline phosphatase increased, Blood bilirubin increased), hepatic function abnormal, and drug-induced liver injury (DILI).

Adverse events reported on savolitinib (AZD6094) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that savolitinib (AZD6094) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia
CARDIAC DISORDERS - Heart failure
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Eye disorders - Other (diplopia)
GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (abdominal incarcerated hernia); Gastrointestinal disorders - Other (GI [anastomotic] perforation); Ileus; Mucositis oral; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Generalized edema; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic pain; Hepatobiliary disorders - Other (hepatic encephalopathy); Hepatobiliary disorders - Other

(hepatomegaly); Hepatobiliary disorders - Other (cholestasis); Hepatobiliary disorders - Other (hepatic lesion)
INFECTIONS AND INFESTATIONS - Abdominal infection; Conjunctivitis; Fungemia; Lung infection; Sepsis; Upper respiratory infection; Urinary tract infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Injury, poisoning and procedural complications - Other (craniocerebral injury)
INVESTIGATIONS - GGT increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoglycemia; Hypokalemia; Hyponatremia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Flank pain; Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression)
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia; Headache; Spinal cord compression
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Renal and urinary disorders - Other (urine albumin/creatinine ratio increased)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Dyspnea; Hypoxia; Pleural effusion; Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Photosensitivity; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Thromboembolic event

Note: Savolitinib (AZD6094) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Females of childbearing potential should use reliable methods of contraception from the time of screening until 3 months after discontinuing study treatment.

Acceptable methods of contraception include abstinence, tubal ligation, combined oral, transdermal or intra-vaginal hormonal contraceptives, medroxyprogesterone injections (e.g. Depo-provera), copper-banded intra-uterine devices, hormone impregnated intra-uterine systems and vasectomised partners. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse.

Male patients must use a condom during sexual intercourse with all sexual partners including a pregnant female partner during the study and for 4 weeks after discontinuing study treatment. However, where a sexual partner of a male participant is a woman of childbearing potential who is not using effective contraception, men must use a condom during sexual intercourse during the study and for 6 months after discontinuing study treatment.

Male patients should avoid procreation during the trial and for 6 months after discontinuing study treatment.

Male patients should refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment.

3. Potential Drug Interactions: According to in vitro studies, savolitinib (AZD6094) is primarily metabolized by CYP 3A4/5 and 1A2 and some NADPH-independent non-CYP enzymes. Avoid administration of strong CYP 3A4/5 and 1A2 inducers and inhibitors within 2 weeks of starting and during savolitinib (AZD6094) study treatment. Savolitinib (AZD6094) is not a P-glycoprotein (P-gp) substrate.

   In vitro, savolitinib (AZD6094) and its metabolites weakly and reversibly inhibited CYP450 1A2, 2C8, 2C9, 2D6 and 3A4/5 isoforms and UGT1A1. A drug interaction with substrates of CYP2C8/9 and/or CYP3A4/5 or UGT1A1 may occur when savolitinib (AZD6094) is dosed at the maximum tolerated dose. Use caution in patients who are taking concomitant medications whose clearance is exclusively dependent on CYP2C8, CYP2C9, CYP3A4/5 or UGT1A1 because exposure of the concomitant medication may be increased. Since there is limited clinical experience with this agent, patients on concomitant drugs with narrow therapeutic ranges, such as warfarin, should be monitored closely.

   Studies indicate that savolitinib (AZD6094) has little induction potential for major CYP isoforms.

   In vitro studies demonstrate that savolitinib (AZD6094) and its major metabolite inhibit a number of drug transporters to varying degrees. The manufacturer cautions that when administered at clinically relevant doses, savolitinib (AZD6094) has the potential to inhibit P-gp, BCRP (breast cancer resistance protein), OATP1B1, MATE1 and MATE2K. Therefore, co-administration of substrates that are dependent on these drug transporter systems should be used with caution. The potential for drug-drug interaction is considered unlikely when co-administering substrates of OATP1B3, OAT1, OAT3 or OCT2

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Astra Zeneca supplies and CTEP, NCI, DCTD distributes savolitinib ((AZD6094) as coated tablets. Bottles are secured with a child-resistant closure; induction-sealed membranes provide tamper evidence. Savolitinib (AZD6094) tablets are supplied in 24-count HDPE bottles containing desiccant in the following strength and description:

- 200 mg yellow, plain, oval (7.25 x 14.5 mm)

Savolitinib (AZD6094) tablets consist of drug substance, microcrystalline cellulose, mannitol, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, black iron oxide, yellow iron oxide and red iron oxide.

f. STORAGE AND STABILITY

1. Store the AZD6094 tablets at controlled room temperature (20°-25°C). Brief excursions are permitted between 15°C and 30°C.

2. Stability studies are ongoing. The manufacturer does not have stability information to support repackaging tablets. Dispense in the original container.

If a storage temperature excursion is identified, promptly return AZD6094 to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

3.4 Sunitinib Malate (Sutent®; SU011248 L-Malate salt; SU010398; PHA-290940AD; SU011248) (NSC 736511) (IND #129330)

a. PHARMACOLOGY

Mechanism of Action: Sunitinib inhibits several receptor tyrosine kinases (RTKs), including platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). RTKs are involved in tumor growth, angiogenesis and metastasis.

b. PHARMACOKINETICS

1. Absorption: Maximum plasma concentrations (C_{max}) of sunitinib are between 6 and 12 hours (T_{max}) following oral administration. In the dosing range of 25-100 mg, the area under the plasma concentration-time curve (AUC) and C_{max} increase proportionately with dose. Food has no effect on the bioavailability of sunitinib.

2. Distribution: Binding of sunitinib and its primary active metabolite to human plasma protein *in vitro* was 95% and 90%, respectively, with no concentration dependence in the range of 100 – 4000 ng/mL. The volume of distribution (Vd/F) is 2230 L.

3. Metabolism: Sunitinib is metabolized primarily by the cytochrome P450 enzyme, CYP3A4, to produce its primary active metabolite, which is further metabolized by CYP3A4. The primary active metabolite comprises 23 to 37% of the total exposure.

4. Elimination: Elimination is primarily via feces. In a human mass balance study of [14C] sunitinib, 61% of the dose was eliminated in feces, with renal elimination accounting for 16% of the administered dose. Sunitinib and its primary active metabolite were the major drug-related compounds identified in plasma, urine, and feces, representing 91.5%, 86.4% and 73.8% of radioactivity in pooled samples, respectively. Minor metabolites were identified in urine and feces but generally not found in plasma. Total oral clearance (CL/F) ranged from 34 to 62 L/hr with an inter-patient variability of 40%. Following administration of a single oral dose in healthy volunteers, the terminal half-lives of sunitinib and its primary active metabolite are approximately 40 to 60 hours and 80 to 110 hours,

respectively. With repeated daily administration, sunitinib accumulates 3- to 4-fold while the primary metabolite accumulates 7- to 10-fold. Steady-state concentrations of sunitinib and its primary active metabolite are achieved within 10 to 14 days. By Day 14, combined plasma concentrations of sunitinib and its active metabolite ranged from 62.9 – 101 ng/mL. No significant changes in the pharmacokinetics of sunitinib or the primary active metabolite were observed with repeated daily administration or with repeated cycles in the dosing regimens tested.

c. ADVERSE EFFECTS

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 7115 patients. Below is the CAEPR for Sunitinib malate (SU011248 L-malate).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.14, February 15, 2019[1]

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Heart failure	
		Left ventricular systolic dysfunction	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Myocardial infarction	
ENDOCRINE DISORDERS			
		Endocrine disorders - Other (thyroiditis)	
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 2)***
EYE DISORDERS			
		Eye disorders - Other (macular edema)	***Eye disorders - Other (macular edema) (Gr 2)***
	Papilledema		***Papilledema (Gr 2)***
		Vision decreased	***Vision decreased (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal distension		***Abdominal distension (Gr 2)***
Abdominal pain			***Abdominal pain (Gr 3)***
Anal mucositis			***Anal mucositis (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
Dyspepsia			***Dyspepsia (Gr 2)***
		Esophagitis	
	Flatulence		***Flatulence (Gr 2)***
	Gastritis		***Gastritis (Gr 2)***
	Gastroesophageal reflux disease		
		Gastrointestinal perforation[2]	
Mucositis oral			***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Oral pain		***Oral pain (Gr 2)***
		Pancreatitis	
Rectal mucositis			***Rectal mucositis (Gr 2)***
Small intestinal mucositis			***Small intestinal mucositis (Gr 2)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Flu like symptoms		
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 2)***
HEPATOBILIARY DISORDERS			
		Cholecystitis	
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (necrotizing fasciitis)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	CPK increased		
	Creatinine increased		***Creatinine increased (Gr 3)***
		Electrocardiogram QT corrected interval prolonged	
	Lipase increased		***Lipase increased (Gr 4)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Serum amylase		***Serum amylase increased***

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	increased		***(Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperuricemia		***Hyperuricemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		
		Hypoglycemia	
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (fistula formation)	
	Myalgia		***Myalgia (Gr 2)***
		Osteonecrosis of jaw	
	Pain in extremity		***Pain in extremity (Gr 2)***
		Rhabdomyolysis	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
Dysgeusia			***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 3)***
		Leukoencephalopathy	
		Nervous system	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		disorders - Other (cerebral infarction)	
	Paresthesia		
		Reversible posterior leukoencephalopathy syndrome	
		Transient ischemic attacks	
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Nephrotic syndrome	
		Proteinuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		***Epistaxis (Gr 2)***
Laryngeal mucositis			***Laryngeal mucositis (Gr 2)***
Pharyngeal mucositis			***Pharyngeal mucositis (Gr 2)***
Tracheal mucositis			***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Dry skin		***Dry skin (Gr 2)***
		Erythema multiforme	
	Hair color changes		***Hair color changes (Gr 2)***
Palmar-plantar erythrodysesthesia syndrome			***Palmar-plantar erythrodysesthesia syndrome (Gr 3)***
	Pruritus		
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (pyoderma gangrenosum)	

Adverse Events with Possible Relationship to Sunitinib malate (SU011248 L-malate) (CTCAE 5.0 Term) [n= 7115]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
	Hypertension		***Hypertension (Gr 3)***
		Thromboembolic event	
	Vascular disorders - Other (hemorrhage)[4]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[3]Allergic reactions observed include anaphylaxis and angioedema.

[4]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI tract, GU system, respiratory tract, nervous system [including fatal intracranial hemorrhage, and cerebrovascular accident], and tumor site) have been reported.

Adverse events reported on Sunitinib malate (SU011248 L-malate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Sunitinib malate (SU011248 L-malate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Pericardial effusion
GASTROINTESTINAL DISORDERS - Ascites; Dysphagia; Gastrointestinal disorders - Other (enteritis); Hemorrhoids; Ileus; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Pain
INVESTIGATIONS - GGT increased; INR increased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain
NERVOUS SYSTEM DISORDERS - Cognitive disturbance; Peripheral sensory neuropathy; Seizure; Spinal cord compression; Syncope
PSYCHIATRIC DISORDERS - Anxiety; Confusion
RENAL AND URINARY DISORDERS - Hematuria; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Hematosalpinx
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleural effusion; Pneumothorax
VASCULAR DISORDERS - Flushing; Hypotension

Note: Sunitinib malate (SU011248 L-malate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. Sunitinib can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of Sunitinib should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic and fetotoxic.

   Sunitinib and its metabolites are excreted in rat milk. It is not known whether this drug or its primary active metabolite are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from sunitinib, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.

3. Drug Interactions: Sunitinib is metabolized primarily by liver enzymes, particularly CYP3A4. Due to potential drug interactions, a complete patient medication list, including sunitinib, should be screened prior to initiation of and during treatment with sunitinib. See Appendix 18.2.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Sunitinib malate capsules are supplied by Pfizer, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Capsules are packaged in 28-count bottles with mannitol, croscarmellose sodium, povidone (K-25) and magnesium stearate as inactive ingredients in the following strengths:

- 12.5 mg hard gelatin capsule (size 4) with orange cap and orange body, printed with white ink "Pfizer" on the cap and "STN 12.5 mg" on the body.

- 25 mg hard gelatin capsule (size 3) with caramel cap and orange body, printed with white ink "Pfizer" on the cap and "STN 25 mg" on the body.
- 50 mg hard gelatin capsule (size 2) with caramel top and caramel body, printed with white ink "Pfizer" on the cap and "STN 50 mg" on the body.

Orange gelatin capsule shells contain titanium dioxide, and red iron oxide. Caramel gelatin capsule shells contain titanium dioxide, red iron oxide, yellow iron oxide and black iron oxide. White printing ink contains shellac, propylene glycol, sodium hydroxide, povidone and titanium dioxide.

f. STORAGE AND STABILITY

1. Store at 25˚C (77°F); excursions permitted to 15°-30°C (59°-86°F).

   If a storage temperature excursion is identified, promptly return sunitinib malate to between 15 and 30°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

2. Stability: Shelf life is consistent with commercially-labeled product.

3.5 Drug Ordering, Accountability and Returns

Agent ordering: NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number **S1500** must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution. Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

a. Starter supply is not allowed. Patient must be first assigned to a treatment arm before ordering agent

b. Agent Accountability

1. The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record Form (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

2. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

c. Drug Returns

1. All unused drug supplies should be recovered to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

2. Drug expiration: Indicate drug expiration date on the DARF under Manufacturer and Lot # or follow institutional procedures. Use the drug lots with shorter expiration date first.

d. Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

3.6 Drug Information Useful Links and Contacts

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
  PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

4.0 STAGING CRITERIA

This section is not applicable to this study.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at guquestion@crab.org or 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have histologically or cytologically confirmed papillary histology renal cell carcinoma which is metastatic or locally advanced disease not amenable to surgical resection. (NOTE: A designation of type I or type II should be made by the local pathologist if possible.) Mixed histologies containing type I

or type II will be allowed provided that they contain ≥ 50% of the papillary component.

b. Patients must also have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (see Section 10.1). Disease X-rays, scans or physical examinations used for tumor measurement must have been completed within 28 days prior to registration. If there is clinical suspicion for bone metastases at the time of enrollment (at the discretion of the investigator), bone scan should be performed at baseline (within 42 days prior to registration). All disease must be assessed and documented on the Baseline Tumor Assessment Form.

c. Patients with a history of treated brain metastases who are asymptomatic and have not received steroid therapy in the 14 days prior to registration are eligible. Anti-seizure medications are allowed provided they are non-enzyme inducing (e.g. topiramate, levatiracetam, gabapentin).

d. Patients must not have cavitating pulmonary lesions. Patients must not have tumor invading the GI tract or evidence of endotracheal or endobronchial tumor within 28 days prior to registration.

5.2 Prior/Concurrent Therapy Criteria

a. Patients may have received prior surgery. At least 28 days must have elapsed since surgery and patient must have recovered from any adverse effects of surgery.

b. Patients may have received up to one prior systemic therapy for advanced or metastatic renal cell carcinoma with the exception of another VEGF inhibitor FDA-approved for advanced RCC (i.e., pazopanib, bevacizumab, sorafenib or axitinib). If a patient develops metastatic disease within six months of discontinuation of adjuvant therapy, this will constitute one prior systemic therapy for advanced or metastatic RCC. If a patient develops metastatic disease and more than six months has elapsed since discontinuation of adjuvant therapy, this will not constitute prior systemic therapy for advanced or metastatic RCC. Patients may have also received prior immunotherapy. Patients must not have received a MET/HGF inhibitor or sunitinib as prior therapy. At least 14 days must have elapsed since completion of prior systemic therapy. Patients must have recovered from all associated toxicities at the time of registration.

c. Patients may have received prior radiation therapy, but must have measurable disease outside the radiation port. At least 14 days must have elapsed since completion of prior radiation therapy. Patients must have recovered from all associated toxicities at the time of registration.

d. Patients must not be taking, nor plan to take while on protocol treatment, strong CYP3A4 inhibitors (e.g. boceprevir, cobicistat, danoprevir, elvitegravir/RIT, fluvoxamine, indinavir, itraconazole, ketoconazole, lopinavir/RIT, nefazodone, nelfinavir, posaconazole, ritonavir, telaprevir, telithromycin, tipravavir/RIT, or voriconazole,); strong CYP3A4 inducers (e.g. avasimibe, phenytoin, rifampin, rifabutin); potent inhibitors of CYP1A2 (e.g. ciprofloxacin); and/or drugs known to be CYP3A4 substrates with a narrow therapeutic range (e.g., diergotamine, ergotamine) within 14 days prior to randomization. (Moderate inhibitors or inducers of isoenzyme CYP3A4 should be avoided, but if necessary can be used with caution (see Section 18.2).

e. Patients must not be receiving or planning to receive any other investigational agents.

5.3 Clinical/Laboratory Criteria

a. Patients must have a complete physical examination and medical history within 28 days prior to registration.

b. Patients must have a Zubrod performance status of 0 - 1 (see Section 10.4).

c. Patients must have adequate hematologic function as documented by a WBC ≥ 2,000/mcL, an ANC ≥ 1,000/mcL, and a platelet count ≥ 75,000/mcL. These tests must be obtained within 28 days prior to registration.

d. Patients must have adequate hepatic function as evidenced by serum bilirubin ≤ 1.5 x institutional upper limits of normal (ULN). Serum transaminase (SGOT/AST and SGPT/ALT) must be ≤ 2.5 x the institutional ULN unless the liver is involved with the tumor, in which case serum transaminase (SGOT/SGPT) must be ≤ 5 x the institutional ULN. These tests must be obtained within 28 days prior to registration.

e. Serum creatinine must be ≤ 2 x the institutional ULN OR creatinine clearance (either measured or calculated) must be > 30 mL/min and obtained within 28 days prior to registration.

f. Patients must not have any clinical evidence of congestive heart failure (CHF) (specifically, New York Heart Association [NYHA] Class III [moderate] or Class IV [severe]) at the time of registration. Baseline echocardiogram within 28 days of registration must demonstrate an EF ≥ 50%. Due to the potential cardiac toxicity of the agents utilized in this protocol, patients must have QTc interval < 500 msec on prestudy EKG and no known history of congenital long QT syndrome. Patients must not have experienced unstable angina pectoris, clinically significant cardiac arrhythmias, or stroke (TIA or other ischemic event) within 3 months prior to registration and not have experienced myocardial infarction or thromboembolic event requiring anticoagulation within 6 months of registration. Prestudy EKG must be obtained within 28 days prior to registration.

g. Baseline urinalysis should show urine protein < 3+ and must be obtained within 28 days prior to registration. If urine protein is 3+ or greater, then urine protein by 24 hour collection must show less than 3 grams of protein.

h. Patients must not have inadequately controlled hypertension. Patients must have documented blood pressures of SBP < 150 and DBP < 90 within 14 days of starting randomization. Blood pressure medications (any number) are permitted.

i. Patients must be able to take oral medications (i.e., swallow pills whole). Patients must not have gastrointestinal tract disease resulting in an inability to take oral medication or a requirement for IV alimentation, prior surgical procedures that could in the opinion of the treating investigator affect absorption, or active peptic ulcer disease. Patients with intractable nausea or vomiting are not eligible.

j. Patients must not have had any clinically-significant GI bleeding within 6 months prior to registration and patients must not have a GI disorder which (at the discretion of the investigator) bears a high risk of perforation or fistula. Examples of this include (but are not limited to) Crohn's disease or tumor with transmural extension through the gastrointestinal lining.

k. Patients must not have had hemoptysis of ≥ 0.5 teaspoon (2.5 ml) of red blood within 3 months prior registration.

l. Patients must not demonstrate any other signs indicative of pulmonary hemorrhage within 3 months prior to registration.

m. Patient's baseline imaging must not indicate the presence of tumor invading or encasing any major blood vessels.

n. Patients must not have any unresolved wounds from previous surgery.

o. Albumin, alkaline phosphatase, bicarbonate, BUN, chloride, glucose, phosphorus, and total protein must be assessed within 28 days of registration.

p. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for 3 years. Men receiving active surveillance for prostate cancer may also be enrolled.

q. Due to the unknown effects of the study drugs, patients must not be pregnant or nursing. Women/men of reproductive potential must have agreed to use an effective contraceptive method while receiving study drug and for three months after last dose of study drug. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

r. HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cabozantinib, crizotinib, savolitinib or sunitinib. In addition these patients are at increased risk of lethal infections when treated with marrow suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

s. Patients must be ≥ 18 years of age.

5.4 Specimen Submission Criteria

a. Patients must have tissue available and be willing to submit for independent pathologic review in order to classify type I versus type II papillary disease (see Section 12.0).

b. Patients must be offered the opportunity to participate in specimen banking for future translational medicine studies (see Section 15.0).

5.5 Regulatory Criteria

a. Patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.2) for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be randomized in a 1:1:1:1 allocation using a dynamic balancing algorithm *(20)* with stratification based on:

a. Predominant pRCC histologic subtype: type I versus type II versus Not Otherwise Specified (NOS).

b. Prior treatment (see Section 5.2b): 0 vs. 1 line of systemic therapy.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Sumanta K. Pal or Dr. Primo Lara at S1500question@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

7.1 Pre-Medication

No pre-medications are required for sunitinib, crizotinib, savolitinib or cabozantinib.

7.2 Treatment

Patients will be randomized to either Arm 1: sunitinib, Arm 2: cabozantinib, Arm 3: crizotinib or Arm 4: savolitinib. NOTE: All treatments are administered in the outpatient setting. **As of 12/5/18, patients will only be randomized to Arm 1: sunitinib or Arm 2: cabozantinib.**

It is recommended that the patient be provided with the Patient Drug Information Handout and Wallet Card (see Section 18.3a-d).

a. Treatment schedule for Arm 1: sunitinib.

AGENT	DOSE	ROUTE	DAYS	INTERVAL	DURATION
Sunitinib*	50 mg	Oral	1-42	Daily on Days 1-28 Hold Days 29-42	See Section 7.6

* Sunitinib can be taken with or without food.

b. Treatment schedule for Arm 2: cabozantinib.

AGENT	DOSE	ROUTE	DAYS	INTERVAL	DURATION
Cabozantinib*	60 mg	Oral	1-42	Daily	See Section 7.6

* Cabozantinib must be taken on an empty stomach (i.e., patient must not eat within 2 hours before or 1 hour after each dose). Cabozantinib must not be crushed or chewed. Do not take a missed dose within 12 hours of the next dose. Avoid grapefruit, grapefruit juice, and Seville oranges.

c. Treatment schedule for Arm 3: crizotinib **(Treatment arm closed to accrual 12/5/18).**

AGENT	DOSE	ROUTE	DAYS	INTERVAL	DURATION
Crizotinib*	250 mg per dose (500 mg total daily dose)	Oral	1-42	Twice daily	See Section 7.6

* Crizotinib can be taken with or without food.

d. Treatment schedule for Arm 4: savolitinib **(Treatment arm closed to accrual 12/5/18).**

AGENT	DOSE	ROUTE	DAYS	INTERVAL	DURATION
Savolitinib*	600 mg	Oral	1-42	Daily	See Section 7.6

* Savolitinib must be taken with food (specifically, within 1 hour after the start of a meal). Tablet must be swallowed whole with water.

NOTE: A cycle of therapy is defined as 42 days. There will be no pause between cycles. Patients will be evaluated for response/progression every 12 weeks and will continue on therapy until progression or other reason for removal from treatment (see Section 7.7).

7.3 Administration through G-tube

Administration of the study medications through a G-tube is not allowed.

7.4 Drug Compliance Documentation

Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.1). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.5 Full CDUS Reporting Requirement

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirements for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4, the **S1500** Treatment Form, and the **S1500** Adverse Event Form). A cycle is defined as 42 days.

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Unacceptable toxicity.

c. Delay in planned treatment for any reason > 4 weeks.

d. Pregnancy.

e. The patient may withdraw from the study at any time for any reason.

7.7 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.8 Follow-Up Period

All patients will be followed until death or 3 years after randomization, whichever occurs first

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized for SAE reporting only. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 Dose Modifications

Dose reduction guidelines for hematologic and non-hematologic toxicities are shown in the table below. If ≥Grade 3 toxicity that is expected to be manageable and reversible with a dose reduction occurs, treatment should be held until toxicity resolves to ≤ Grade 1. Study drug should be permanently discontinued in any patient with ≥Grade 3 hematologic or non-hematologic toxicity lasting ≥7 days that does not resolve to ≤Grade 1 within 2 weeks.

Dose modifications for hematologic and non-hematologic toxicities

NCI CTCAE v4.03 Toxicity Grade	Action
Grade 0, 1, or 2	**None**
Grade 3 or 4 Expected manageable/reversible with dose reduction	Hold[a]
Toxicity remains Grade ≥ 3 for >7 days	Discontinue study drug
Toxicity lasts ≥ 7 days and resolves to ≤ Grade 1	Reduce one dose level

Dose modifications for hematologic and non-hematologic toxicities

NCI CTCAE v4.03 Toxicity Grade	Action
Grade 0, 1, or 2	**None**
Recurrence of Grade 3	Hold[a]
Toxicity remains Grade ≥ 3 for >7 days	Discontinue study drug
Toxicity lasts ≥ 7 days and resolves to ≤ Grade 1	Reduce one dose level or discontinue study drug[a]
Recurrence of Grade 4	Discontinue study drug
Grade 3 or 4 (new or recurrent) Not expected to be manageable/reversible with dose reduction	Discontinue study drug

[a] Study drug should be held until toxicity resolves to ≤ Grade 1. Study drug should be discontinued in any patient with ≥Grade 3 hematologic or non-hematologic toxicity lasting ≥7 days that does not resolve to ≤Grade 1 within 2 weeks.

Dose modifications are drug specific. Notably, no dose re-escalation is permitted, even in the context of resolving toxicities that initially warranted dose reduction. Dose modifications of sunitinib should be conducted using the following dose levels.

Sunitinib dose level modification*

Dose level	Sunitinib PO daily dose
Starting Dose	**50 mg QD**
-1 Dose Level	37.5 mg QD
-2 Dose Level	25 mg QD

*Of note, patients who receive a dose reduction on sunitinib should still be maintained on the conventional 4 week on, 2 week off dosing regimen.

Notably, patients should be carefully monitored for clinical signs and symptoms of CHF while on sunitinib.

Dose modifications of cabozantinib should be conducted using the following dose levels:

Cabozantinib dose level modification

Dose level	Cabozantinib PO daily dose
Starting Dose	**60 mg QD**
-1 Dose Level	40 mg QD
-2 Dose Level	20 mg QD

Dose modifications of crizotinib should be conducted using the following dose levels:

Crizotinib dose level modification

Dose level	Crizotinib PO daily dose
Starting Dose	**250 mg BID**
-1 Dose Level	200 mg BID
-2 Dose Level	250 mg QD

Dose modifications of savolitinib should be conducted using the following dose levels:

Savolitinib dose level modification

Dose level	Savolitinib PO daily dose
Starting Dose	**600 mg QD**
-1 Dose Level	400 mg QD
-2 Dose Level	200 mg QD

Notably, G-CSF is not recommended for neutropenia.

8.3 Dose Modifications for Hypertension

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation.

Recommended Hypertension Monitoring and Management
(BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Dose Modification
Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No change
Grade 2- Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	Step 1) Initiate LA DHP CCB treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another antihypertensive Rx, a BB, ACE1, ARB, or ABB; increase dose of this drug as described in Step 1	BP should be monitored as recommended by the treating physician	No change except as described in Step 4

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Dose Modification
	Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in Step 2; increase dose of this drug as described in Step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of study drug or stopping study drug. *NOTE: Stopping or reducing the dose of* study drug *is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.*		

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Dose Modification
Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	HOLD study drug until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see Steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the patient is symptomatic: optimal management with intensive IV support in ICU; STOP study drug and notify hospital staff that stopping study drug may result in a decrease in BP** **and** **2) If systolic BP >180**	BP should be monitored as recommended by the treating physician **unless the patient is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD study drug until systolic BP ≤159 and diastolic BP ≤99. In most circumstances, if BP cannot be controlled after an optimal trial of anti-hypertensive medications, consider either 1 dose reduction of study drug or stopping study drug. **HOWEVER, if the patient requires hospitalization for management of symptomatic**

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Dose Modification
	or diastolic BP >110 and the patient is asymptomatic, 2 new anti-hypertensives must be given together in Step 1 (and dose escalated appropriately as in Step 1). *NOTE: Stopping or reducing the dose of study drug is expected to cause a decrease in BP The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medication(s) Accordingly*		**systolic BP >180 or diastolic BP >110,** permanently discontinue study drug or if BP is controlled, re-start study drug at 1 lower dose level after consultation with the Study Chair

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Dose Modification
Grade 4 Life-threatening consequences of hypertension	Optimal management with intensive IV support in ICU; STOP study drug and notify hospital staff that stopping study drug may result in a decrease in BP	Intensive	Permanently discontinue study drug or if BP is controlled, re-start study drug at 1 lower dose level after consultation with the Study Chair

Abbreviations: dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), angiotensin converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), alpha beta blocker (ABB)

- If patients require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If patients require >2 dose reductions, discontinue protocol therapy
- Patients may have up to 2 drugs for management of hypertension prior to any dose reduction in study drug
- 24-48 hours should elapse between modifications of anti-hypertensive therapy

Hypertension should be graded using CTCAE v4.

8.4 Dose modifications for QTc prolongation in patients receiving savolitinib

Dose modifications for savolitinib-related QTc prolongation

NCI CTCAE Toxicity Grade	Action
Grade 0, 1, or 2	None
Grade 3	Hold dosing and follow algorithm bello
• Patients with QTcF prolongation to >500 msec on at least two separate ECGs	• Consult with cardiologist to validate ECG finding. Ensure cardiac surveillance and take actions in accordance with clinical standards. Regular ECGs performed until resolution to QTcF < 481 msec. Restart drug at one reduced dose level.
• If the toxicity does not resolve to QTcF < 481msec within 21 days	• Discontinue study drug and consult with a cardiologist to validate ECG finding and further management as clinically indicated.
Grade 4	
• QTcF >= 501 or >60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	• Discontinue study drug and consult with a cardiologist to validate ECG finding and further management as clinically indicated

Drug

Drugs that prolong QT interval

GUIDANCE REGARDING POTENTIAL INTERACTIONS WITH CONCOMITANT MEDICATIONS KNOWN TO PROLONG QT INTERVAL

The drugs listed in this section are taken from information provided by the Arizona Center for Education and Research on Therapeutics website: https://www.crediblemeds.org. The website categorizes drugs based on the risk of inducing Torsades de Pointes (TdP). During screening the drugs that patients are currently prescribed should be checked opposite the ArizonaCert website above.

Drugs with a known risk of Torsades de Pointes

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended. These drugs must have been discontinued prior to the start of administration of study treatment in accordance with guidance provided in the table below and should not be co-administered with savolitinib and for a period of one week after discontinuing study treatment. The list of drugs may not be exhaustive and is subject to change as new information becomes available. As such investigators are recommended to search the website to provide the most up to date information.

Drugs with a known risk of TdP

Drug name	Withdrawal period prior to study treatment start
Anagrelide, ciprofloxacin, clarithromycin, cocaine, droperidol, erythromycin, levofloxacin, ondansetron, papaverine hydrochloride, procainamide, sulpiride, sultopride, terfenadine, terlipressin	2 days
Cilostazol, Cisapride, disopyramide, dofetilide, domperidone, flecainide, gatifloxacin, grepafloxacin, ibutilide, moxifloxacin, oxaliplatin, propofol, quinidine, roxithromycin, sevoflurane, sotalol, sparfloxacin, thioridazine	7 days
Azithromycin bepridil, citalopram, chlorpromazine, dronedarone, escitalopram, fluconazole, halofantrine, haloperidol, levomepromazine, levosulpiride, mesoridazine	14 days
Donepezil, terodiline	3 weeks
Levomethadyl, methadone, pimozide	4 weeks
Arsenic trioxide*, Ibogaine	6 weeks
Pentamidine	8 weeks
Astemizole, Probucol, vandetanib	4 months
Amiodarone, chloroquine	1 year

* Estimated value as pharmacokinetics of arsenic trioxide has not been studied

8.5 Dose Modifications Contacts

For treatment or dose modification questions, please contact Dr. Sumanta K. Pal or Dr. Primo Lara at S1500question@swog.org.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Arm A

REQUIRED STUDIES	BASE-LINE	Cycle 1						Cycle 2						Cycle 3 +							
		W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18	FU Prior to Prog**	FU After Prog**
PHYSICAL																					
History & Physical exam£	X	X			X			X			X			X q 6 wks						X	X
Weight & Performance Status£	X	X			X			X			X			X q 6 wks						X	
Disease Assessment	X													X q 12 wks							
Toxicity Notation£					X			X			X			X q 6 wks							
Blood Pressure Monitoring≠		X	X	X	X			X			X			X q 6 wks							
LABORATORY																					
CBC w/diff, plts£	X	X			X			X			X			X q 6 wks						X	
Serum chemistry ϖ£Ω	X	X			X			X			X			X q 6 wks						X	
TSH, free T3 and T4¿		X			X			X			X			X q 6 wks							
Urinalysis ۞	X	X			X			X			X			X q 6 wks							
Pregnancy test (if applicable) ↄ	X																				
TREATMENT Δ																					
ARM 1: Sunitinib		X	X	X	X			X	X	X	X			X	X	X	X				
ARM 2: Cabozantinib		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ARM 3: Crizotinib		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ARM 4: Savolitinib		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Calendar continued on next page. Click here for footnotes.

Version Date 9/15/2020

Cal 9.1 (contd.)

REQUIRED STUDIES	Cycle 1							Cycle 2						Cycle 3+						FU Prior to Prog**	FU After Prog**
	BASE-LINE	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12	W 13	W 14	W 15	W 16	W 17	W 18		
X-RAYS AND SCANS																					
CT of chest, abdomen & pelvis	X													X q 12 wks							
Bone scan	X¥													X¥ q 12 wks							
EKG and Echocardiogram$^{\Sigma}$	X	X	X	X	X	X	X	X						X						X	X
SAMPLES$^{€}$																					
1 H&E slide (Mandatory for independent pathology review)	X																				
Tissue block or 12 unstained slides	X																				
Plasma & buffy coat	X							X						X						X Ъ	X Ъ
Serum	X							X						X						X Ъ	X Ъ

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
Click here for footnotes.

FOOTNOTES:

≠ See Section 8.3 regarding blood pressure monitoring.

ϖ Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. If prestudy labs are obtained ≥ 14 days prior to beginning Cycle 1, they must be repeated.

Ω Patients randomized to Arm 4: savolitinib must have liver function tests monitored weekly for the first two months and then monthly thereafter since liver damage is a known side effect. Laboratory monitoring may be conducted remotely if chosen by the patient/investigator.

Δ For treatment plan and doses, see Section 7.2. Treatment and follow-up continues until progression or patient is removed from protocol treatment per Section 7.6.

¥ If there is clinical suspicion for bone metastases at the time of enrollment (at the discretion of the investigator), bone scan should be performed at baseline. If bone metastases are detected, a bone scan should be conducted at the time of each radiologic evaluation.

€ For description of correlative studies, see Section 15.0.

£ For the first two cycles (i.e., 12 weeks), patients will be followed on Days 1 and 22 in clinic. For the third cycle and beyond, patients will be followed-up on day 1 of each cycle. Please report AEs from all assessments within a single cycle at the end of that cycle.

** All patients will be followed until death or 3 years after registration, whichever occurs first. If patient is removed from protocol treatment for reasons other than progression, patient will continue to be followed at same intervals as if on treatment. Once disease progresses, follow-up is at the discretion of the treating investigator.

¿ TSH, free T3 and T4 must be collected each cycle for patients randomized to Arms 1 (Sunitinib) and 2 (Cabozantinib) prior to study drug administration.

Urinalysis (UA) must be collected each cycle for patients randomized to Arms 1 (Sunitinib) and 2 (Cabozantinib) prior to study drug administration. If urine protein on urinalysis is ≥ 3+, then perform 24-hour urine protein. Interrupt sunitinib and cabozantinib if 24-hour urine protein is ≥ 3 grams. Discontinue sunitinib or cabozantinib for patients with nephrotic syndrome or repeat episodes of urine protein ≥ 3 grams despite dose reductions.

Ъ Collect at the time of removal from protocol treatment (recurrence or other reason, whichever occurs first).

ф It is at the discretion of the treating investigator to determine whether to and when to perform pregnancy testing if applicable.

∑ QTcF evaluation will be done based on triplicate 12-lead EKGs during the screening period. For patients **randomized to savolitinib only,** triplicate EKG must be performed every week in the first cycle, on Day 1 of every cycle thereafter, and at the end of treatment. Twelve-lead EKGs (triplicate) will be obtained after the patient has been rested in a supine position for at least 5 minutes. The investigator or designated physician will review the 12-lead EKGs. EKGs will be recorded at 25 mm/sec. All EKGs should be assessed by the investigator to determine whether they are clinically significantly abnormal vs. not clinically significantly abnormal. If the treating investigator feels there is a clinically significant abnormal finding, the investigator will record it as an adverse event (AE). The original EKG traces must be stored in the patient medical record as source data. A 28-day follow-up assessment will be required if an on-treatment assessment was abnormal at the time of discontinuation of study therapy, to confirm reversibility of the abnormality.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension by ≥ 1.0 cm with CT or MRI scans or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease)

including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

   Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

   1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

   2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response

This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Symptomatic deterioration: Objective status of symptomatic deterioration within 12 weeks of registration, not qualifying as anything else above.

h. Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	**DESCRIPTION**
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of 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.

10.5 Time to Death

Time of death is calculated from date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.6 Progression-Free Survival

Progression-free survival is calculated from date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual Goal

Accrual Rate: 7 pts/month.

Total Expected Accrual: Minimum 86 eligible Maximum 164 eligible (180 total)

Note: As of 12/05/18, patients will no longer be randomized to either the crizotinib or savolitinib arm due to a planned interim futility analysis. Updated accrual goals are as follows:

Accrual rate: 7 pts/month

Total expected accrual: 41 eligible/45 total patients per arm for the sunitinib and cabozantinib arms for a maximum of 148

The cabozantinib has not yet had an interim analysis. It will be conducted when the requisite number of PFS events have occurred.

11.2 Analysis of Primary Endpoint

With a total of 164 eligible patients (41 patients per arm) with pRCC accrued over a span of 2 years (with 1 year of follow-up), we will have 85% power to detect a 75% improvement in median PFS (1-sided α=0.10) in any one of the 3 treatment arms relative to sunitinib. This makes the assumption of PFS with sunitinib of approximately 6 months, and an expected PFS on the experimental arm of approximately 10.5 months (HR=1.75). Assuming that 10% will be ineligible, an additional 16 patients will likely be accrued, thus totaling 180 patients in order to reach 164 eligible patients. A proportional hazards model will be used to evaluate each pair wise treatment comparison of PFS, adjusting for the two stratification factors as covariates in the model. If accrual is efficient, we will consider an amendment to decrease alpha to 0.05 prior to the one futility analysis.

Although accrual of type I patients is preferable, this study design does not require minimum number of type I patients per arm. For all subset analyses of papillary type, the independent pathology review categorization will be used.

A futility analysis for each MET inhibitor treatment arm versus sunitinib comparison will be conducted after 15 PFS events are observed in each treatment group (e.g., half of the intended cohort).

	Interim*		**Final**	
	# of events (under H_a)	**Expected time**	**# of events** (under H_a)	**Expected time**
Standard	20/sunitinib	20 months	37/sunitinib	3 years
Experimental	15/arm	20 months	31/arm	3 years

* 50% of expected events on the experimental arms assuming 10.5 month median PFS

If the PFS HR (sunitinib vs. met inhibitor) is < 1 corresponding to worse progression-free survival for the respective met inhibitor arm, that particular met inhibitor arm will be recommended for closure to further accrual. The other met inhibitor arms that do not satisfy the futility criteria would continue to full accrual. The study will continue to enroll patients during the interim analysis phase. The sunitinib arm will continue to accrue as long as at least one of the MET inhibitor arms is still accruing.

Results of the first futility analysis after events were reached for savolitinib and crizotinib suggest futility of these arms based on the aforementioned criteria. Thus, randomization to these arms was terminated on 12/05/18. Randomization to sunitinib and cabozantinib continues thereafter.

11.3 Secondary Endpoints

Survival curves will be estimated by the Kaplan-Meier method, and a log-rank test will be used to compare OS between treatment arms. Assuming a median survival of 15 months for the sunitinib arm, two years of follow-up after accrual is completed (one year beyond the time of the PFS primary analysis) and a one-sided alpha=0.10 and 41 patients per arm, there will be 0.83 statistical power to detect a difference in median survival of 15 months versus 27 months (comparable to a HR=1.80) between the control group and each MET inhibitor.

The chi-square test will be used to compare response rate between the control arm of sunitinib and the MET inhibitor treatment arms. With 41 patients per arm with measurable disease, and assuming a 7% response rate in the sunitinib arm, there will be 80% statistical power to detect a 7% versus 27% response rate on a MET inhibitor arm, assuming a one-sided alpha=0.10.

11.4 TM Aims:

a. Met Mutation and Activity

Preliminary analysis of the TCGA patients with papillary RCC have a 9% MET mutation rate (includes germline and somatic mutation) and 2% rate of high level MET amplification. Additionally, a significant number of patients, approximately 20% have overexpression of MET as detected by RNAseq in the setting of low copy number gain. We hypothesize that patients with MET mutations, high level level MET amplification or high levels of MET expression in the setting of low copy number amplification, will have a higher response to putative MET inhibitors as compared to patients treated with sunitinib. This hypothesis is based in part on data from the aforementioned study of foretinib (Choueiri et al. J Clin Oncol 2011), where RR was significantly higher in patients bearing germline mutations in *MET* (5 of 10, or 50%) as compared to those without (5 of 57, or 9%). In this study the overall RR was 13%.

Given patient heterogeneity and the multiple potential mechanisms for increased Met activity and the relatively low rate of germline mutations in MET or MET amplification, we likely will perform a pooled analysis amongst patients with mPRCC treated with putative MET inhibitors in the current study (n=123, assuming 3 arms with MET-directed therapy and 41 eligible patients per arm) to determine if increased MET activity is correlated with PFS and RECIST response. In total, approximately 30% of patients are anticipated to bear germline or somatic MET mutations, increase in MET copy number or increased Met expression. We would expect better PFS in that group. If we assume the 70% group has a median PFS of 6 months and those with a mutation, or an increase in MET copy number or MET expression (30% group) has a median PFS of 10 months (HR=1.67), then we will have 81% statistical power to detect this difference using a two-sided alpha=0.05.

However, this does not indicate a predictive response to treatment – only prognostic. Ideally, we would compare the hazard ratio between the MET inhibitor vs. sunitinib in those with versus without the mutation (i.e., the

interaction). As can be seen by the following table, the cell counts are low for this interaction, but there is moderate power for large interactions.

	Combined Met Inhibitor Arms		Sunitinib	
	N	Estimated Median PFS	N	Estimated Median PFS
MET mutation/expression (30%)	37	18 mo.	12	6 mo
No mutation/expression (70%)	86	6 mo.	29	6 mo.
Total (n=123)	123		41	

As illustrated in the above table, if the MET mutation status has no impact on prognosis so those receiving sunitinib have a median PFS of 6 months in either group, and among those randomized to a MET inhibitor arm, median PFS is three times longer in those with a MET mutation/increased expression, then there will be 81% statistical power to identify this interaction using a two-sided alpha=0.05.

RECIST response rate (confirmed and unconfirmed PR and CR) based on MET mutation/expression level will be compared using the chi-square test. In exploratory analyses we will also assess whether one of the three subtypes 1) mutation; 2) copy number alteration; or 3) increased Met expression has a more favorable response to MET inhibitor drugs.

b. Assessment of Type I and Type II Renal Papillary Cancer

Those with inadequate tissue submitted or for whom the independent review is unable to designate type, will not be included in this analysis. Ideally, we would test the interaction of type I/II categorization with the treatment comparison of met inhibitors compared to sunitinib. However, since we only expect that approximately 15% of patients on **S1500** will have type I papillary disease, we would only expect about 6 type I patients and 32 type II patients in the sunitinib arm, thereby providing very little statistical power for evaluating the interaction.

We have chosen to pool the three met inhibitor arms (n=123) and we will evaluate the response to these treatments by type I vs. II status. We will primarily look at RECIST response, but we will also look at PFS. We expect approximately 18 patients in the combined met inhibitor arms will be type I and n=95 will be type II, and we'll assume 10 are not able to be categorized. If we assume that there will be a 10% CR + PR rate among those with type II disease and 30% RECIST response rate for type I disease, then by using a one-sided alpha=0.05 there will be 39% statistical power to detect this difference. If the response rate difference is 10% vs. 40% between the type II versus I groups respectively, there will be 76% statistical power. Similarly, if the 6 month PFS rate is 20% for those with type II disease and 50% for those with type I disease, there will also be 76% power to detect this difference.
We will also describe the response rate and PFS estimates for type I and II for the sunitinib arm along with 95% confidence intervals.

11.5 Data and Safety Monitoring Committee Oversight

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3

non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistics and Data Management Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Independent pathologic assessment will be conducted for this study to determine: (1) type I vs type II pRCC histologic subtype for those patients deemed subtype NOS by the local pathologist, (2) confirmation of local pathologist subtype assignment of type I vs. type II. This independent pathologic assessment will be conducted in a retrospective fashion (i.e., pathologic subtype type I or type II assignment is NOT necessary prior to consent, registration or enrollment). We expect local pathologists to designate 6% of randomized patients as type I, 42% type II and 52% NOS (i.e. not able to definitively assign type I or type II). Disagreement with the local site pathologists will not make the patient ineligible. **However, failure to submit specimen for independent pathologic assessment will deem the patient ineligible.**

Type I or type II designations will be arbitrated by a group of expert pathologists. Electronic images of the slides will be transmitted to the expert pathologists.

Sites must submit one Hematoxilyn-eosin (H&E)-stained slide and local pathology report from initial diagnosis. If H&E slide is not available, submit an unstained slide. This slide must be submitted within 3 months after registration via standard mail to the SWOG Biospecimen Bank, Lab #201. Specimens should be wrapped in sufficient packing to prevent breakage during transport. See Section 15.3 for shipping instructions.

Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample. The local pathologist must review prior to enrolling patient noting that the tumor volume is at least 0.2mm^3 and the tumor tissue contains at least 20% viable tumor cells.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than ten working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored clinical trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to

OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

b. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. **IRB Approval:**

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

2. **Downloading Site Registration Documents**:

Site registration forms may be downloaded from the **S1500** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol # **S1500**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

3. **Requirements for S1500 *S*ite Registration**:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted).

4. **Submitting Regulatory Documents**:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 in order to receive further instruction and support.

5. **Checking Your Site's Registration Status**:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval. If a DTL is required for the study, the IVR or NPIVR must also be assigned the appropriate OPEN-related tasks on the DTL.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the

website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login

(https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members’ website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 888/823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1500 Advanced Renal Carcinoma Onstudy Form

Baseline Abnormalities Form

Baseline Tumor Assessment Form

Pathology Report from Nephrectomy or Diagnostic Biopsy/Surgery (Pathology report should indicate a diagnosis of PRCC and indicate subtype)

Submit radiology reports from all scans performed to assess disease at baseline.

b. WITHIN 60 DAYS AFTER REGISTRATION:

Submit specimens as outlined in Section 15.0.

c. WITHIN 90 DAYS AFTER REGISTRATION:

Submit specimens as outlined in Section 12.0.

d. WITHIN 14 DAYS AFTER EACH TREATMENT CYCLE:

Submit the following:

S1500 Treatment Form

S1500 Adverse Event Form

e. IMMEDIATELY PRIOR TO CYCLES 1-3:

Submit specimens as outlined in Section 15.0.

f. WITHIN 28 DAYS AFTER EACH RESPONSE ASSESSMENT:

Submit the following:

Follow Up Tumor Assessment Form

Relevant radiology reports (corresponding to disease assessment).

g. WITHIN 28 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

Final **S1500** Treatment Form

Final **S1500** Adverse Event Form

Submit specimens as outlined in Section 15.0.

h. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the following:

Follow Up Tumor Assessment Form

Radiology reports documenting progression and Off Treatment Notice (if the patient was still on protocol treatment).

Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

Submit specimens as outlined in Section 15.0.

i. IF PATIENT IS OFF PROTOCOL TREATMENT, EVERY 3 MONTHS FOR UP TO 3 YEARS FROM RANDOMIZATION

Submit the following:

Follow Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and a final **S1500** Treatment Summary Form, **S1500** Adverse Event Summary Form, and Follow Up Tumor Assessment Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

The specimens outlined in this section are optional for the patient. See Section 12.0 for details regarding MANDATORY specimen submission.

15.1 Translational Study: Next generation sequencing (Optional for patient)

a. If the patient consents, the following must be submitted to the SWOG Biospecimen Bank, Lab #201:

1. Tissue block (preferred) or at least 12 (4-5 micron) unstained slides (20 slides are strongly recommended).

2. Local pathology report

b. Specimen collection kits are not being provided for this submission; sites will use institutional supplies. When submitting tissue to the SWOG Biospecimen Bank, be prepared to provide answers to the following questions in the SWOG specimen Tracking System:

- Protocol #:
- Patient #:
- Patient Initials #:
- Time point:
- Collection Date:
- Specimen Type:
- Surgery Path #:
- Block #:

c. Tissue Specifications

Most optimally, core needle biopsies should be obtained. Cytology smear specimens are not sufficient for the molecular studies proposed. However, fine needle aspirates with good cellularity are acceptable if the paraffin-embedded cell blocks are available. Specimens containing less than 80% nucleated cells require greater total volume and may not be suitable to assay. The key sample consideration is to submit a total mass of cells that is sufficient to extract the amount of DNA necessary for analysis. Bone biopsies are not allowed.

d. Specimen Use

The SWOG Biospecimen Bank will forward tumor blocks and whole blood to Yale School of Medicine. Translational research efforts will include next-generation DNA sequencing, SNP array for copy number analysis, and gene expression. With patient's consent, any remaining tissue will be banked in the SWOG Repository, Lab #201, for future exploratory analysis. Specimen banking is optional for the patient.

15.2 Plasma, Buffy Coat, and Serum Blood Specimen Banking (Optional for patient)

If the patient consents, plasma and buffy coat and serum specimens must be submitted at the timepoints listed below. Collection instructions and submission instructions are outlined below. Plasma, buffy coat and serum specimens for banking and future translational medicine studies will be submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201.

a. Plasma and Buffy Coat

Blood specimens (two purple top EDTA tubes for plasma and buffy coats) will be collected after registration, but prior to Cycle 1 treatment; at the beginning of Cycles 2 and 3; and at the time of removal from protocol treatment (regardless of timepoint). These specimens must be shipped within 28 days after obtaining to Lab #201. These specimens will be banked until funding is obtained to perform translational medicine studies which will include assessing molecular biomarkers relevant to MET kinase signaling (such as plasma HGF levels) and other pathways implicated in the pathogenesis of renal carcinoma and investigating their potential predictive and prognostic value.

b. Plasma, Buffy Coat, and Processing Instructions:

1. Blood samples should be collected using standard venipuncture technique.

2. Cryovials must be labeled with SWOG patient number, patient’s initials, and date and time of specimen collection and specimen type.

3. Collect ~6 mL whole blood in each of two (2) purple top tubes (EDTA tubes).

4. Immediately invert tube (gently) 8-10 times. This reduces the possibility of clot formation.

5. Centrifuge sample at 800 x g for 10 minutes (~1500-2000 rpm, determined by centrifuge rotor size).

6. Immediately after centrifuging, transfer plasma in 1 mL aliquots to labeled cryovials.

7. Pipette slowly to avoid disturbing the buffy coat layer.

8. Leave a small amount of plasma (~.5 cm) above the buffy coat layer in each tube.

9. After removing plasma from both tubes, transfer buffy coat to labeled cryovials.
   - The buffy layer is the off-white layer between the plasma and the red blood cells.
   - Pipette slowly in a circular motion to obtain as many buffy coat cells as possible.
   - Contamination of the buffy coat with red blood cells is expected and not a concern.

10. Immediately freeze vials on dry ice or in a -80°C freezer. Store frozen plasma vials in a -70°C to -80°C freezer until ready to ship. If a -70°C to -80°C freezer is not available, a -20°C would be sufficient.

c. Serum

10 mL of venous blood will be collected in a SST red/grey marble top tube immediately prior to Cycles 1-3 and at the time the patient is removed from protocol treatment. These specimens must be shipped within 28 days after obtaining to Lab #201. These specimens will be banked until funding is obtained to perform translational medicine studies which may include evaluation of changes in serum cytokines induced by MET signaling inhibition.

d. Serum Specimen Collection Instructions:

1. Draw peripheral blood into SST red/grey marble top vacutainer

2. Allow blood to clot for 20 minutes, then centrifuge at 25°C, 1500xg (2700-3000 rpm) for 15 minutes

3. Four Cryovials must be labeled with the SWOG patient number, patient's initials, and date and time of specimen collection and specimen type.

4. Immediately after centrifuging, transfer serum in 1-2 mL aliquots to four labeled cryovials.

5. If you are using plastic vacutainer tubes, samples can be directly frozen at -70°C (preferred) or at -20°C until shipped.

e. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

15.3 SHIPPING SAMPLES:

a. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you

have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. First time non- SWOG users must refer to start-up instructions located at https://gill.crab.org/SpecTrack/.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. The Specimen Submission Form is NOT required when the online system is used.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of plasma, serum and tissue specimens for SWOG Biospecimen Bank submission is identified as follows:

Lab #201: SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division
Contact: SWOG Biospecimen Bank
Phone: 614/722-2865
Email: bpcbank@nationwidechildrens.org

Plasma, buffy coats, and serum must be shipped on dry ice by overnight courier Monday through Wednesday.

b. Shipping guidelines for formalin-fixed paraffin embedded (FFPE) tumor tissue specimens:

1. **Specimens must be packaged to comply with IATA standards (www.iata.org).**

2. Blocks and/or slides will be shipped in a padded envelope and should not be shipped in the same chamber as frozen specimens. If frozen and FFPE specimens are to be shipped together, they must be shipped in a dual-chambered shipper.

3. When shipping slides, place them in a plastic slide holder and stabilize by placing cotton or soft paper under the lid. Tape the lid so that it does not pop open during shipment (one piece of tape is sufficient).

4. Wrap any slide cartridge(s) in bubble wrap and mail in a padded envelope if available.

c. Shipping guidelines for frozen specimens:

1. **Specimens must be packaged to comply with IATA standards (www.iata.org).**

2. First, place the specimen in a leak-proof biohazard envelope. Include an absorbent material. Next, place the biohazard envelope containing the specimen in a puncture and pressure resistant envelope (e.g. Tyvek envelope).

3. Place the packaged specimen(s) in an appropriate shipping container (composed of an inner styrofoam and outer cardboard layer). Place a layer of dry ice in the bottom of the shipping container, then set the specimen on top of the dry ice. Cover the specimen with dry ice until the shipping container is full.

4. Include required paperwork (e.g. SpecTrack-generated packing list(s)) in the shipment.

5. Close the shipping container and tape shut. Do not completely seal the container. Complete a dry ice label. Attach an "Exempt Human Specimen" label and the dry ice label to the side of the shipping container.

6. Attach a shipping label to the top of the shipping container.

7. Batch shipments are permitted and must have specimens from 5 or fewer patients per shipping container. Batches should be shipped at least quarterly to avoid sites storing specimens in freezers long term.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and

Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's

confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis, either by FTP burst of data or via the CDS web application. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: As this study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agents/Intervention[1] Cabozantinib, Crizotinib, Savolitinib, or Sunitinib Malate.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

1. Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

- **Group-specific instructions**

  Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:
  - Printed copy of the first page of the CTEP-AERS Report.
  - Copies of clinical sourced documentation of the event.
  - If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. Reporting Secondary Malignancy, including AML/ALL/MDS

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Intake Calendars

a. Intake Calendar: Arm 1 Sunitinib

b. Intake Calendar: Arm 2 Cabozantinib

d. Intake Calendar: Arm 3 Crizotinib

e. Intake Calendar: Arm 4 Savolitinib

18.2 Examples of Clinically Relevant Drug Interactions: Substrates, Inducers and Inhibitors of the Isoenzyme CYP3A4

18.3 Patient Drug Information Handouts and Wallet Cards

a. Cabozantinib

b. Crizotinib

c. Savolitinib

d. Sunitinib

18.4 Identification and Characterization of Oncometabolite-Induced DNA Repair Defects in Sporadic Papillary Kidney Cancer

18.5 Specimen Banking and Translational Medicine Material Instructions for SWOG Biospecimen Bank (BB)

18.1a Intake Calendar: **S1500** Arm 1 Sunitinib

Cycle: ________ Start Date: ____________ Start Day (circle one): Sun M Tu W Th Fr Sat

Instructions for the participant: Sunitinib is taken once a day. This is a 42 day cycle calendar on which you are to put the date in the box on the calendar and record the dose and time you take sunitinib (or the reason a dose was not taken). Take medication as directed by study doctor. Swallow sunitinib whole. Sunitinib may be taken with or without food. You must not drink grapefruit juice or eat grapefruit or Seville oranges during your treatment with sunitinib. You will take sunitinib every day for four weeks and then not take it for the next two weeks. If you develop any side effects from the drug, mark this on the calendar on the day you note the effect.

Storage: Sunitinib should be stored at room temperature (not to exceed 25ºC/77ºF) in their original container.

Site Personnel: Site personnel must ensure that patients clearly understand the guidelines for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

If you have questions contact: ____________________ Telephone: __________________

Research Staff Comments:

Number of pills taken:________
Number of pills returned: ________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____

Patient Signature:______________________

18.1b Intake Calendar: S1500 Arm 2 Cabozantinib

Cycle: _________ Start Date: _____________ Start Day (circle one): Sun M Tu W Th Fr Sat

Instructions for the participant: Cabozantinib is taken once a day. This is a 42 day cycle calendar on which you are to put the date in the box on the calendar and record the dose and time you take cabozantinib (or the reason a dose was not taken). Take medication as directed by study doctor. Swallow cabozantinib whole. Cabozantinib must be taken on an empty stomach (do not eat within the 2 hours before you take it and for 1 hour after). If you miss a pill, take it as soon as you remember EXCEPT if your next scheduled dose is in less than 12 hours. In that case, just take the next pill at your regular time. Cabozantinib is taken continuously. There are no scheduled times when you stop taking it and then begin again. You must not drink grapefruit juice or eat grapefruit or Seville oranges during your treatment with cabozantinib. If you develop any side effects from the capsules, mark this on the calendar.
Storage: Cabozantinib should be stored at room temperature (not to exceed 25ºC/77ºF) in their original container.
Site Personnel: Site personnel must ensure that patients clearly understand the guidelines for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

If you have questions contact: ____________________ Telephone: _____________________

Research Staff Comments:
Number of pills taken:________
Number of pills returned: ________

Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____

Patient Signature:_____________________

18.1c Intake Calendar: S1500 Arm 3 Crizotinib

Cycle: ________ Start Date: ____________ Start Day (circle one): Sun M Tu W Th Fr Sat

Instructions for the participant: Crizotinib is a pill you take twice a day. This is a 42 day cycle calendar on which you are to put the date in the box on the calendar and record the dose and time you take each crizotinib capsule (or the reason a dose was not taken). Take medication as directed by study doctor. Swallow crizotinib capsules whole. Crizotinib may be taken with or without food. Crizotinib is taken continuously. There are no scheduled times when you stop taking crizotinib and then begin again. If you develop any side effects from the capsules, mark this on the calendar on the day you note the effect.

Storage: Crizotinib tablets should be stored at room temperature (not to exceed 25ºC/77ºF) in their original container for light protection. Keep the medication in the bottles provided and do not transfer it to any other container. Protect from moisture.

Site Personnel: Site personnel must ensure that patients clearly understand the guidelines for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

If you have questions contact: ____________________ Telephone: _____________________

Research Staff Comments: Number of pills taken:________
Number of pills returned: ________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____

Patient Signature:_____________________

18.1d Intake Calendar: S1500 Arm 4 Savolitinib

Cycle: ________ Start Date: ____________ Start Day (circle one): Sun M Tu W Th Fr Sat

Instructions for the participant: Savolitinib is taken daily. This is a 42 day cycle calendar on which you are to put the date in the box on the calendar and record the dose and time you take savolitinib (or the reason not taken). Take medication as directed by study doctor. Swallow savolitinib whole. Savolitinib must be taken with food (specifically within 1 hour after the start of a meal). You must not drink grapefruit juice or eat grapefruit or Seville oranges during your treatment with savolitinib. Savolitinib is taken continuously. There are no scheduled times when you stop taking savolitinib and then begin again. If you develop any side effects from the medication, mark this on the calendar on the day you note the effect.

Storage: Savolitinib should be stored at room temperature (not to exceed 25ºC/77ºF) in their original container.

Site Personnel: Site personnel must ensure that patients clearly understand the guidelines for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

If you have questions contact: ____________________ Telephone: ____________________

Research Staff Comments:

Number of pills taken:________
Number of pills returned: ________

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____
AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____	AM:_____ PM: _____

Patient Signature:______________________

18.2 Drugs Known to be Metabolized by CYP450 Isoenzymes 2D6 and 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis/; medical reference texts such as the Physicians' Desk Reference may also provide this information.

CYP2D6	
SUBSTRATES	
Amitriptyline (hydroxylation)	Methamphetamine
Amphetamine	Metoclopramide
Betaxolol	Metoprolol
Bisoprolol	Mexitetine
Brofaromine	Mianserin
Buturolol	Mirtazapine (hydroxylation)
Bupropion	Molindone
Captopril	Morphine
Carvedilol	Nortriptyline (hydroxylation)
Cevimeline	Olanzapine (minor, hydroxymethylation)
Chlorpheniramine	Ondansetron
Chlorpromazine	Orphenadrine
Cinnarizine	Oxycodone
Clomipramine (hydroxylation)	Papaverine
Clozapine (minor pathway)	Paroxetine (minor pathway)
Codeine (hydroxylation, o-demelhylation)	Penbutolol
Cyclobenzaprine (hydroxylation)	Pentazocine
Cyclophosphamide	Perhexiline
Debrisoquin	Perphenazine
Delavirdine	Phenformin
Desipramine	Pindolol
Dexfenfluramine	Promethazine
Dextromethorphan (o-demethylation)	Propafenone
Dihydrocodeine	Propranolol
Diphenhydramine	Quetiapine
Dolasetron	Remoxipride
Donepezil	Risperidone
Doxepin	Ritonavir (minor)
Encainide	Ropivacaine
Fenlluramine	Selegiline
Flecainide	Sertindole
Fluosetine (minor pathway)	Sertratine (minor pathway)
Fluphenazine	Sparteine
Haiofantrine	Tamoxifen
Haioperidol (minor pathway)	Thioridazine
Hydrocodone	Tiagabine
Hydrocortisone	Timolol
Hydroxyamphetamine	Tolterodine
Imipramine (hydroxylation)	Tramadol
Labetalol	Trazodone
Loratadine	Trimipramine
Maprotiline	Tropisetron
m-Chlorophenylpiperazine (m-CPP)	Venlafaxine (o-desmethylation)
Meperidine	Yohimbine
Methadone	

INHIBITORS	
Amiodarone	Methadone
Celecoxib	Mibefradil
Chloroquine	Moclobemide
Chlorpromazine	Nortluoxeline
Cimelidine	Paroxetine
Citalopram	Perphenazine
Clomipramine	Propafenone
Codeine	Quinacrine
Deiavirdine	Quinidine
Desipramine	Ranitidine
Dextropropoxyphene	Risperidone (weak)
Diitiazem	Ritonavir
Doxorubicin	Sertindole
Entacapone (high dose)	Sertraline (weak)
Fluoxetine	Thioridazine
Fluphenazine	Vaiprolc acid
Fluvoxamine	Venlafaxine (weak)
Haloperidol	Vinblastine
Labetalol	Vincristine
Lobeline	Vinorelbine
Lomustine	Yohimbine
CYP3A3/4	
Substrates	
Acetaminophen	Chlorpromazine
Aifentanil	Cimetidine
Alosetron	Cisapride
Alprazolam	Citałopram
Amiodarone	Clarithromycin
Amitriptyline (minor)	Clindamycin
Amlodipine	Clomipramine
Anastrozole	Clonazepam
Androsterone	Clozapine
Antipyrine	Cocaine
Astemizole	Codeine (demethylation)
Atorvastatin	Cortisol
Benzphetamine	Cortisone
Bepridil	Cyclobenzaprine (demethylation)
Bexarotene	Cyclophosphamide
Bromazepam	Cyclosporine
Bromocriptine	Dapsone
Budesonide	Dehydroepiandrostendione
Bupropion (minor)	Delavirdine
Buspirone	Desmethyldiazepam
Busutfan	Dexamethasone
Caffeine	Dextromethorphan (minor, N-demethylation)
Cannabinoids	Diazepam (minor; hydroxylation, N-demethylation)
Carbamazepine	Nefazodone
Cevimeline	Nelfinavir
Cerivastatin	Nevirapine
Diergotamine	Nicardipine
Digitoxin	
Diltiazem	
Disopyramide	

Docetaxel	Nifedipine
Dolasetron	Niludipine
Donepezil	Nimodipine
Doxorubicin	Nisoldipine
Doxycycline	Nitrendipine
Dronabinol	Omeprazole (sulfonation)
Enalapril	Ondansetron
Ergotamine	Oral contraceptives
Erylhromycin	Orphenadrine
Estradiol	Paclitaxel
Ethinyl estradiol	Pantoprazole
Ethosuximide	Pimozide
Etoposide	Pioglitazone
Exemestene	Pravastatin
Dofetilide (minor)	Prednisone
Felodipine	Progesterone
Fentanyl	Proguanil
Fexotenadine	Propafenone
Finaxteride	Quercetin
Fluoxetine	Quetiapine
Flutamide	Quinidine
Glyburide	Quinine
Granisetron	Repaglinide
Halofantrine	Retinoic acid
Hydrocortixone	Rifampin
Hydroxyarginine	Risperidone
Ifosfamide	Ritonavir
Imipramine	Salmeterol
Indinavir	Saquinavir
Isradipine	Sertindole
Itraconazole	Sertraline
Ketoconazole	Sibutramine
Lansoprazole (minor)	Sildenafil citrate
Letrozole	Simvastatin
Levobupivicaine	Sirolimus
Lidocaine	Sufentanil
Loratadine	Tacrolimus
Losartan	Tamoxifen
Lovastatin	Temazepam
Methadone	Teniposide
Mibefradil	Terfenadine
Miconazole	Testosterone
Midazolam	Tetrahydrocannabinol
Mifepristone	Theophylline
Mirtazapine (N-demethylation)	Tiagabine
Montelukast	Tolterodine
Navelbine	Vincristine
Toremifene	Warfarin (R-warfarin)
Trazodone	Yohimbine
Tretinoin	Zaleplon (minor pathway)
Triazolam	Zatoestron
Troglitazone	Zileuton
Troleandomycin	Ziprasidone
Venlafaxine (N-demethylation)	Zolpidem
Verapamil	
Vinblastine	

	Zonisamide
INDUCERS	
Avasimibe Carbamazepine Dexamethasone Ethosuximide Glucocorticoids Griseofulvin Nafcillin Nelfinavir Nevirapine Oxcarbazepine Phenobarbital Phenylbutazone	Phenytoin Primidone Progesterone Rifabutin Rifampin Rofecoxib (mild) St John's wort Sulfadimidine Sulfinpyrazone Troglitazone
INHIBITORS	
Amiodarone Anastrozole Azithromycin Boceprevir Cannabinoids Cimetidine Clarithromycin Clotrimazole Cobicistat Cyclosporine Danoprevir Danazol Delavirdine Dexamethasone Diethyldithiocarbamate Diltiazem Dirithromycin Disulfiram Elvitegravir/RIT Entacapone (high dose) Erythromycin Ethinyl estradiol Fluconazole (weak) Fluoxetine Fluvoxamine Gestodene Grapefruit juice Indinavir Isoniazid Itraconazole	Ketoconazole Lopinavir/RIT Metronidazole Mibefradil Miconazole (moderate) Nefazodone Nelfinavir Nevirapine Norfloxacin Norfluoxetine Omeprazole (weak) Oxiconazole Paroxetine (weak) Posaconazole Propoxyphene Quinidine Quinine Quinupristin and dalfopristin Ranitidine Ritonavir Saquinavir Sertindole Sertraline Telaprevir Telithromycin Tipranavir/RIT Troglitazone Troleandomycin Valproic acid (weak) Verapamil Voriconazole Zafirlukast Zileuton

CYP1A2	
INHIBITORS	
Ciprofloxacin	

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In : Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 8th ed. Hudson, OH; LexiComp Inc. 2000: 1364-1371)

18.3a Cabozantinib Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **XL184 (cabozantinib).** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

XL184(cabozantinib) interacts with a certain specific enzyme in your liver, a certain transport protein that helps move drugs in and out of cells, and the heart's electrical activity (QTc prolongation).

- The enzyme in question is **CYP 3A4**. XL184 (cabozantinib) is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.
- The protein in question are **P-glycoprotein (P-gp) and MRP2.** XL184 (cabozantinib) is an inhibitor of P-gp and may be affected by other drugs that are "substrates." XL184 is also a substrate of MRP2 and may be affected by other drugs that are "inhibitor" or "inducers" of MRP2.
- XL184 (cabozantinib) may affect the heart's electrical activity causing QTc prolongation. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

XL184 (cabozantinib) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

XL184 (cabozantinib) must be used very carefully with other medicines that use certain **liver enzyme, transport proteins to be effective or to be cleared from your system or that may affect your heart's electrical activity.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***"strong inducers/inhibitors of CYP3A4, substrate of P-gp, or any medicine associated with greater risk for having QTc prolongation."***

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

- Do not drink or eat grapefruit/juice or Seville oranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug cabozantinib. This clinical trial is sponsored by the NCI. Cabozantinib may interact with drugs that are **processed by your liver, or use certain transport proteins in your body or affect the electrical activity of your heart**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges.

XL184 (cabozantinib) must be used very carefully with other medicines that interact with **CYP3A4 enzyme, transporter proteins (P-gp) and MRP2, or drugs that may trigger your heart's electrical activity (QTc prolongation)**.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors CYP3A4; P-gp substrates; or drugs that cause risks for QTc prolongation."**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

18.3b Crizotinib Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, crizotinib**.** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Crizotinib interacts with a certain specific enzyme in your liver and a certain transport protein that helps move drugs in and out of cells.

- The enzymes in question are **CYP 3A4/5**, **2C8**, **2C19, 2B6 and 2D6**. Crizotinib is primarily metabolized by CYP3A4, with minor contributions from **CYP2C8**, **2C19**, and **2D6** and may be affected by other drugs that inhibit or induce these enzymes. Crizotinib is an inhibitor of CYP 3A4 and 2B6 and may affect the metabolism of other drugs.
- The protein in question are **P-glycoprotein (P-gp), OCT1 and OCT2.** Crizotinib is an inhibitor of P-gp and may be affected by other drugs that are "substrates."

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Crizotinib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Crizotinib must be used very carefully with other medicines that use certain **liver enzyme, transport proteins to be effective.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors or substrates of CYP 3A4/5,2C8, 2C19, 2D6, 2B6, P-gp, OCT1 and OCT2."**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **crizotinib.** This clinical trial is sponsored by the NCI. **Crizotinib** may interact with drugs that are **processed by your liver or use certain transport proteins in your body**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Crizotinib must be used very carefully with other medicines that interact with **CYP 3A4/5, C2C8, 2C19, 2D6 and 2B6 enzymes, or transporter proteins (P-gp), OCT1 and OCT2.**

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors or substrates of CYP 3A4/5, 2C8, 2C19, 2D6, 2B6, P-gp, OCT1 and OCT2."**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be

18.3c Savolitinib Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug **savolitinib (AZD6094).** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Savolitinib (AZD6094) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4, 3A5, 1A2, 2C8, 2C9, and 2D6. Savolitinib (AZD6094) is primarily metabolized by CYP 3A4/5 and 1A2 and some NADPH-independent non-CYP enzymes and may be affected by other drugs that strongly inhibit or induce CYP3A4/5 and CYP1A2. Savolitinib (AZD6094) inhibits CYP 3A4, 3A5, 1A2, 2C8, 2C9, 2D6 and UGT1A1 and may affect other drugs that are substrates of these enzymes.
- Savolitinib (AZD6094) inhibits P-gp, BCRP, OATP1B1, MATE1 and MATE2K transporters and this may affect transport of other drugs that is dependent on any of these transport proteins.
- Since there is limited clinical experience with this agent, patients on concomitant drugs with narrow therapeutic ranges, such as warfarin, should be monitored closely.

September 2017

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Savolitinib (AZD6094) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Savolitinib (AZD6094) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4, 3A5 and 1A2." Savolitinib (AZD6094) inhibits enzymes CYP 3A4, 3A5, 1A2, 2C8, 2C9, 2D6 and transport proteins P-glycoprotein (P-gp), BCRP (breast cancer resistance protein), OATP1B1, MATE1 and MATE2K. These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking savolitinib (AZD6094).
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is
- _____ and he or she can be contacted at

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **savolitinib (AZD6094).** This clinical trial is sponsored by the NCI. savolitinib (AZD6094) may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

➢ Tell your doctors if you stop taking any medicines or if you start taking any new medicines.

➢ Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.

➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

➢ Avoid ingesting grapefruit, grapefruit juice and Seville oranges.

➢ You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges, such as warfarin.

➢ savolitinib (AZD6094) interacts with CYP 1A2, 3A4/5, 2C8, 2C9, 2D6 and transport proteins, P-gp, BCRP, OATP1B1, MATE1 and MATE2K, and must be used very carefully with other medicines that interact with these enzymes and proteins.

➢ Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP 3A4/5, 1A2." savolitinib (AZD6094) inhibits CYP 3A4/5, 1A2, 2C8, 2C9, 2D6 and transporters, P-gp, BCRP, OATP1B1, MATE1 and MATE2K. It may change how other medicine works in your body.

➢ Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.

➢ Your study doctor's name is

_____ and can be contacted

at _____.

18.3d Sunitinib Patient Drug Information Handout and Wallet Card

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, sunitinib**.** This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Sunitinib interacts with a certain specific enzyme in your liver.

- The enzyme in question is **CYP 3A4**. Sunitinib is metabolized by CYP3A4 and may be affected by other drugs that inhibit or induce this enzyme.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Sunitinib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Sunitinib must be used very carefully with other medicines that use certain **liver enzyme.** Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered ***"strong inducers/inhibitors of CYP3A4."***

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Do not drink or eat grapefruit/juice or Seville oranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **sunitinib.** This clinical trial is sponsored by the NCI. **Sunitinib** may interact with drugs that are **processed by your liver**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges.

Sunitinib must be used very carefully with other medicines that interact with **CYP3A4 enzyme**.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors CYP3A4."**
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

18.4 Identification and Characterization of Oncometabolite-Induced DNA Repair Defects in Sporadic Papillary Kidney Cancer

a. **Objectives:**

1. To estimate the frequency of high oncometabolite levels in formalin-fixed, paraffin-embedded (FFPE) tissues of patients with advanced papillary renal cell carcinoma by liquid chromatography–mass spectrometry (LC-MS/MS) and estimate progression free survival for those with and without high oncometabolite levels being treated.

2. To correlate the mutational signature suggestive of a homologous recombination defect with high oncometabolite levels in patients with papillary renal cell carcinoma pRCC.

b. **Brief justification:**

Papillary renal cell carcinoma (pRCC), although a rare disease, is the second most common form of kidney cancer and there no effective treatment options for patients with metastatic disease. Prior SWOG studies S0317 and S1107 have proven disappointing while the ongoing **S1500** protocol had 2 arms closed for futility while two arms continue to accrue patients. Accrual is expected to be completed on **S1500** in late fall 2019. Comprehensive genomic sequencing projects have greatly advanced our understanding of pRCC. *(1)*It is now established that both hereditary and sporadic RCCs harbor alterations in key tricarboxylic acid (TCA) genes, including the *fumarate hydratase* (*FH*) and *Succinate Dehydrogenase (SDH)* complex genes. Germline loss of *FH* leads to an aggressive kidney cancer syndrome known as Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) where individuals are at risk to develop a lethal form of RCC often appearing similar to type 2 pRCC. *(2) SDH* mutations are associated with a second form of inherited RCC, referred to as SDH-RCC. *(*3*)* HLRCC- and SDH-RCC-associated tumors produce extremely high levels of fumarate and succinate, respectively, which drive tumorigenesis via the inhibition of αketoglutarate (αKG)-dependent dioxygenases. *(4)* It was recently discovered that the (S) enantiomer of 2HG (S-2HG) is produced in subsets of sporadic renal tumors, which also potently inhibits αKG-dependent dioxygenases. *(5,6)* Collectively, these “oncometabolites” represent novel therapeutic targets.

The homologous recombination (HR) pathway is responsible for double strand DNA repair. Our team recently discovered that oncometabolites induce HR defects which render tumor cells exquisitely sensitive to poly(ADP)-ribose (PARP) inhibitors. *(7)* We initially reported this finding in isocitrate dehydrogenase-1 and -2 mutant cancers, and we recently extended our findings to HLRCC- and SDHRCC-associated tumors. *(8)* Furthermore, our new preliminary data suggests that subsets of sporadic pRCCs exhibit a similar phenotype, which forms the basis for this proposal. Our findings reveal a novel pathway by which tumors acquire an HR-defective phenotype, in the absence of *BRCA1/2* mutations, often referred to as BRCAness. Our discovery is now being directly translated into an ongoing phase II trial with IDH1/2mutant tumors with PARP-inhibitor, olaparib. We have already observed efficacy signals in several patients including an IDH1-mutant chondrosarcoma and an IDH-1 mutant glioma, suggesting our findings are clinically relevant.

Based on these findings and that some forms of sporadic pRCC can have a similar metabolic HLRCC phenotype, we hypothesize that subsets of advanced pRCC exhibit oncometabolite-induced BRCAness, which can be exploited with PARP inhibitors. We will validate that these tumors have prespecified levels

consistent with known HLRCC samples. The **S1107** and **S1500** trials have enrolled large subsets of patients with metastatic pRCC, an orphan disease where translation of preclinical science to the bedside is hindered by lack of available samples. Therefore, samples from this trial are an ideal cohort to test the hypothesis that there are a subset of patients with massively elevated levels of oncometabolites (**Aim 1).** We will utilize a novel methodology recently developed by our team (accepted to Scientific Reports) that will allow us to qualify the oncometabolite levels in archival formalin-fixed, paraffin embedded (FFPE) specimens. We previously demonstrated that a subset of pRCC submitted to the TCGA has a mutational signature suggestive of a defect in homologous recombination. In parallel, we will determine whether high levels of oncometabolites suggestive of the HLRCC phenotype can be linked to the mutational signatures suggestive of a defect in homologous recombination (**Aim 2**).

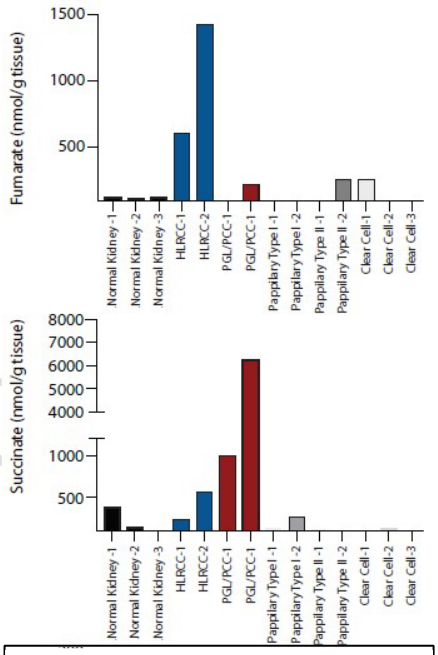

Fig. 1. Fumarate and succinate levels in normal kidney and RCC tissues vs HLRCC and SDH tumors

The potential impact of our translational medicine proposal is that it will provide further insight into how common the oncometabolite-induced, HR defect is in sporadic pRCC and set the foundation to design rational, biologically targeted clinical trials focused on exploiting this unique biology. This proposal will also leverage the strength of a recently established, cross-disciplinary collaboration between the laboratories of **Drs. Shuch**, **Bindra** and **Li**. Lead PI **Dr. Shuch** is a surgeon-scientist and an early-stage investigator (ESI) at the UCLA School of Medicine, with a major interest in the genetic characterization and clinical management of RCC *(9, 10, 11, 12, 13, 14, 15, 16 17)* Co-PI **Dr. Bindra** is a physician-scientist and clinical trialist at Yale, who is focused on developing novel synthetic lethal strategies to target solid tumors. *(18, 19, 20, 21, 22)* Finally, co-PI **Dr. Li** is an expert in metabolomics at the Karmanos Cancer Institute. *(23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34)*

c. **Eligibility:**

Subjects with metastatic papillary kidney cancer treated on **S1500** who submitted tissue.

d. **Clinical Endpoint to be used in analyses:**

Although not the primary focus of the project, patients with high oncometabolite levels will be compared to those without high levels in terms of progression-free survival.

e. **Experimental approach, validated assays employed and expertise of PI:**

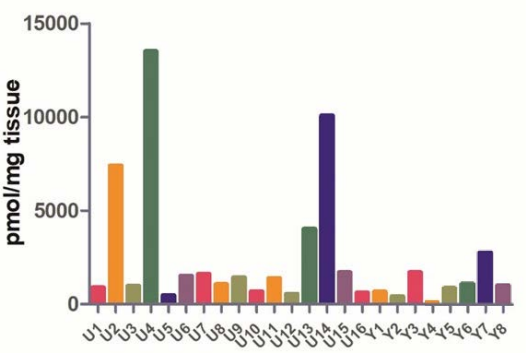

Fig. 2 Fumarate levels from sporadic papillary cancers at UCLA (U) and Yale (Y) (frozen samples). Some of the specimens have >5-10mmol concentrations.

Aim 1: Estimate the frequency of high oncometabolite levels in formalin-fixed, paraffin-embedded (FFPE) **tissues of advanced pRCC by LC-MS/MS.**

The central hypothesis of Aim1 is that a significant subset of pRCC produces high levels of oncometabolites. We have previously demonstrated that massive elevations of fumarate, succinate, or 2-HG can induce a BRCAness phenotype, seen in IDH1/2-mutant, HRLCC kidney cancer, and SDH-associated tumors. Our hypothesis is supported by: (a) previous reports of elevated S-2HG in cases of sporadic RCC (~10% of cases),5,6 (b) our preliminary data showing abnormally high fumarate and/or succinate levels in sporadic RCC cases (Fig.2), and c) the fact that some sporadic pRCC are in fact unidentified HLRCC cases or are HLRCC-like (despite having no germline FH mutation). Here, we will determine oncometabolite levels in a large cohort of pRCC FFPE specimens from two SWOG trials. We will quantitate oncometabolites (including succinate, fumarate, total total 2-HG, and R- and S-2HG enantiomers) in pRCC FFPE specimens by using a multiplex LC-MS/MS platform that has been established in the **Li** laboratory and has been accepted for publication (*Scientific Reports*). *(35)* In brief, FFPE tissue will be deparaffinizated and aliquots of tissue homogenate will be subjected to LC-MS/MS analysis of succinate, fumarate, and 2-HG. *(36, 37, 38)* No LC-MS/MS methods have been published for profiling oncometabolites in FFPE tissue, however the **Li** laboratory has successfully developed and validated a multiplex LC-MS/MS platform that allows simultaneous determination of succinate, fumarate, total 2-HG, and R- and S-2HG enantiomers in FFPE tissues. The lower quality control (LQC) concentrations for this assay based on spike-in experiments are 0.06, 0.2, and 0.006 µM of succinate, fumarate and 2-HG spiked in FFPE. The succinate/ alpha-keto-glutarate and fumarate/alpha-keto-glutarate ratios can also be used to accurately measure of the true concentration of oncometabolites for FFPE tissue. Normal kidney tissue FFPE specimens (not from SWOG trials) will be included as negative controls as we have demonstrated that fumarate levels are generally less than 25 uM in frozen tissue and less than the lower limit of 0.2 uM in the FFPE specimens. HLRCC, SDH-RCC, and IDH1/2 mutant glioma tissues with known oncometabolites will be used as positive controls. While 99% of fumarate is lost with fixation, to date all confirmed HLRCC kidney specimens run with FFPE assay (n=12) have detectable levels of fumarate at concentrations exceeding 1.5 umol/g of tissue) (Figure 3).

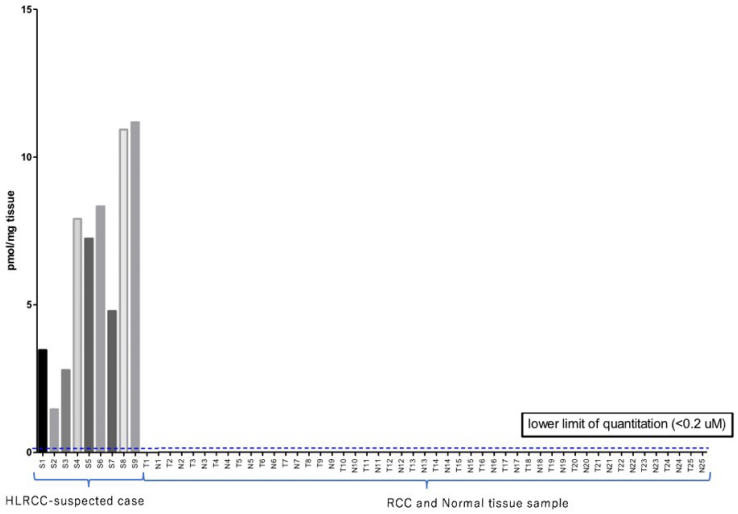

Figure 3: FFPE samples from HLRCC kidney cancers (high) and matched tumor/normal cases from sporadic renal tumors (less than lower limit of quantification)

Aim 2: Correlate the mutational signature suggestive of a homologous recombination defect with high oncometabolite levels in patients with papillary renal cell carcinoma pRCC.

Exome sequencing is ongoing as part of an already approved TM study with BIQSFP funding in SWOG **S1500**. A clinical pipeline with strict mutational calls has been applied to interrogate clinically relevant cancer genes including MET, the integrated biomarker of the trial. To evaluate alterations across the entire exome, BAM files will be reprocessed and exome mutation calls performed with Mutect2. *(39)* Interrogation of mutations that could lead to the oncometabolite and HRD phenotype will be performed for germline and somatic alterations. Critical TCA genes (n= 32, from Gene set enrichment analysis (GSEA) set, M3985) will be analyzed since if these metabolic enzymes were altered, there may be an upregulation of structurally similar oncometabolites. While FH, the SDH genes, and IDH1/2, have been well-characterized, there is emerging data that other genes if altered, can lead to metabolic dysregulation and cancer. *(40, 41, 42)* Similarly, a HR gene set (n=28, from GSEA set M11675) will be analyzed to see if other alteration could lead to double-strand DNA damage. Any alterations in both gene sets will be confirmed in the TCGA pRCC dataset.

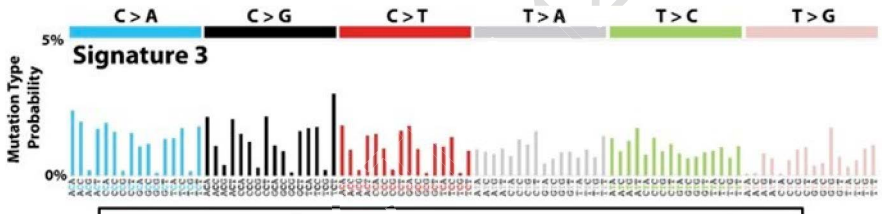

Figure 4: Mutational signature 3 from an intrinsic HR Defect

Different mutational processes such as exogenous or endogenous mutagen exposure may generate somatic single-nucleotide variants (sSNVs) with a unique nucleotide context pattern (signatures). Since nucleotides are paired, there are only six possible base substitutions (C>A, C>G, C>T, T>A, T>C, and T>G). Additional information on the adjacent 5' and 3' base to the sSNV can be useful to distinguish a particular mutational signature. Beyond sSNV patterns, signature 3 (Figure 4) is associated with high number of large insertion/deletions with microhomologous sequences flanking breakpoints due to an "alternative (or salvage)" DNA repair process: nonhomologous end joining. To identify signatures in the mutation spectra, post-processing of the variant call files (VCF) will be performed. We will use a robust, objective regression method (least absolute shrinkage and selection operator- LASSO) to identify operative mutational signature from 30 established signatures downloaded from COSMIC. *(43)* This methodology has

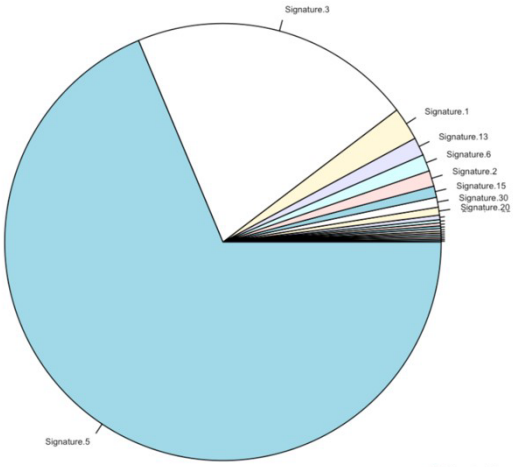

Figure 5: Approximate 25% of pRCC cases in TCGA had mutational signature 3 suggestive of an HR defect

been performed in our prior work with pRCC approximately 25% of TCGA samples had a suggestive signature of a defect in HR (Figure 5). *(44)* The oncometabolite and DNA mutational profile from aims 1 will be correlated with the mutational signature 3.

f. **Statistical Plan:**

Statistical Analyses will be conducted in conjunction with the SWOG Statistical Center under the direction of Dr. Catherine Tangen's team.

Based on submission rates for **S1500** and the trial accrual goal of 148 (currently at 132), we anticipate receiving adequate tissue specimens for at least n=120 patients. We have not had any issues with this assay so expect all cases with available tissue to be successfully run. **S1107** has residual tissue at City of Hope that can be used from 16 subjects once proper MUA agreements have been executed. With both cohorts we would have a total sample size of ~136 patients with metastatic pRCC that have FFPE tissue available for this project. Used tissue from **S1107** and the current TM project for **S1500** will not be returned to Nationwide for banking.

Aim 1 will evaluate oncometabolites in FFPE specimens from **S1500** and **S1107** patients. Based on the published data, 7-12% of pRCC should behave like HLRCC kidney cancer.

Elevations in tumors with Krebs Cycle defects have massive elevation of metabolites by a factor of 50100X. Much of the fumarate is lost with formalin fixation, therefore only samples with very high levels will be identified (the presence/absence) with very high levels for the fumarate or alpha-keto-glutarate ratio (figure 3). We will determine the frequency of cases with HLRCC-like levels of oncometabolites. With a sample size of 136 patients, we will be able to estimate the proportion with high oncometabolite levels to within at least +/-9% (95% confidence interval). If 12% have high oncometabolite levels, we'd expect 16 patients in this group and 120 without high levels. Descriptive Kaplan-Meier curves of progression-free survival will be generated, stratified by presence or absence of high oncometabolite levels.

Aim 2 will correlate the mutational landscape with oncometabolite-induced DNA repair defects in pRCC. Specifically, we will correlate mutational signature 3 (present vs. absent) using established COSMIC signature. We will compare the having measurable oncometabolites with by LC-MS/MS to the mutational signature**.** Based on our prior work with TCGA data, we estimate that 25% of the patients will have a signature 3 (i.e., n=34), leaving 102 without the signature. A generalized chi-square will be used to evaluate the association between positive mutational panel status and high oncometabolite levels.

g. **Data analysis performed by:**

Assays developed by Drs. Shuch, Bindra, and Li will be employed for oncometabolite and DDR detection as shown above. Evaluation of the exome sequencing will be performed by Dr. Shuch and members of Dr. Paul Boutros' computational biology laboratory. Members of the Boutros lab are experts at deconvoluting mutational signatures and will perform that particular analysis similar to what was performed with whole genome samples from the Cancer Genome Atlas pRCC cohort. *(16)* These data will be shared with the SWOG Statistical Center where estimation and correlations will be performed.

h. **Who will be performing testing?**

Brian Shuch, MD (UCLA)	Ranjit Bindra, MD PhD (Yale)	Jing Li, PhD (Karmanos)
UCLA School of Medicine Factor Health Science Bld. Room 12-956 700 Tiverton Avenue, Los Angeles, CA 90095	Yale School of Medicine 789 Howard Avenue, New Haven CT 06460	Karmanos Cancer Institute Wayne State University School of Medicine 4100 John R, HWCRC/Room 523 Detroit, MI 48201

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18.5 Specimen Banking and Translational Medicine Material Instructions for SWOG Biospecimen Bank (BB)

FFPE for Independent Pathology Review, NGS Analysis, and Banking

For each patient, the SWOG BB will receive either 1 FFPE tissue block or 12-20 unstained charged slides with 1 H&E stained slide from the pre-study biopsy. Upon receipt, the Bank will accession, barcode, and bank FFPE tissue blocks or slides at ambient temperature until distribution.

The Bank will cut a slide and H&E stain (4-5 µm) from the specimens received as FFPE blocks, and scan the H&E slide up to 2 times per case at 40X magnification for Independent Pathology Review in batches of 20 cases. Independent pathology review will be conducted with the Bank's Virtual Imaging for Pathology, Education & Research (VIPER) application; the Bank will create an electronic pathology data form.

At each quarter of enrollment (n=41), the Bank will receive a case list for distribution from the SWOG Statistics and Data Management Center, and then will prepare and distribute the FFPE tissue block (when available) or up to 20 unstained slides and a copy of the corresponding pathology report to Yale School of Medicine for next-generation sequencing (NGS) analysis at the address below:

Brian Shuch, MD/Urology Laboratory
Yale School of Medicine
Brady Memorial Laboratory
310 Cedar Street, BML 246
New Haven, CT 06510

After NGS analysis, residual FFPE specimens will be returned in batches to the SWOG Biospecimen Bank to store for future research.

Additionally, the SWOG BB will receive frozen, processed plasma, buffy coat, and serum aliquots from up to 4 time points per patient: pre-study, Weeks 7 and 13, and at follow-up after progression. Upon receipt, the Bank will accession and barcode the frozen cryovials of plasma, buffy coat, and serum to store in a -80°C freezer for future TM studies (TBD). For NGS analysis, one aliquot of the buffy coat from one time point (preferably pre-study time point) per patient as the reference genomic sequence will be sent to Yale School of Medicine with the tissue samples.