August 18, 2017

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #8 to E2810, *Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy*. This addendum is being submitted in response to an RRA from Drs. Fernanda Arnaldez, James Zwiebel, and Meg Mooney, dated August 4, 2017.

The following revisions to E2810 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated the version date.
2.	Section 5.5	Updated the Pazopanib CAEPR.

The following revisions to E2810 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated the version date.
2.	What Side Effects or Risks Can I Expect From Being in the Study?	Updated the Pazopanib Condensed Risk List per CTEP's request.

If you have any questions regarding this addendum, please contact corkery.james@jimmy.harvard.edu or 857-504-2900.

We request review and approval of this addendum to E2810 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Director, Protocol Development

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

Enclosure

CC: Leonard J. Appleman MD, PhD
Wayne B. Harris, MD
Michael Carducci, MD
Naomi Haas, MD
Michael Pins, MD
Jill Kolesar, PharmD
Maneka Puligandla, MS
Lynne Wagner, PhD
Sumanta K. Pal, MD
Brian Costello, MD
Diana Long RN
Khemraj Hirani, MPharm, PhD, RPh, CPh, CCRP, MBA
Michelle Hobbs, PharmD
Mark D. Walsh, PharmD, BCOP
Heidi D. Finnes, PharmD, BCOP
Carol Chami, R.N.
Melinda Flood
Bruce Giantonio, M.D.
Peter O'Dwyer, MD
Kerry Higgins
Donna Marinucci
Gayle Ipock
Jean MacDonald
James Corkery
Lauren Lambert
Mike Balco
Sarah Archambault
Becky Fillingham

ECOG-ACRIN cancer research group
Reshaping the future of patient care

E2810

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

STUDY CHAIR:	Leonard J. Appleman MD, PhD
STUDY CO-CHAIR:	Wayne B. Harris, MD
STUDY STATISTICIAN:	Judith Manola, MS
PATHOLOGY CO-CHAIR:	Michael Pins, MD
LABORATORY CO-CHAIR:	Jill Kolesar, PharmD
PATIENT OUTCOMES & SURVIVORSHIP:	Lynne Wagner, PhD
RENAL SUBCOMMITTEE CHAIR:	Naomi Haas, MD
GENITOURINARY COMMITTEE CHAIR:	Michael Carducci, MD
SWOG CO-CHAIR:	Sumanta K. Pal, MD
CALGB CO-CHAIR	Brian Costello, MD

Rev. 8/13

Version Date: August 18, 2017
NCI Update Date: July 31, 2012

STUDY PARTICIPANTS

US Sites Only
Rev. 4/14 **SWOG** / SWOG
Rev. 8/13 **ALLIANCE** / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology Foundation, Inc
Rev. 11/14

ACTIVATION DATE

August 8, 2012
Addendum #1 – Incorporated Prior to Activation
Addendum #2 – Incorporated Prior to Activation
Update #1– Incorporated Prior to Activation
Addendum #3 – 8/13
Addendum #4 – 4/14
Addendum #5 - 11/14
Addendum #6 – 2/15
Addendum #7 - 3/15
Addendum #8 – 8/17

NCI Supplied Investigational Agent: Pazopanib (GW 786034; NSC 737754, IND#75648)

Table of Contents

STUDY CHAIR

Leonard Appleman, MD, PhD
University of Pittsburgh Cancer Institute
5150 Centre Avenue
Pittsburgh PA 15232
Phone: (412) 648-6507
Fax: (412) 648-6579
Email: applemanlj@upmc.edu

STUDY CO-CHAIR

Wayne B. Harris, MD
Winship Cancer Institute of Emory University
1365 Clifton Rd., NE, Ste 68204
Atlanta, GA 30322
Phone: (404) 778-4189
Fax: (404) 778-3904
Email: wayne.harris@emoryhealthcare.org

STUDY CHAIR LIAISON (SCL)

Diana Long RN
University of Pittsburgh Cancer Institute
5115 Centre Avenue
Suite A410
Pittsburgh, PA 15232
Phone: (412) 647-8475
Fax: (412) 647-3768
Email: longdl@upmc.edu

SWOG CO-CHAIR

Sumanta K. Pal, M.D.
City of Hope Medical Center
Department of Medical Oncology
1500 E. Duarte Road
Duarte, CA 91010
Phone: (626) 256-4673
Fax: (626) 301-8233
Email: spal@coh.org

Rev. 8/13

CALGB CO-CHAIR

Brian Costello, M.D.
Mayo Clinic
200 First Street Southwest
Rochester, MN 55905
Phone: (507) 266-5365
Fax: (507) 284-1803
Email:costello.brian@mayo.edu

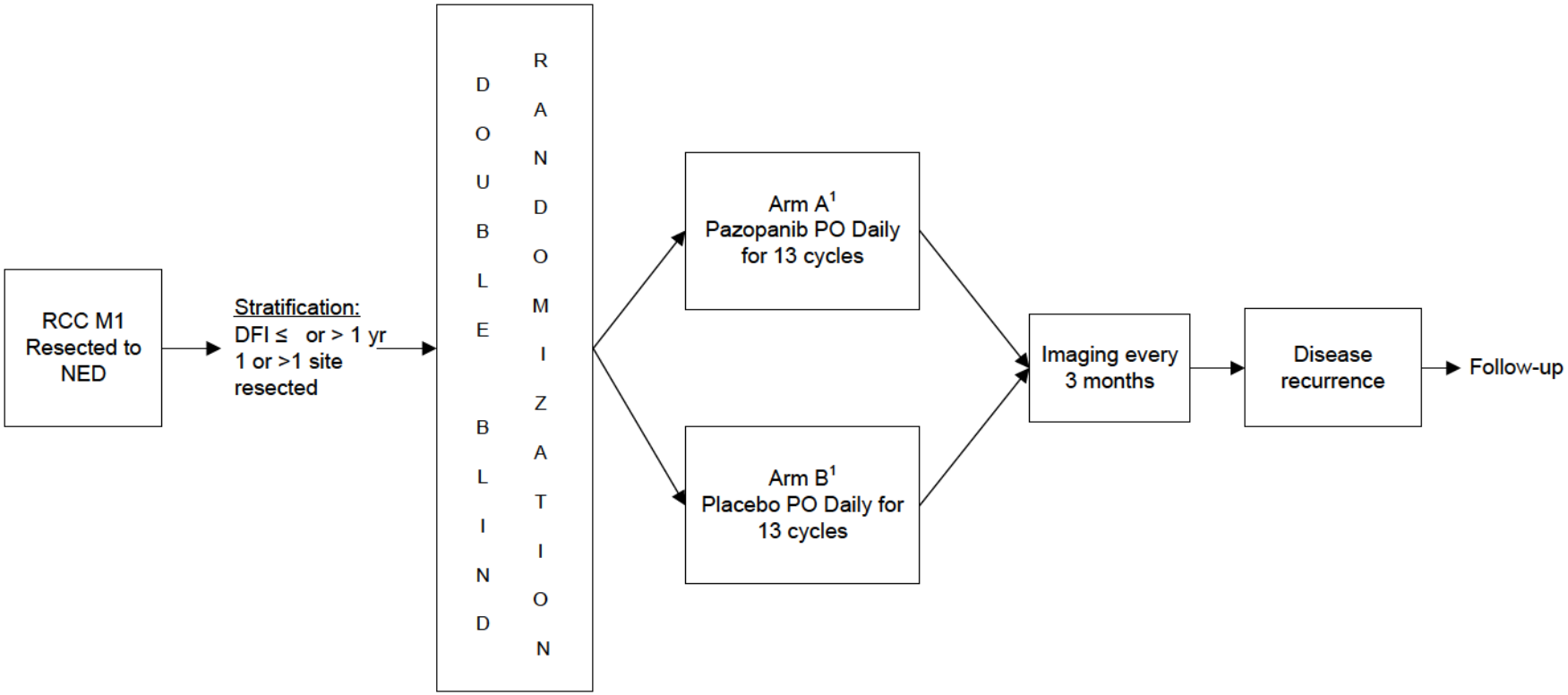
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

Rev. 11/14

To submit site registration documents:	**For patient enrollments:**	**Data collection will be performed exclusively in Medidata Rave**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	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.
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' websiteis 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. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
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.**		
For detailed information on the regulatory and monitoring procedures for CTSU sitesplease review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org> education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Website is located at https://www.ctsu.org.		

Rev. 11/14

Schema



Accrual Goal= 128 patients
Cycle= 28 days
NOTE: QOL will be assessed at several timepoints during this study. See Section 5.3.1 for details of the assessment schedule.

1. Blinded treatment:
Arm A= Pazopanib 4 tablets PO daily
Arm B= Placebo 4 tablets PO daily

1. Introduction

Renal cell carcinoma (RCC) is diagnosed each year in approximately 270,000 people worldwide, including 58,000 in the United States (1, 2). Surgical resection results in long-term disease-free survival in the majority of patients with localized RCC. However, a stage-dependent proportion of these patients will relapse with advanced disease following surgery. In addition, approximately 20-30% of patients with RCC are diagnosed with Stage IV disease at presentation (3). Median survival is approximately 1-2 years for patients with stage IV RCC in contemporary series, and long-term survival is uncommon (4-7). There are an estimated 116,000 deaths each year from RCC including 13,000 in the U.S.

1.1 Treatment of Advanced RCC

1.1.1 Cytokine Therapy

Recombinant interleukin-2 (aldesleukin) was approved by the FDA in 1992 for treatment of metastatic RCC based upon a durable complete response rate of 5-10% (8). Most patients do not receive a demonstrable benefit from cytokine therapy. In addition, the toxicity of high-dose interleukin-2 limits its use to a carefully selected minority of patients with metastatic disease. Lower intensity cytokine regimens are better-tolerated, but do not generally lead to durable responses (9).

1.1.2 Molecularly-Targeted Therapy for RCC

Clear cell RCC is a feature of the autosomal dominant von Hippel-Lindau syndrome (VHL), and somatic loss of VHL function is found in the majority of sporadic clear cell cases (10-12). The VHL gene product is the substrate recognition component of a ubiquitin ligase complex that plays a critical role in oxygen sensing by targeting the alpha subunit of hypoxia-inducible factor (HIF)-1 and -2 for proteasomal degradation (13). Loss of VHL function in hereditary and sporadic clear cell RCC leads to overabundance of HIF and subsequent overexpression of hypoxia-inducible genes. The vascular endothelial growth factor (VEGF) is an important transcriptional target of HIF and plays a critical role in processes including angiogenesis, wound healing, tumor invasion and migration (14). Circulating VEGF binds to the extracellular domain of dimeric transmembrane receptors VEGFR1 (Flt-1), VEGFR2 (KDR) and VEGFR3, activating tyrosine kinase enzymatic activity within the cytoplasmic domain of these proteins. This leads to activation of signaling pathways including the Raf-MEK-ERK and PI3K-Akt pathways, which promote cellular survival, growth, and morphogenesis (15).

Several drugs that target VEGF signaling have shown clinical activity in advanced clear cell RCC. These agents include the neutralizing anti-VEGF monoclonal antibody, bevacizumab (16) and a soluble fusion protein (aflibercept) containing the ligand-binding sequences of VEGFR2 (17). Small-molecule tyrosine kinase inhibitors (TKIs) targeted against VEGFR and related kinases (sorafenib, sunitinib, pazopanib, axitinib) have also shown activity in metastatic RCC.

These agents have shown significant improvement in progression-free survival vs. comparators (placebo or subcutaneous interferon alpha) and significant rates of radiographic tumor response (6,7,18,19). Complete tumor responses and durable disease control, however, are rarely seen with these agents. Mechanisms of acquired resistance are under investigation. Inhibitors of the mammalian target of rapamycin (mTOR) tyrosine kinase have also shown clinical activity in advanced RCC and two of these agents, temsirolimus and everolimus, and approved for use in advanced RCC (5,20).

1.1.3 Pazopanib

Pre-Clinical Pharmacology: Pazopanib is a selective, ATP-competitive inhibitor of the tyrosine kinases VEGFR (-1, -2, and -3), PDGFR (-α and -β) and c-Kit (21,22). Pazopanib has been demonstrated to inhibit recombinant kinase domain enzymatic activity in cell-free systems as well as ligand-dependent phosphorylation in viable tissue cultured cells. In animal models, oral pazopanib inhibited phosphorylation of the relevant kinases, as well as angiogenesis as determined by a number of assays. Pazopanib showed activity in mouse xenograft studies. In mice, plasma concentrations ≥ 40 μM were required for optimal inhibition of VEGFR2 kinase activity, angiogenesis and xenograft growth.

Pharmacokinetics: Pazopanib is orally bioavailable (median 21%), and oral absorption is significantly enhanced by food (approximate 2-fold increase in AUC and C_{max}). Therefore it is recommended to administer pazopanib on an empty stomach: at least 1 hour prior to and 2 hours after a meal. Oral bioavailability is limited above doses of 800 mg once daily due to solubility.

In human, rat and monkey species, oxidation by CYPP450 3A4 is the primary route of pazopanib biotransformation. There are minor contributions from CYP1A2 and CYP2C8. One of the circulating metabolites of pazopanib, GSK1268997, inhibited VEGF-induced endothelial cell proliferation with similar potency to that of pazopanib. The other 3 circulating metabolites, GSK1268992, GSK1071306 and GW700201, showed at least 10-to 20-fold less activity than pazopanib. The circulating levels of the metabolites are significantly lower than that of the parent compound, and are not likely to be clinically important.

Pazopanib is highly protein-bound in humans and other species. Half-life in patients with cancer ranged from 18 to 52 hours (Mean 30.9 hours). Studies with ^{14}C-labeled pazopanib showed that 67% of the ingested material was excreted unchanged in feces, as were the bulk of the metabolites. Less than 4% of radiolabeled material was excreted in urine. There was no correlation between estimated GFR and pazopanib exposure (range 30-150 ml/min). A phase I study of pazopanib in patients with solid tumors and varying degrees of hepatic dysfunction is being conducted by the CTEP Organ Dysfunction Group (clinicaltrials.gov NCT00674024). Results are not yet available.

Clinical toxicology: (See also Section 5.5: Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754))

The most common AEs reported in patients receiving pazopanib included diarrhea (55%), hypertension (41%), hair color changes (40%), nausea (32%), fatigue (29%), anorexia (24%), vomiting (21%), and ALT increased (17%). Most of these events were Grade 1 or 2 using the NCI CTCAE Version 3.0. Commonly reported AEs with the most frequent Grade 3 classification were hypertension (6%). ALT increased (5%), and AST increased (4%). Grade 4 and Grade 5 events were infrequently reported (9% and 4%, respectively).

- **Hepatic effects:** Cases of hepatic failure (including fatalities) have been reported during the use of pazopanib. In clinical trials with pazopanib, increase in serum transaminases (ALT, AST) and bilirubin were observed. In the majority of the cases, isolated increases in ALT and AST have been reported, without concomitant elevations of alkaline phosphatase or bilirubin. The vast majority (92.5%) of all transaminase elevations of any grade occurred in the first 18 weeks.
- **Hypertension:** In clinical studies with pazopanib, events of hypertension including hypertensive crisis have occurred. Hypertension (systolic blood pressure ≥ 150 or diastolic blood pressure ≥ 100 mm Hg) occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks).
- **Clinical efficacy of pazopanib in RCC:** A randomized discontinuation phase II study of pazopanib was conducted in patients with metastatic RCC (23). Eligible patients were either treatment-naïve or refractory to cytokines or bevacizumab. Two hundred and twenty five patients were enrolled. The partial response rate was 33% and complete response rate 1.3% by independent review. A randomized, double-blind study of pazopanib vs. placebo was recently reported (6). Patients who had received prior cytokine therapy or who were treatment-naïve were eligible. The pazopanib group showed a significant advantage in progression-free survival (9.2 vs. 4.2 months). The progression-free survival was 11.1 months in the patients who were treatment-naïve at study entry. The overall survival analysis of this study is not yet mature. The adverse event (AE) profile of pazopanib is similar to other TKIs targeting VEGFR and related kinases: diarrhea and hypertension were among the most frequent treatment-emergent AEs. However, certain events noted in other class members such as neutropenia, hand-foot syndrome and decreased left ventricular ejection fraction were seen less frequently with pazopanib (6,22). Pazopanib is currently being compared directly to sunitinib in patients with previously untreated metastatic RCC (clinicaltrials.gov id. NCT00720941).

1.2 Adjuvant Therapy for Localized RCC

Probability of recurrence after resection of localized RCC is dependent upon surgical stage and grade, and can be greater than 50% in high risk disease. Randomized studies have failed to show a benefit of adjuvant therapy with subcutaneous interferon alpha, interleukin-2 or an autologous heat shock vaccine (24-26). Two VEGFR TKIs, sorafenib and sunitinib, are currently being evaluated *vs.* placebo in ECOG study E2805 as adjuvant treatment for patients with resected renal cell carcinoma, stage Ib (Gr3-4)--T3N2M0 (clinicaltrials.gov #NCT00326898). An adjuvant study of pazopanib is also ongoing (Clinicaltrials.gov NCT01235962). No intervention has previously shown benefit in the adjuvant setting after nephrectomy, and the current standard of care after surgery outside of a clinical trial remains surveillance.

1.3 Metastatectomy in Advanced RCC

Surgical resection for metastatic RCC was first reported in 1939 (27), and a number of case series with long-term follow-up data have been published. These reports demonstrate that a proportion of patients remain free of disease for years after metastatectomy, but most will ultimately recur. Kavolius *et al.* at the Memorial Sloan-Kettering Cancer Center retrospectively reviewed 141 patients with stage M1-NED RCC after metastatectomy (28) and reported a 5-year overall survival of 40%. Zerbi *et al.* reported a series of 23 patients who underwent resection of pancreatic RCC metastases over an 8 year period (29). At a median follow up of 31 months, 12 patients were alive and free of disease. Adam *et al.* reported a large series of patients who underwent surgery for metastatic liver lesions, including 85 with primary RCC. Of these, 38 patients were alive at 5 years (45%) and median survival was 36 months (30). A study of 105 patients with pulmonary metastases showed a survival rate of 40% at 5 years and 33% at 10 years (31). Analysis of these retrospective data suggests that the best outcomes with surgery are obtained in patients who have solitary sites of metastasis and a long disease-free interval (i.e. greater than one year). However, there has never been a randomized study comparing metastatectomy to no surgical intervention, and the role of metastatectomy in the management of advanced RCC remains poorly defined in the current era of targeted therapy. The ability to delay disease progression with well-tolerated systemic therapy might argue against the need for surgical intervention. However, the availability of active systemic therapy suggests the possibility of favorable long-term disease control with a multi-modality approach incorporating metastatectomy and pre- and/or post-operative systemic therapy.

1.4 Post-operative Management After Metastatectomy

The disease status of patients who have undergone surgical resection of all detectable metastatic sites will be referred to herein as M1 surgically resected to no evidence of disease (**M1-NED).** A study of adjuvant high-dose interleukin-2 (one course) vs. observation conducted by the Cytokine Working Group was designed to detect a benefit in patients who received treatment after nephrectomy for locally advanced disease (T3b-4 and/or N1,2; M0) (24). Although they were excluded from the primary analysis, the study permitted enrollment of stage M1-NED patients as well. Surprisingly, 25 out of 69 patients enrolled in the study had stage M1-NED disease. The study was terminated after

an interim analysis determined that high-dose IL-2 was unlikely to demonstrate a 30% absolute improvement in 2-year disease-free survival in the locally-advanced group. No benefit in disease-free or overall survival was seen in either the locally-advanced or M1-NED cohorts. However, this study highlights the existence of a significant population of patients with renal cell carcinoma who are stage M1-NED, and demonstrates the feasibility of enrolling these patients into randomized clinical trials.

1.5 Studies of Stage M1 NED Patients in Other Solid Tumors

Colorectal cancer: Colorectal cancer is another malignancy for which surgical resection of metastatic disease (primarily to the liver) is widely practiced. Two phase III clinical trials were recently performed to assess the role of adjuvant chemotherapy vs. observation after resection of colorectal cancer liver metastases: The *Fédération Francophone de Cancérologie Digestive (**FFCD**) Trial 9002* and the *European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia (**ENG**)* trial. Both studies found a trend favoring adjuvant chemotherapy. A pooled analysis of the progression-free survival data showed a borderline statistically significant trend in favor of adjuvant chemotherapy (32). Multivariate analysis determined that adjuvant chemotherapy was associated with both improved disease-free and overall survival.

Melanoma: ECOG completed accrual of protocol **E4697**- "A Randomized, Placebo-Controlled Phase III Trial of Yeast-Derived GM-CSF Versus Peptide Vaccination Versus GM-CSF Plus Peptide Vaccination Versus Placebo in Patients with "No Evidence of Disease" after Complete Surgical Resection of "Locally Advanced" and/or Stage IV Melanoma". Enrollment was successful, and results are pending (Clinicaltrials.gov NCT00005034).

1.6 Study Rationale

Resection of metastatic disease is an accepted clinical practice for selected patients with advanced RCC. The clinical utility of VEGFR TKI therapy for patients with no evidence of disease following metastatectomy is unknown. TKI therapy is associated with significant chronic toxicity, and a proportion of resected patients will have favorable disease-free survival without systemic therapy. The goal of this proposed study is to compare the outcomes in patients treated with the anti-VEGFR multi-targeted TKI pazopanib following metastatectomy to those treated with placebo. The primary endpoint of disease-free survival is designed to be a feasible and expeditious measure of clinical benefit. The results of this study will inform the clinical management of RCC stage M1-NED patients in the future. A significant improvement in DFS and acceptable toxicity profile would support the post-operative use of VEGFR TKI therapy after complete metastatectomy. A lack of benefit would suggest that systemic treatment of stage M1-NED should remain investigational, and TKI therapy should be withheld until recurrence.

In addition to the primary objective of measuring the potential benefit of post-operative systemic therapy, this randomized phase III study will also provide valuable information on the utility of metastatectomy in RCC. Single-institution series have shown that there are a proportion of patients who undergo

metastatectomy for advanced RCC who enjoy durable disease-free remission. However, patient selection and outcomes varied widely from series to series. The placebo arm of the current study will address this knowledge gap by providing prospective, multi-institutional outcomes data for patients with stage M1-NED RCC. These data will assist in the identification of patients who are likely to benefit from metastatectomy. Even if the results of the placebo arm are unfavorable, a favorable outcome in the pazopanib arm would support metastatectomy for selected patients who are candidates for post-operative systemic therapy with a VEGFR TKI. Alternatively, poor outcomes in both study arms would suggest that metastatectomy should be not be recommended outside of a clinical trial. Although a randomized study of metastatectomy *vs.* no surgery would better assess the utility of surgery, such a study has not been completed in the 80 years since the first outcomes of metastatectomy were reported (27), and a randomized design is unlikely to be accepted by patients or practitioners.

This study will also provide a unique opportunity to collect paired primary and metastatic tumor samples and will enable exploration of histological and genetic changes that occur as renal cell carcinoma undergoes metastasis. These changes may provide insight into the mechanisms of metastasis and thus an opportunity for identification of drug targets.

1.7 Rationale for Quality of Life Analysis

Systemic cancer therapies (in the adjuvant and metastatic setting) are generally deemed to be of clinical benefit if they demonstrate an improvement in overall and/or progression-free survival. However, systemic therapies can cause significant toxicity, and it is important to balance the impact of treatment on health-related quality of life (HRQoL) with any improvement in OS or DFS. Instruments that capture patient-reported outcomes have become powerful tools to measure the impact of cancer- and treatment-related symptoms and their impact on quality of life. These techniques have been incorporated into several recent studies of targeted therapy in renal cell carcinoma. Patient reported outcomes were examined for subjects participating in a randomized phase III trial of the mTOR inhibitor, everolimus vs. placebo in patients with metastatic renal cell carcinoma who had progressed through sunitinib and/or sorafenib (33). Patients completed the Functional Assessment of Cancer Therapy Kidney Symptom Index—Disease-Related Symptoms (FKSI-DRS) and European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) questionnaires at baseline and at the start of each cycle of blinded study treatment. Decline from baseline in physical functioning and global quality of life was greater in the everolimus arm by a small but significant degree compared to placebo. The FKSI-DRS and the Functional Assessment of Cancer Therapy-Kidney Cancer Symptom Index (FKSI-15) were used in another second-line metastatic study in which patients who had progressed through sunitinib were randomized axitinib vs. sorafenib (34). Progression-free survival was superior for axitinib, and there was no significant difference in the patient-reported outcomes obtained by the FKSI-DRS and FKSI-15 instruments between the two study treatments. Patient-reported outcomes were evaluated using the EORTC QLQ-C30 and the EQ-5D in a randomized study of pazopanib vs. placebo in patients with metastatic renal cell carcinoma who were either treatment-naïve or had received prior cytokine therapy (35).

There was a trend toward decreased deterioration in HRQoL in patients treated with pazopanib compared to placebo. There was greater decline in HRQoL in patients whose best tumor response was progressive disease vs. those whose best response was stable disease or partial/complete response. The authors conclude that these findings support the tolerable safety profile of pazopanib, and suggest that HRQoL was not significantly compromised by pazopanib treatment. Patient-reported outcomes were also assessed in a phase III study of sunitinib vs. interferon in previously untreated metastatic disease using the FKSI-15 as well as the EQ-5D and the Functional Assessment of Cancer Therapy-General (FACT-G). The results obtained with all three of these instruments favored sunitinib over interferon (36-37).

An analytical technique for integrating survival benefit and treatment toxicity has been established and is known as Quality Time Without Symptoms or Toxicity (Q-TWiST) (38). Q-TWiST has generally been defined using overall survival, but this technique has also been used to integrate progression-free survival and toxicity data to model the utility of cancer treatment (39). Q-TWiST analysis is especially useful to evaluate potentially toxic therapy that is administered to patients who are free of subjective symptoms of disease. Therefore, Q-TWiST is well suited to the current study by integrating the toxicity and potential benefit of pazopanib to determine the net utility in patients with RCC M1-NED. Q-TWiST analysis using the EQ-5D has been applied to compare the quality of life in patients treated with temsirolimus vs. subcutaneous interferon in a randomized phase III study for previously untreated, unfavorable risk metastatic RCC. Q-TWiST was found to be longer for temsirolimus compared to interferon (6.5 vs. 4.7 months). Q-TWiST analysis will be used in the current study of pazopanib vs. placebo to integrate the impact of study treatment on HRQoL with the potential benefit in survival. The EQ-5D will be the instrument that is used to capture patient-reported health status. The EQ-5D measures the patient's assessment of overall health status in five health dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and has been well-validated in patients with cancer (40-42). The EQ-5D instrument will be administered at baseline, every cycle, then at each follow-up visit.

Rev. 11/14

The goal of the assessment of kidney symptoms using the FKSI is to characterize changes in symptoms associated with treatment and, among patients whose disease recurs, with disease. The FACIT-Fatigue and PROMIS Fatigue Short Form will be administered to assess fatigue, the most common cancer-related symptom. In patient and expert interviews on a Northwestern University-based study, we have identified fatigue as the most common symptom associated with anti-angiogenesis therapy. This is consistent with the literature as well (33, 36, 37). We will compare FACIT-Fatigue and PROMIS Fatigue scores between treatment arms to quantify the extent to which pazopanib is associated with fatigue in comparison to placebo. We propose administering the FACIT-Fatigue and PROMIS Fatigue Short Form to allow us to compare results from this trial to E2805, which also administered both measures. The FACIT-Fatigue has well established psychometric properties, including clinically meaningful change scores. The 13-item FACIT-Fatigue has been administered to participants on numerous ECOG trials and administering this brief instrument to E2810 participants will allow us to compare this sample to other trial samples. Administration of the PROMIS Fatigue Short Form will allow us to compare

fatigue among trial participants to numerous other disease populations (cancer and non-cancer) given extensive descriptive data available among thousands of PROMIS participants. Length of assessment: FKSI (15 items), FACIT Fatigue (13 items), PROMIS Fatigue Short Form (7 items) = 35 items. We anticipate this assessment will take approximately 30 minutes. The assessment will be administered at baseline, cycle 7, month 15, and at recurrence (if patient has terminated treatment prior to cycle 7, questionnaire will be administered 6 months from randomization).

2. Objectives

2.1 Primary Endpoint

2.1.1 To evaluate disease-free survival with pazopanib as compared to placebo, defined as the time from randomization to the development of recurrent disease, second primary cancer (other than localized breast, localized prostate, or non-melanoma skin cancer) or death from any cause for patients with metastatic RCC with no evidence of disease following metastatectomy.

2.2 Secondary Endpoints

2.2.1 To describe the overall survival of patients with advanced RCC randomly assigned to receive placebo or pazopanib for one year following metastatectomy to NED.

2.2.2 To describe treatment and (at recurrence) disease-related adverse events in the two treatment arms.

2.2.3 To analyze quality-adjusted time without symptoms of disease or treatment (Q-TWiST) for subjects in the two treatment arms.

2.2.4 To characterize changes in patient-reported fatigue and (at recurrence) kidney cancer-related symptoms during and following treatment with pazopanib compared to placebo.

2.2.5 To explore the association between plasma trough levels of pazopanib and disease-free and overall survival.

2.2.6 To prospectively bank preserved tissue from primary tumors and associated metastatic sites in patients with RCC.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

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 four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be at least 18 years of age at the time of randomization.

_____ 3.1.2 Patient must have pathologically confirmed renal cell carcinoma with a clear cell component. Pure papillary and chromophobe histologies are excluded. There must be pathologic confirmation of metastatic disease in the resected metastatectomy specimen.

_____ 3.1.3 Patient must have undergone nephrectomy or partial nephrectomy to remove primary renal cell carcinoma (at any time in the past).

_____ 3.1.4 Patient must have undergone surgical resection to remove one or more sites of metastatic disease, with successful removal of all known sites 2- 12 weeks prior to randomization. Any number of prior metastatectomies may have been performed in the past, so long as the most recent procedure was within the 12 weeks of registration.The most recent procedure may be nephrectomy for a renal primary tumor.

Rev. 8/13

Rev. 4/14

Rev. 8/13 _____ 3.1.5 Patients with synchronous disease at initial diagnosis must have metastatic (M1) disease (AJCC 7th edition T1-4N0-1M1).

Rev. 8/13 _____ 3.1.6 Positive surgical margins are permitted if the surgeon confirms complete resection of gross metastatic disease, and post-operative scans are negative.

Rev. 8/13 _____ 3.1.7 Patients presenting with metachronous disease may have distant metastases, regional lymph node or renal bed recurrence. Recurrences at a partial nephrectomy resection site are not eligible if it is the only site of disease.

Rev. 8/13 _____ 3.1.8 Patients presenting with tumors within the kidneys (multiple synchronous or single/multiple metachronous) are not eligible if there

are no extrarenal sites of disease (i.e. potential multifocal primary disease).

Rev. 8/13, 4/14

_____ 3.1.9 Patient must have no evidence of disease on post-operative imaging:

3.1.9.1 A CT of the chest must be obtained within 4 weeks prior to randomization with or without contrast.

3.1.9.2 A CT of the abdomen/pelvis must be obtained within 4 weeks prior to randomization with IV contrast (oral contrast may be added at the radiologist's discretion). An MRI of the abdomen/pelvis with gadolinium may be substituted for the CT if the CT with IV contrast is contra-indicated.

3.1.9.3 An MRI of the brain with and without gadolinium must be done within 8 weeks prior to randomization. A CT of the brain with and without IV contrast is permitted if MRI is contra-indicated (i.e., pacemaker).

_____ 3.1.10 Patient must not have received any prior or concurrent systemic therapy for RCC. Adjuvant placebo administration is permitted.

Rev. 8/13

_____ 3.1.11 Patient must have no active peptic ulcer disease.

Rev. 8/13

_____ 3.1.12 Patient must have no active inflammatory bowel disease.

Rev. 8/13

_____ 3.1.13 Patient must have no New York Heart Association (NYHA) class II or greater congestive heart failure.

Rev. 8/13

_____ 3.1.14 Patient must have no prior history or current clinically apparent central nervous system metastases.

_____ 3.1.15 Patient must have an ECOG performance status of 0 or 1 at the time of randomization.

_____ 3.1.16 Patient must have the following baseline laboratory values within 2 weeks prior to randomization:

3.1.16.1 Absolute granulocyte count > 1,500/mcL

AGC_____ Date of Test_____

3.1.16.2 Platelets > 100,000/mcL

Platelet count_____ Date of test_____

3.1.16.3 Total bilirubin < 1.5 X institutional upper limit of normal

Total bilirubin_____ Date of test_____

3.1.16.4 AST(SGOT)/ALT(SGPT) < 2.5 X institutional upper limit of normal

ALT_____ Date of test_____ ULN_____

AST_____ Date of test_____ ULN_____

3.1.16.5 Calculated creatinine clearance (CrCl) > 30mL/min (pazopanib is not cleared by the kidney). CrCl= Wt (kg) x (140-age)*/72 x Cr. Level; (*female x 0.85).

Creatinine Clearance_____ Date_____

Rev. 8/13

3.1.16.6 Subjects must have a urine protein/creatinine ratio < 1. If UPC ≥ 1, then a 24-hour urine total protein must be obtained. Subjects must have a 24-hour urine protein value < 1g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

_____ 3.1.17 Women must not be pregnant or breast-feeding due to the unknown effects of pazopanib on the developing fetus.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.18 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception or to abstain from sexual intercourse for the duration of their participation in the study. Should a woman become pregnant while participating in this study, she should inform her treating physician immediately. If a man impregnates a woman while participating in this study, he should inform his treating physician immediately.

_____ 3.1.19 Patient must be able to swallow pills and have no significant impairment in gastrointestinal absorption including history of gastric bypass surgery.

_____ 3.1.20 Patient must have no history of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib.

_____ 3.1.21 Patient must have no uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 3.1.22 Patient must have a QTc interval on ECG ≤ 0.48 seconds by Bazett's calculation (≤ CTCAE v.4 Grade 2) prior to randomization.

_____ 3.1.23 Patient must have a systolic blood pressure ≤ 140 mmHg and diastolic blood pressure must be ≤ 90 mmHg, measured within 4 weeks prior to randomization. Initiation or adjustment of anti-hypertensives prior to starting study treatment is allowed.

_____ 3.1.24 Patient must not have serious or non-healing wound, ulcer, or bone fracture at the time of randomization.

_____ 3.1.25 Patient must have no history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to randomization.

_____ 3.1.26 Patient must have no history of cerebrovascular accident (CVA) within 6 months of randomization.

_____ 3.1.27 Patient must have no history of myocardial infarction, hospital admission for unstable angina, cardiac angioplasty or stenting within 6 months of randomization.

_____ 3.1.28 Patient must have no history of venous thrombosis within 12 weeks of randomization.

_____ 3.1.29 Patient cannot be taking strong CYP3A4 inhibitors such as: (See Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

3.1.30 Appendix IX for CYP interaction information)

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV antiviral protease inhibitors: ritonavir, indinavir, saquinovir, nelfinavir, amprenavir, lopinavir
- Antifungals: itraconazole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone

_____ 3.1.31 Patient must not have history of hemoptysis in excess of 2.5 mL (1/2 teaspoon) within 8 weeks prior to randomization.

Rev. 8/13 _____ 3.1.32 Patient must not be taking drugs known to prolong the QTc interval. Such drugs should be discontinued at least 5 half-lives prior to randomization. See Appendix VII for a list of agents that that are associated with a risk for QTc prolongation and/or Torsades de Pointes.

Rev. 4/14 3.1.33 [Removed in Addendum 4]

Rev. 8/13 _____ 3.1.34 Patients must not have any history of other cancer within 3 years from time of randomization with the exception of basal cell skin cancer, squamous cell skin cancer, in situ cervical cancer, ductal or lobular carcinoma in situ of the breast, or resected non-invasive (Ta) urothelial carcinoma.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. 11/14

4. Randomization Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by email at pmbregpend@ctep.nci.nih.gov.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the *CTEP Associate Registration Help Desk* by email at ctepreghelp@ctep.nci.nih.gov.

CTSU Registration Procedures

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

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. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering

credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the E2810 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
- Click on the ECOG-ACRIN link to expand, then select trial protocol E2810
- Click on the Site Registration Documents link

Requirements For E2810 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval *and* Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.
3. **A. CTSU IRB Certification Form.**

   Or

   B. HMS OMB No. 0990-0263.

   Or

   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - **Indicate all sites approved for the protocol under an assurance number.**
   - **OHRP assurance number of reviewing IRB**
   - **Full protocol title and number**
   - **Version Date**

- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- 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

Patient Enrollment

Patients must not start protocol treatment prior to randomization.

Treatment must start within ten working days after randomization.

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

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://eapps-ctep.nci.nih.gov/iam/index.jsp) and a 'Registrar' role on either the LPO or participating organization roster.

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. 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.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria has been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com. The following information will be requested:

Patients must not start protocol treatment prior to randomization.

Treatment must start within 14 calendar days after randomization.

4.1 Protocol Number

4.2 Investigator Identification

4.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2 Investigator's name (NCI number)

4.2.3 Cooperative Group to be Credited

4.2.4 Investigator to be Credited

4.2.5 Protocol specific contact information

4.3 Patient Identification

4.3.1 Patient's initials (first and last)

4.3.2 Patient's Hospital ID and/or Social Security number

4.3.3 Patient demographics

4.3.3.1 Gender

4.3.3.2 Birth date

4.3.3.3 Race

4.3.3.4 Ethnicity

4.3.3.5 Nine-digit ZIP code

4.3.3.6 Method of payment

4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Stratification Factors

4.5.1 Disease-free interval (time from nephrectomy or most recent previous metastatectomy to current metastatectomy):

- Less than or equal to one year
- More than one year

4.5.2 Number of sites of metastatic disease resected at metastatectomy:

- One
- More than one

4.6 Additional Requirements

4.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operating Office - Boston.

4.6.2 Pathology materials MUST be submitted for central diagnostic review and classification as outlined in Section 10. Biological samples from

consenting patients are to be submitted for research studies as indicated in Sections 10 and 11.

Rev. 11/14

4.6.3 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, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

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 site 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 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

If the patient has been a participant on a previous ECOG-ACRIN trial, the treatment protocol number(s) and the ECOG-ACRIN patient ID on the treatment protocol(s) will be requested.

4.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted by Medidata Rave according to the schedule in the E2810 Forms Completion Guidelines.

4.8 Emergency Unblinding

NOTE: The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor's office in the event of an emergency or adverse event that may result in the need to unblind the patient.

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Leonard Appleman at (412) 648-6507 or Email: applemanlj@upmc.edu, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operating Office - Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. **Remember, Answer Connect should only be contacted outside of normal business hours and only in the event of an emergency.** The ECOG-ACRIN Operating Office - Boston or AnswerConnect will require the protocol number (i.e., “E2810”), the patient ID number (e.g., “44444”), and the patient initials (e.g., “FL”) to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

5. Treatment Plan

5.1 Screening and Randomization

Patients may undergo the informed consent process and study screening 2-12 weeks following metastatectomy for metastatic RCC. Patients will be randomized in a double-blinded fashion to receive pazopanib 800 mg once daily or placebo at a 1:1 ratio. Study treatment must begin between 4 and 14 weeks following metastatectomy.

5.2 Administration Schedule

Study Arm assignment is double-blinded.

5.2.1 Study Treatment

Pazopanib (Arm A) or Placebo (Arm B) 800 mg (200 mg tablets x4) orally once daily for 28 days

Repeat cycles every 28 days for a total of 13 cycles.

Pazopanib/Placebo should be taken without food (at least one hour before or two hours after a meal).

Pazopanib/Placebo should be taken whole with water and must not be broken or crushed.

If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Patients should not eat grapefruit or drink grapefruit juice or other grapefruit product while taking the study medication as they may increase the amount of pazopanib in the body.

5.3 HRQL Assessment

Questionnaires will be available on-line for centers to print as needed. They will be administered by trained personnel. At each time point, patient responses on the completed questionnaire will be data entered using Medidata Rave. The original completed questionnaire must be kept in the patient's chart.

The following assessments are to be administered by the research staff and performed on all patients.

EQ-5D: The EQ-5D is a brief instrument which consists of five questions, related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, along with a question about global health which is rated from 0 (the worst health you can imagine) to 100 (the best health you can imagine). For each patient, EQ-5D assessments will be averaged during each of the health states. We have chosen the EQ-5D as a tool for assessing overall quality of life because of its previous use in this context (35,42,44,45). It is very short and easy to administer making it suitable for the frequent administration necessary to derive health utilities. It targets overall quality of life, rather than specific symptoms, which is our primary interest.

Fatigue Instruments: We will administer the FACIT-Fatigue subscale (13 items) and the PROMIS Fatigue Scale (7 items) to measure fatigue. Evaluating fatigue

in this otherwise healthy population will enable us to better understand the relative contributions of treatment and disease burden to this prevalent symptom. We will use the FACIT-Fatigue and PROMIS Fatigue short form to assess fatigue at baseline, 6 months, and 15 months. The 6-month assessment will enable assessment of fatigue levels on-treatment, while the 15-month assessment will allow us to assess recovery following treatment for the subset of patients who are still free of disease at that time point. The FACIT-Fatigue has been used to measure fatigue in many previous ECOG trials, including in renal cancer (E2805). We have established minimally important differences for this measure facilitating interpretation of change over time. We will administer the PROMIS Fatigue short form, which has also previously been administered in an ECOG renal cell cancer trial (E2805). PROMIS Fatigue short form data will allow us to compare this study sample to other disease populations and the general population, using normative data that has been collected through the PROMIS network.

FKSI-15: The Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index (FKSI) was developed and validated to enhance treatment decision-making, practice guidelines, symptom management and treatment efficacy for kidney cancer patients. Use of this instrument in this trial will provide a unique opportunity to collect valuable information about symptoms associated with treatment in an otherwise disease-free patient population, when compared with patients randomized to placebo.

5.3.1 Assessment Schedule

Rev. 8/13

The EQ-5D will be administered at baseline (following randomization, prior to start of any protocol therapy) and at the end of every cycle

Rev. 11/14

until the end of treatment, then at every follow-up visit.

Rev. 8/13

The FACIT-Fatigue scale, the PROMIS Fatigue scale, and the FKSI-15 will be administered at baseline (following randomization, prior to start of any protocol therapy), cycle 7 (if patient discontinues treatment prior to Cycle 7, will be administered 6 months from randomization),15 months from randomization and at recurrence.

5.3.2 Administration Instructions

HRQL should be administered at all scheduled assessments, even if treatment is discontinued for any reason.

The pre-treatment baseline assessment of HRQL will be administered during the patient's clinic visit following randomization prior to start of any protocol therapy. Follow-up HRQL assessments should coincide with scheduled clinic visits. For those assessments for which patients will not be seen within the clinic, patients are to be given blank HRQL assessments and asked to complete HRQL forms at home at these time points, or are to be given the option to complete for forms by phone. Administration instructions for the assessments are detailed below.

- Whenever possible, the HRQL assessment should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed and before test results are shared with the patient. In the event that the

questionnaires are not administered at the clinic visit, the HRQL data can be collected by telephone or mail as backup methods.

- The CRN/CRA should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.
- Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on his/her own (e.g. difficulty in reading, vision problems). It is important not to influence the response of the patient. Note why the patient required assistance and the type of assistance given on the Assessment Compliance Form.
- Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's responses.
- Review the questionnaire for completeness before the patient leaves. If the patient has marked more than one answer per question, ask the patient which answer best reflects how they are feeling. If the patient has skipped a question or questions, confirm that he or she intended to leave the question blank.

Rev. 8/13

- If the patient refuses or cannot complete the questionnaire at any time point, he or she should be asked to do so at the next scheduled HRQL assessment.
- The patient may decline to complete the HRQL assessment for any reason. The reason must be documented on the Assessment Compliance Form.
- If blank HRQL assessment forms are given to the patient to complete at home, the CRN/CRA should calculate the target dates for completing follow-up assessments that coincide with required time points and write these dates on blank assessment forms in the space indicated. The patient should be given the blank assessment forms along with pre-stamped envelopes addressed to the attention of the CRN/CRA at their institution's address (or the CRN/CRA work address if it differs from the institution's address).
- The CRN/CRA should instruct the patient to complete these HRQL assessments as close as possible to the target date and mail them as soon as possible to the CRN/CRA at the institution or work address.
- For assessments that will be mailed:
  - the CRN/CRA should contact the patient by telephone, e-mail or postal mail 1-3 days prior to the target assessment date to remind the patient to complete their assessments. If the

returned questionnaires are not received at the site, a reminder contact phone call should occur no longer than 5 days following the target completion date.

- Patients should complete the HRQL assessment forms on or as close as possible to the target assessment date. If the patient misses the target assessment, on-study EQ-5D assessment will resume at the next cycle. For post-treatment follow-up assessments, patient should be encouraged to complete the form and submit despite missing the target date.
- Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Remind patients not to ask assistance from family members to reduce possible influence on the patient's responses.
- The CRN/CRA should confirm that the patient has a stamped, addressed envelope to return his/her completed HRQL assessment forms.
- The CRN/CRA may offer to complete the HRQL assessment by telephone.
- The CRN/CRA should instruct the patient to record the actual date the patient completed the HRQL assessment on each form, reminding the patient that the date written on the forms is their target date of assessment completion. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.
- The mode of administration (mail, telephone) should be noted on the Assessment Compliance Form. If the patient has misplaced the forms, the site can send new blank forms by mail, fax or email

- If follow-up assessments cannot be completed on site or by mail as requested, patients should be offered the option of completing the follow-up HRQL Assessments via telephone. If the patient is unable to complete the questionnaires on his/her own (e.g. difficulty in reading, vision problems) follow-up HRQL assessments should be conducted by telephone. Telephone administration of HRQL assessment by the CRN/CRA is preferable to having the patient ask a family member or someone in the household for assistance with completing the forms. It is important not to influence the response of the patient. Note why the patient required assistance and the type of assistance given on the Assessment Compliance Form.
- For telephone administration of HRQL assessment:
  - Encourage the patient to have the written form in front of them to read along during the assessment.
  - Read the instructions printed on the questionnaires to the patient and ensure the patient understands the instructions.

- Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Remind patients not to ask assistance from family members to reduce possible influence on the patient's responses.
- It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.
- The mode of administration (mail, telephone) should be noted on the Assessment Compliance Form. If the patient has misplaced the forms, the site can send new blank forms by mail, fax or email.

Rev. 4/14

5.4 Adverse Event Reporting Requirements

5.4.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner via CTEP-AERS for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

Rev. 8/13

5.4.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

Rev. 4/14

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a 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.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

Rev. 11/14

5.4.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's 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 electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the NCI (301-897-7497) and
- the AE Team at ECOG-ACRIN (617-632-3610)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Rev. 4/14

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact CTEP Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.4.4 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

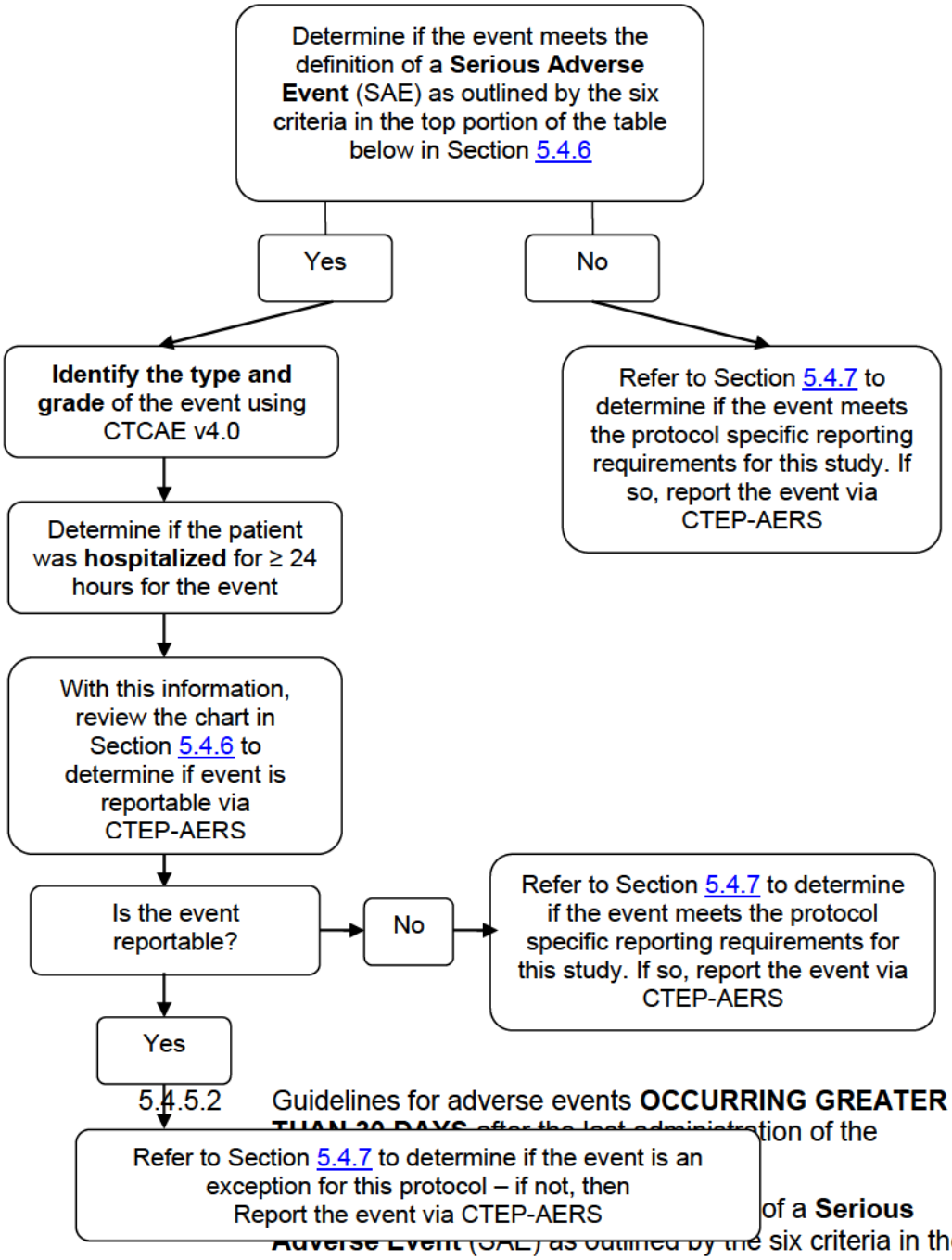
Using these factors, the instructions and tables in the following sections have been customized for protocol E2810 and outline the specific expedited adverse event reporting requirements for study E2810.

5.4.5 Steps to determine if an adverse event is to be reported in an expedited manner via CTEP-AERS

Investigational Agents:	Pazopanib/Placebo

Rev. 8/13

5.4.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT OR WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.4.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the

Refer to Section 5.4.7 to determine if the event is an exception for this protocol – if not, then Report the event via CTEP-AERS

of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.4.6, AND has an

attribution of possible, probably or definite, the following events require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study

Expedited 10 calendar day reports for:

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

5.4.6 Phase III Reporting Requirements – Arm X (Arm A Pazopanib/Arm B Placebo)

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention* [1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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:

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

5.4.7 Additional Instructions, Requirements and Exceptions for Protocol E2810

Additional Instructions:

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case by case basis.

E2810 specific expedited reporting requirements:

Rev. 8/13, 4/14

- **Pregnancy**

  Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) occurring while the subject is on Pazopanib/Placebo, or within 28 days of the subject's last dose of Pazopanib/Placebo, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix X for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies

E2810 specific expedited reporting exceptions:

Rev. 8/13

For study arm X (Arm A Pazopanib/Arm B Placebo), the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

Rev. 11/14
Rev.2/15

If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.4.8 Other Recipients of Adverse Event Reports and Supplemental Data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.4.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave:

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

Rev. 11/14

1. Complete a ECOG Second Primary Form within 14 days via Medidata Rave.
2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

1. Complete a Second Primary Form within 14 days via Medidata Rave.
2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should <u>not</u> be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 8/13

5.5 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Event 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 via CTEP-AERS (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 2383 patients.* Below is the CAEPR for pazopanib (GW786034).

Rev. 11/14

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Rev. 3/15

Version 2.7, June 2, 2017[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			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[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Cardiac disorders - Other (Torsades de Pointes)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		
EYE DISORDERS			
		Eye disorders – Other (eye/retinal hemorrhage)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	

		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
		Infection[6]	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Ejection fraction decreased	
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Hematuria	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
		Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[7]		***Respiratory hemorrhage[7] (Gr 2)***
		Respiratory, thoracic and mediastinal disorders – Other (interstitial lung disease)[7]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation)			***Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[8]	
		Vascular disorders - Other (arterial thromboembolic event)[8]	

[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]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal 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.

[4]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.

[5]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.

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

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

[8]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

[9]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

Adverse events reported on pazopanib (GW786034) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pazopanib (GW786034) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis

CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia

ENDOCRINE DISORDERS - Adrenal insufficiency

EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear

GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising

INVESTIGATIONS - Cardiac troponin T increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain

METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain

NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt

RENAL AND URINARY DISORDERS - Urinary frequency

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration

VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

NOTE: Pazopanib (GW786034) 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.

5.6 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

NOTE: Protocol treatment must be discontinued if the patient's treatment is interrupted or held for four continuous weeks for any reason.

If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Appropriate dose modifications for agent-related toxicities are outlined in the following subsections. Dose level reductions follow:

Dose level	Pazopanib/Placebo
0	800 mg (4 tablets) once daily
-1	600 mg (3 tablets) once daily
-2	400 mg (2 tablets) once daily

5.6.1 Hematologic Toxicity

Patients who develop grade 3 or grade 4 thrombocytopenia, neutropenia or anemia should hold pazopanib/placebo. When toxicity recovers to ≤ grade 2, pazopanib/placebo may be resumed with a dose reduction of 200 mg. If Grade 3-4 hematologic toxicity recurs, then patients should discontinue study treatment permanently.

5.6.2 Hypertension

Decisions to hold or decrease the pazopanib/placebo dose during treatment must be based on BP readings taken in the clinic by a medical professional.

Recommended Hypertension Monitoring and Management

(BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib/placebo Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No Change
Persistent Grade 2-Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	Step 1) Initiate BP 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 anti-hypertensive Rx, a LA DHP CCB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 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 pazopanib/placebo or holding pazopanib/placebo **NOTE**: *Holding or reducing the dose of pazopanib/placebo is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician	No change except as described in step 4

Persistent Grade 3 Severe **Systolic ≥ 160** **Diastolic ≥ 100** **Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4**	HOLD pazopanib/placebo 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 subject is symptomatic: optimal management with intensive IV support in ICU; HOLD pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP** **and** **2) If systolic BP > 180 or diastolic BP > 110 and the subject is asymptomatic, 2 new antihypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** **NOTE:** *Holding or reducing the dose of pazopanib is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the subject is symptomatic with systolic BP > 180 or diastolic BP > 110 in which case, monitoring should be intensive.**	HOLD agent until systolic BP ≤ 159 and diastolic BP ≤ 99. After this, agent may be re-administered. If BP is still grade 2, manage as described above for grade 2 hypertenison. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of agent when systolic BP ≤ 159 and diastolic BP ≤ 99 or holding agent. **HOWEVER,** **If the subject requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110, permanently discontinue agent or if BP is controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting agent at 1 lower dose level after consultation with the study chair**
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP**	Intensive	Permanently discontinue agent or if systolic BP ≤ 159 and diastolic BP ≤ 99, consider re-starting agent 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)

- *See table below for suggested antihypertensive medications by class
- If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If subjects require >2 dose reductions, discontinue protocol therapy
- Subjects may have up to 2 drugs for management of hypertension prior to any dose reduction in pazopanib
- 24-48 hours should elapse between modifications of antihypertensive therapy

Hypertension should be graded using CTCAE v4

In some instances of treatment for hypertension, a lower dose of the medication may be sufficient to provide the required antihypertensive control. In other instances, the standard dose of such a medication may be associated with AEs because of increased exposure. Alternatively, the investigator may choose to replace the medication with another in the same pharmacologic class that is less likely to interact with pazopanib/placebo. If such a medication is discontinued and replaced, the transition period should occur no less than 7 days prior to the first dose of pazopanib/placebo. Based on prior clinical experience with pazopanib/placebo, the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

Oral Antihypertensive Medications

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with pazopanib/placebo through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetolol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

5.6.3 Proteinuria

If, at any time, a subject has a urine protein/creatinine ratio greater than 1, a 24-hour urine collection must be performed. If a subject develops the nephrotic syndrome, treatment must be discontinued.

Although subjects with ≥ 1+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

Management of Proteinuria	
UPC > 1 and < 3	Obtain 24-hr urine protein and if <3 g, continue at current dose and monitor as clinically indicated
UPC ≥ 3 or 24-h urine protein ≥ 3 g	Step 1. Interrupt IP. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is < 3 or 24-hr urine protein is < 3 grams. Then restart agent dose-reduced by 200 mg. Step 3. If UPC > 3 or 24-h urine protein ≥ 3g recurs, repeat steps 1 and 2 Step 4. If UPC ≥ 3 or 24-hr urine protein ≥ 3 recurs and the agent dose can no longer be reduced, permanently discontinue study treatment.
Nephrotic syndrome	Permanently discontinue study treatment

Rev. 8/13

5.6.4 Management of Subjects with Elevations in AST, ALT and/or Bilirubin

AST, ALT and/or Bilirubin	
Isolated AST/ALT elevations between 3 X ULN and 8 X ULN	Continue pazopanib/placebo, but monitor weekly until AST/ ALT returns to ≤ 2.5 X ULN or baseline.
Isolated AST/ALT >8 X ULN	Hold pazopanib/placebo until AST/ALT returns to ≤ 2.5 X ULN or baseline. If the potential benefit of reinitiating pazopanib/placebo treatment is considered to outweigh the risk for hepatotoxicity, then consider reintroducing pazopanib/placebo at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks only after discussion with the PI and CTEP. If AST/ALT elevations >3 X ULN recur, then pazopanib/placebo should be permanently discontinued.
AST/ALT >3 X ULN and concurrent bilirubin elevations >2 X ULN	Permanently discontinue pazopanib/placebo.
ALT/AST >3 x ULN, known or suspected Gilberts with mild indirect hyperbilirubinemia*	Continue pazopanib/placebo, but monitor weekly until ALT/AST returns to grade 1 (NCI CTCAE) or baseline.

*Total bilirubin ≤ 6 mg/dL with direct bilirubin < 35%

5.6.5 Management of Other Toxicity

Rev. 8/13

Adverse Event	Grade	Treatment Modification
Hemorrhage/ Bleeding	Grade 1	No interruption in treatment except for hemoptysis. If hemoptysis, contact study chair to determine if it is appropriate to continue agent. Maintain current dose.
	Grade 2	For non-pulmonary bleeding, hold pazopanib/placebo unless resolved to ≤ grade 1; reduce dose to next lower dose level, and continue treatment. For pulmonary bleeding, permanently discontinue agent. If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction.
	Grades 3 or 4	Discontinue treatment and withdraw subject from study.
Vascular/ Thrombosis	Grade 1	No interruption in treatment; maintain current dose.
	Grade 2 or 3	Hold agent until subject is receiving a stable dose of Low Molecular Weight Heparin (LMWH). Treatment may resume during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have been treated with an anticoagulant at the desired level for at least one week. • The subject must not have had a grade 3 or 4 or significant grade 2 hemorrhagic event while on anticoagulant. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib/placebo dosing (*e.g.*, re-initiating, escalating/de-escalating, or discontinuing pazopanib/placebo), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.
	Grade 4 or pulmonary embolus	Permanently discontinue study treatment.
Arterial Thrombosis/ ischemia	All grades	Permanently discontinue study treatment.
Thrombo-cytopenia/ Neutropenia/Anemia [1]	Grade 1 or 2	No interruption in treatment; maintain current dose.
	Grade 3 or 4	Interrupt treatment until toxicity is ≤ grade 2; reduce one dose level. If no recovery to ≤ grade 2 or recurrent grade 3 or 4, permanently discontinue study treatment.

[1] The dose delays and modifications for anemia apply only to anemia which is due to hemorrhage or bleeding. No specific dose delays or dose reductions are required for anemia due to other causes, but the investigator should dose delay and dose-decrease, if he/she feels it is necessary, in a manner consistent with good medical practice.

5.6.6 QTc Interval Prolongation

Management of QTc Prolongation

Management of QTc prolongation of 500 msec *and* management of QTc prolongation of 60 msec or more from baseline.

Rev. 8/13

Management of QTc Prolongation	
If ECG reveals an increase in the QTc to > 500 msec or an increase in the QTc by at least 60 msec from baseline	Repeat ECG before re-administration of agent.
If repeat ECG shows QTc interval is ≥ 500 msec	Permanently discontinue study treatment.
If on repeat ECG, QTc remains at least 60 msec longer than baseline but is less than 500 msec	Consider permanently discontinuing study treatment.

5.6.7 Management of Other Clinically Significant Toxicities which are Not Specifically Addressed Above

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Lower grade but related AEs (*e.g.*, abdominal pain)	Reduce one dose level*
AE does not resolve to grade 2 or below after treating subject at the lowest (*i.e.*, 400 mg daily) reduced dose level.	Remove subject from study
* Alternatively and if medically appropriate, investigators may choose to hold dose for up to 14 days or withdraw subject from study.	

5.7 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

Patients taking warfarin for therapeutic anticoagulation should have their INR measured weekly for the first cycle, then at least once per cycle thereafter.

5.7.1 Blood Pressure Monitoring

Frequent blood pressure monitoring is important for patients receiving pazopanib since increases in blood pressure may occur following dosing with pazopanib for a number of weeks and these increases may occur rapidly. Patients will be required to have their blood pressure taken weekly during cycle 1 and on day 1 of each subsequent cycle. If blood pressure monitoring is not done in the doctor's office, patients will be required to phone-in their blood pressure readings for cycle 1. Results must be phoned in to the doctor's office within 24 hours of when the blood pressure recording occurred. Patients are also encouraged to record daily blood pressure measurements during study treatment on their patient pill calendar (See Appendix IV).

5.7.2 Diarrhea

Pazopanib has been associated with an increased incidence of diarrhea. In a Phase III randomized, placebo-controlled study in

advanced RCC, pazopanib monotherapy was associated with an increased incidence of diarrhea compared to placebo treatment (52% vs. 9%, all grades) [6]. Yet only 3% and < 1% of patients experienced Grade 3 and Grade 4 diarrhea, respectively, in the pazopanib arm. Early identification and intervention, including dose reduction and/or interruption of pazopanib until resolution to ≤ Grade 1, and the administration of loperamide is critical for the optimal management of diarrhea. A patient's baseline bowel patterns should be established so that changes in patterns can be identified while on treatment. Patients should be educated on signs and symptoms of diarrhea with instructions to report to any changes in bowel habits promptly.

5.8 Potential Drug Interactions

Pazopanib is primarily metabolized by the human CYP3A4 isoenzyme. Potent CYP3A4 inhibitors and inducers **are prohibited on pazopanib trials. In exceptional circumstances, medications which strongly inhibit CYP3A4 may be administered, with caution, if the dose of pazopanib is decreased to 50% of the dose which would otherwise be administered.**

Medications that strongly inhibit CYP3A4 include (but are not limited to):

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

Medications that strongly induce CYP3A4 include (but are not limited to):

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

Rev. 8/13

Drugs that are inducers, inhibitors or substrates of P450 isoenzymes are listed in Appendix XI and within the following on-line resource below. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website:
http://medicine.iupui.edu/clinpharm/ddis/table.aspx[58]

Pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Drugs that have narrow therapeutic windows and are substrates for these enzymes **should be administered with extreme caution.** Because of pazopanib's long half-life, caution should continue to be exercised for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications.

Medications that are substrates for these enzymes *and* have narrow therapeutic windows medications include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that

includes severe vasospasm leading to peripheral as well as cerebral ischemia)

- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

Pazopanib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (see Appendix VII) should be discontinued or replaced with drugs that do not carry this risk, if at all possible. Subjects who receive potential QTc-prolonging medications (see Appendix VII) should be monitored closely.

Pazopanib may increase bleeding. Subjects receiving pazopanib and anticoagulation agents should be monitored for bleeding.

Pazopanib may cause decreased glucose. Subjects receiving pazopanib and hypoglycemia agents should be monitored for hypoglycemia

5.9 Duration of Therapy

5.9.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the schedule in the E2810 Forms Completion Guidelines.

5.9.2 Patient withdraws consent.

5.9.3 Patient experiences unacceptable toxicity.

5.9.4 Non-protocol therapies are administered.

5.9.5 Development of recurrent measurable or evaluable metastatic disease.

5.10 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until recurrence, even if non-protocol therapy is initiated, and for survival for 10 years from the date of randomization. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Diagnosis of Renal Cell Cancer Recurrence

The diagnosis of a first renal cell carcinoma recurrence can be made only when the clinical and pathology findings meet the criteria acceptable for recurrence as defined below. Anything not listed as acceptable should be considered unacceptable for evidence of renal cell cancer recurrence and should not be an indication to alter protocol therapy. Any recurrence of malignant disease should be proven by core needle biopsy whenever possible. At the time of tumor recurrence the investigator should clearly indicate the site of tumor recurrence and whether multiple sites are involved.

Supporting documentation must be submitted following diagnosis of renal cell carcinoma recurrence or second primary cancer. Refer to the E2810 Forms Completion Guidelines for data to be collected. Copies of the pathology, radiology, and if relevant, surgery reports should be submitted using Medidata Rave. If biopsy material is available, a copy of the pathology report should also accompany the materials submission to the Central Biorepository and Pathology Facility (CBPF)

Rev. 8/13

The following criteria of treatment failure constitute the only acceptable evidence of disease recurrence. Supporting documentation includes a copy of radiology and pathology reports.

NOTE: Patients should continue treatment until recurrence has been proven per guidelines in Sections 6.1.1 through 6.1.8.

6.1.1 Lung

Acceptable: (i) positive cytology or biopsy in the presence of a solitary lesion (ii) radiologic evidence of multiple lesions felt to be consistent with metastases (iii) proof of neoplastic pleural effusion should be established by cytology or pleural biopsy.

6.1.2 Liver

Acceptable: (i) positive cytology or biopsy (ii) multiple new focal defects on MRI scan, CT or ultrasound that are enlarging in size as evidenced by two scans, separated by at least a 4 week interval (iii) proof of neoplastic abdominal ascites should be established by cytology or pleural biopsy.

6.1.3 Central Nervous System

Acceptable: a positive brain CT scan or MRI scan or cerebral spinal fluid (CSF) cytology.

6.1.4 Subcutaneous and Lymph Node Recurrence

Acceptable: (i) positive biopsy (ii) progressively enlarging solid mass or node(s) as evidenced by two CT or MRI scans, separated by at least a 4 week interval (iii) ureteral obstruction in the presence of a mass as documented on CT or MRI scan.

Rev. 8/13

6.1.5 Cutaneous Recurrence

Acceptable: Documentation by digital photography with a centimeter scale ruler included in the photographic field and positive biopsy.

6.1.6 Other Organs

Acceptable: (i) positive radiographic study and biopsy/aspiration cytology (ii) progressively enlarging solid mass or node(s) as evidenced by two CT or MRI scans, separated by at least a 4 week interval.

6.1.7 Renal Bed

Acceptable: (i) positive radiographic study and biopsy/aspiration cytology (ii) progressively enlarging solid mass or node(s) as evidenced by two CT or MRI scans separated by at least a 4 week interval.

6.1.8 Skeletal

Acceptable: (i) positive radiographic study such as bone scan (ii) for a solitary lesion or equivocal finding on scan, a biopsy is required to demonstrate recurrence, (iii) MRI or CT of solitary or equivocal lesion seen on bone scan that confirms metastasis is also acceptable.

6.2 Second primary cancer

Second primary cancer is defined as any cancer other than localized breast cancer, localized prostate cancer, or non-melanoma skin cancer.

The diagnosis of a second primary cancer must be confirmed histologically whenever possible.

6.3 Time to Progression

This interval will be measured from the date of registration to the appearance of new metastatic lesions.

6.4 Local, Regional Recurrence

The development of a local or regional recurrence of cancer.

6.5 Distant Recurrence

The development of a distant recurrence of cancer.

6.6 Disease-Free Survival

Time from randomization to recurrence, development of second primary cancer, or death from any cause. Second primary cancer is defined as any cancer other than localized breast cancer, localized prostate cancer, or non-melanoma skin cancer.

6.7 Survival

Time from randomization to date of death.

7. Study Parameters

7.1 Clinical Parameters

1. Prestudy scans and x-rays used to screen for the presence of measurable or non-measurable sites of disease must be done within **4 weeks** prior to randomization.
2. Prestudy CBC (with differential and platelet count) should be done within **2 weeks** prior to randomization.
3. All required prestudy chemistries, as outlined in Section 3, should be done within **2 weeks** prior to randomization.

		Prior to Randomization	Cycle 1	Cycles 2 through 13	End of Treatment[16]	Follow-up[10]
Rev. 8/13	History and physical examination	X	Day 1	Day 1 (±2 days)	X	X
	ECOG Performance Status	X	Day 1	Day 1 (± 2 days)	X	X
	Blood pressure[1]	X	Weekly	Day 1 (± 2 days)	X	X
Rev. 8/13	Urinalysis for protein/creatinine ratio[2]	X		Day 1 (± 2 days)	X	
	CBC[3]	X		Day 1 (± 2 days)	X	X
Rev. 8/13	Blood chemistries including LFT's[9]	X		Day 1 (± 2 days)	X	X
Rev. 8/13	LFT's		Day 15 (± 2 days)	Day 15 (± 2 days)[17]		
	Serum TSH	X		Day 1 (± 2 days) of Odd-numbered cycles		
	INR, aPTT	X	PRN[4]	PRN[4]		
	C-Reactive Protein (CRP)[11]	X		Day 1 (± 2 days)	X	
	Brain MRI[8]	X	PRN	PRN	X	PRN
	ECG with QTc assessment[13]	X		Day 1 (± 2 days) of cycle 2[14]		
Rev. 8/13 Rev. 4/14	Chest CT[18]	X		Every 3 months (±7 days)[15]	X	X[10]
Rev. 4/14	Abdomen/pelvic CT or MRI[18]	X		Every 3 months (±7 days) [15]	X	X[10]
Rev. 8/13, 4/14	Bone scan[5]	X	PRN	PRN	PRN	X[10]
Rev. 8/13	Clinical Tumor Assessment[6]	X		Every 3 months (±7 days) [15]	X	X[10]
	beta HCG[7]	X				
	Pill Count/Diary		X	X		
Rev. 8/13	Quality of Life Questionnaire[12]	See footnote 12				
	Biological Sample submissions	See Section 7.2				
	Survival Follow-up	Survival will be assessed every 3 months until patient is 2 years from enrollment; every 6 months until patient is 5 years from enrollment and then every 12 months until patient is 10 years from enrollment.				

Rev. 8/13 1. Blood pressure must be done at baseline (prior to randomization) and evaluated weekly during the first cycle. Measurements may be obtained outside of the treating physician's office however; they must be documented on the patient's pill calendar (see Appendix IV). Measurements should be made using a calibrated electronic device, unless performed in a doctor's office where a manual blood pressure measurement is acceptable.

2. Urine analysis for calculation of urine protein: creatinine ratio (UPC ratio) should be performed at baseline (within 2 weeks prior to randomization) and prior to every course of study drug from cycle 2 onward (or more frequently as indicated). Treatment may proceed if UPC ratio is < 3.0. Use of urine dipstick for renal function assessment during screening is not acceptable.

Rev. 8/13

Rev. 8/13 **NOTE:** UPC ratio must be obtained prior to treatment starting cycle 2. Treatment may proceed if a urine protein dip stick result is 0-1+. If results of urine protein dip stick are higher, hold study drug until the UPC ratio is known. UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion: a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 g. UPC ratio is calculated using one of the following formulas:

- [urine protein]/[urine creatinine] - if both protein and creatinine are reported in mg/dL
- [(urine protein) x0.088]/[urine creatinine] - if urine creatinine is reported in mmol/L

3. CBC with differential should be repeated weekly for the duration of a cycle if a CBC reveals an ANC < 1,000/mm^3 or platelet count < 75,000/mm^3.

4. Patients taking warfarin for therapeutic anticoagulation should have their INR measured weekly for the first cycle, then once per cycle thereafter.

5. For patients with elevated alkaline phosphatase or symptoms raising suspicion of bone metastases.

Rev. 8/13 6. Intracutaneous or subcutaneous lesions should be evaluated with digital photography at the time of each tumor assessment. A centimeter-scale ruler must be included in the photographic field on each occasion.

7. For women of childbearing potential, within 2 weeks of the randomization.

Rev. 4/14 8. Pre-study brain MRI with and without gadolinium must be done within 8 weeks prior to randomization. Brain MRI with gadolinium is preferred. CT with and without IV contrast is permitted if MRI contra-indicated (i.e. pacemaker).

Rev. 4/14 9. Sodium, potassium, BUN, serum creatinine, glucose, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, LDH, calcium, albumin, amylase, lipase, phosphorus, magnesium.

10. Patients will have a history and physical, CBC, comprehensive metabolic panel, LDH and CT of chest abdomen and pelvis every 3 months for the first two years, every 6 months for the next 3 years, and then annually through 10 years (or until recurrence). Patients will be followed for survival every 3 months until patient is 2 years from study entry, every 6 months until patient is 5 years from study entry and every year until patient is 10 years from study entry.

Rev. 4/14 **NOTE:** The same studies should be performed in follow up as were performed at screening (brain imaging at end of study only, unless clinically indicated), unless there is a clinical reason to change (decline in renal function, allergic reaction, new pacemaker)

11. Although not required, it is strongly recommended that C-Reactive Protein levels be assessed throughout

Rev. 8/13 Rev.11/14 12. QOL questionnaires to be administered as follows: 1) EQ-5D at baseline, at the end of every cycle, then at each follow-up visit (see footnote 10). 2) Additional questionnaires at baseline, cycle 7, month 15, and recurrence (if patient has terminated treatment prior to cycle 7, questionnaire will be administered 6 months from randomization).

Rev. 8/13 **NOTE:** Baseline questionnaires are to be completed after randomization but prior to receiving protocol therapy.

Rev. 8/13 13. A baseline ECG is a requirement for this study and must be done prior to randomization. Subjects will be excluded if they have a baseline QTc ≥ 480 msec.

Rev. 8/13 14. Repeat ECG must be performed on the cycle 2 day 1 visit. If the QTc interval at 4 weeks is ≥ 500 msec, pazopanib should be held. The ECG should be repeated within 7 days and, if the QTc interval remains ≥ 500 msec, the subject should be removed from the study. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc interval remains at < 500 msec, an ECG should be repeated within 7 days. If the repeat ECG again shows a ≥ 60 msec increase in the QTc interval from baseline, consideration should be given to removing the subject from the study or increasing monitoring, after discussion with the study chair.

Rev. 8/13 Rev. 4/14 15. These assessments should take place every 3 months (± 7 days), counting from the start of cycle 1 for each scan. The scan at the end of month 12 may be delayed or moved up to fall within 14 days of the end of treatment date so that the month 12 assessments will also serve as the end of treatment assessments.

Rev. 8/13, 4/14 16. Should be done +/- 2 weeks of last dose of study treatment.

Rev. 8/13 17. Cycle 2: LFTs on Day 15 (+/- 2 days); Subsequent cycles: Day 15 (+/- 2 days) if clinically indicated.

Rev. 4/14 18. Contrast is preferred when possible for CT of the chest. For CT of the abdomen/pelvis, scan must be done using IV contrast (additionally, oral contrast may be used at the radiologist's discretion). For MRI of the abdomen/pelvis, scan must be done using gadolinium. An MRI may only be substituted for a CT of the abdomen/pelvis if CT with contrast is contra-indicated.

7.2 Biological Specimen Submissions

Pathology materials are to be submitted from all patients for central diagnostic review and classification. Samples for correlatives and banking for future research are to be submitted from patients per consent levels as indicated below.

NOTE: All samples submitted must be logged and tracked in the ECOG-ACRIN Sample Tracking System (STS).

Material	Baseline	Cycle 2, Day 1
MANDATORY: Submit for central diagnostic review and classification per Section 10		
Primary and Metastatic Tumor Tissue Block	X	
H&E of primary and metastatic tumor	X	
Submit per Section 11.1 from patients who answer "Yes" **to "***I agree to participate in the laboratory research studies that are being done as part of this clinical trial.* **"**		
Plasma, EDTA (purple top) tube	X	X[1]
Submit per Section 11.1 from patients who answer "Yes" **to "***I agree to provide additional blood for research.* **"**		
Peripheral Blood, ACD or EDTA tube	Sample may be drawn any time, although baseline (prior to treatment) preferred	

1. Request patient bring the study drug to take AFTER the research and clinical blood draws. Patients should not take study medication on the cycle 2 day 1 study visit prior to the research blood draw.

8. Drug Formulation and Procurement

8.1 Availability

Pazopanib (NSC 737754) and matching Placebo will be provided free of charge by GlaxoSmithKline and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Pazopanib 200 mg and matching Placebo for pazopanib will be supplied as aqueous film coated tablets containing either 200 mg or 0 mg of the free base. Each bottle will contain 34 oval-shaped, white, tablets. Tablet excipients include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate, The film-coat consists of titanium dioxide, hypromellose, polyethylene glycol, and polysorbate 80.

NCI Supplied Agent(s) – General Information

NOTE: Under no circumstances can commercially supplied **pazopanib** be used or substituted for the NCI-supplied **pazopanib**.

Rev. 8/13

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. You may also contact PMB via e-mail at PMBAfterHours@mail.nih.gov.

Drug Orders, Transfers, Returns, Accountability and Unblinding

No blinded starter supplies will be available for this study.

Once a patient has been randomized, blinded, patient specific supplies will be sent automatically to the registering investigator and should arrive within 7 to 10 days. Study drug requests are transmitted by the ECOG-ACRIN Operating Office - Boston the day the patient is randomized and will be processed by PMB the next business day and shipped the following business day. Shipments within the United States are sent by US Priority Mail (generally two to three day delivery) and shipments to Canada are sent by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, ECOG-ACRIN would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. United States sites could expect to receive their order approximately Friday or Monday and Canadian sites could expect to receive their order either Thursday or Friday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the ECOG-ACRIN Operating Office - Boston at the time the patient is randomized.

Rev. 8/13

Rev. 8/13

The initial request will be for 8 bottles of pazopanib or matching placebo. Six (6) weeks after the initial electronic request [i.e., two (2) weeks before needed], sites may reorder an additional 8 bottles of pazopanib or matching placebo by using the On-line Agent Order Processing (OAOP) program. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov). The assigned patient ID number (e.g., "44444") and the patient initials (e.g., "FL") must be entered in the "Patient or Special Code" field. A separate line item is

required for each patient ID number (e.g., "44444") being ordered. All drug orders will be shipped directly to the physician responsible for treating the patient.

Each blinded, patient -specific bottle will be labeled with:

- The protocol number (i.e., “E2810”)
- The bottle number (i.e., “Bottle 1 of 1”)
- The number of capsules (i.e., “34 tablets”)
- The patient ID number (e.g.,"44444", where “44444” represents a unique patient identifier assigned at randomization)
- The patient initials (i.e., first initial, last initial [e.g., "FL"])
- The agent identification (i.e., “pazopanib 200mg or placebo”)
- A blank line for the pharmacist to enter the patient’s name
- Administration instructions (i.e., “Take 4 tablets once daily.”)
- Storage instructions (i.e., “Store between 20ºC and 25ºC)
- Emergency contact instructions
- A Julian date

The Julian date indicates the day the bottles were labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2011 = 11, 2012 = 12) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2010 would have a Julian date of ‘10001’ and a bottle labeled and shipped on December 31, 2010 would have a Julian date of ‘10365’. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles shipped on or before that date thus eliminating any chance of breaking the blind.

Rev. 2/15

NOTE: The Julian Date – Order Number (e.g. 2014352-0003) from the patient-specific label must be used as the Lot number on the NCI DARF.

Rev. 8/13

Drug Transfers: Patient specific study drug supplies MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 240-276-7893) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "44444"') and the patient initials (e.g., "FL”) should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "E2810").

Rev. 8/13

Drug Returns: Only undispensed clinical supplies should be returned to the PMB. When it is necessary to return study drug investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient ID number (e.g., "44444") and the patient initials (e.g., "FL") should be entered in the "Lot Number" field. A separate line item is required for each patient

ID number (e.g., "44444") that is being returned. Bottles with remaining tablets should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged is as “returned by patient” and logged out as “destroyed on site”) and destroyed on site in accordance with institutional policy.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "44444") on this protocol.

Rev. 8/13

8.1.1 Emergency Unblinding

NOTE: **The information provided below is for the use by a physician, nurse, CRA or pharmacist treating the patient. These contact numbers should not be used by patients. Patients should be instructed to call their doctor’s office in the event of an emergency or adverse event that may result in the need to unblind the patient.**

In the event of an emergency or severe adverse reaction necessitating identification of the medication for the welfare of the patient, please contact the Study Chair, Dr. Leonard Appleman at (412) 648-6507 or Email: applemanlj@upmc.edu, first to ensure the reason for unblinding is valid. Then call a member of the ECOG-ACRIN Operating Office - Boston drug team at (617) 632-3610 Monday through Friday between 9:00 AM and 5:00 PM Eastern Time. For unblinding outside of these hours, contact AnswerConnect at 1-866-296-8940. This service will request the reason for unblinding and then page the on-call ECOG-ACRIN staff who will return your call and provide the unblinded treatment assignment if applicable. **Remember, Answer Connect should only be contacted outside of normal business hours and only in the event of an emergency.** The ECOG-ACRIN Operating Office - Boston or AnswerConnect will require the protocol number (i.e., “E2810”), the patient ID number (e.g., “44444”), and the patient initials (e.g., “FL”) to unblind the patient. Note that if a patient is unblinded, he/she must discontinue protocol treatment.

Rev. 2/15

8.2 Pazopanib/Placebo (GW786034, NSC 737754, IND 75648)

8.2.1 Other Names

Pazopanib HCl

GW786034B, Votrient®

The ‘B’ suffix denotes the monohydrochloride salt.

8.2.2 Chemical Name

Rev. 2/15

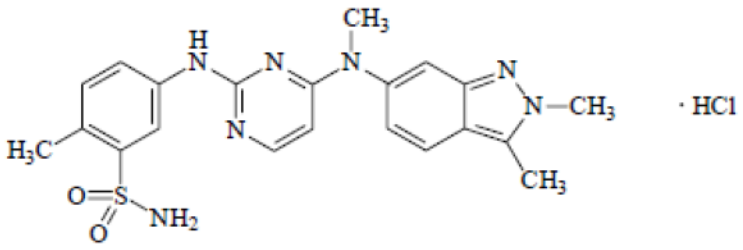
5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2 methylbenzenesulfonamide monohydrochloride

8.2.3 Molecular Formula

Rev. 2/15

$C_{21}H_{23}N_7O_2S$ - HCl

8.2.4 Structural Formula



8.2.5 Molecular Weight

Rev. 2/15

474.0 g/mol (monohydrochloride salt)

437.5 g/mol (free base)

8.2.6 Approximate Solubility

Rev. 4/14
Rev. 2/15

The monohydrochloride salt is very slightly soluble in 0.1 M HCl (0.65 mg/mL), and is practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL), and in pH 11 piperidine buffer (0.0002 mg/mL).

8.2.7 Classification

VEGFR tyrosine kinase inhibitor.

8.2.8 Mechanism of Action

Pazopanib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3), platelet derived growth factor receptor (PDGFR alpha and beta) and C-Kit. Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

8.2.9 Storage and Stability

How Supplied

Rev. 2/15

Pazopanib/Placebo (GW786034 monohydrochloride) is supplied as aqueous film-coated tablets containing 200 mg of the free base. The 200 mg tablets are oval-shaped, white, and packaged in white high density polyethylene (HDPE) bottles with white, plastic induction sealed and child-resistant caps.

Tablet excipients in both tablet sizes include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, macrogol/polyethylene glycol 400, and polysorbate 80.

Storage

Store intact bottles at USP controlled room temperature (20° to 25° C or 68° to 77° F).

Stability

Stability studies are ongoing. An opened original container of tablets is stable for 3 months. If exact quantity must be dispensed, then extra tablets must be removed, documented and destroyed immediately. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration. If repackaging blinded supplies, the bottle dispensed to the patient must have all of the same information on the label that is contained on the original packaging from the PMB.

8.2.10 Dose Specifics

Starting dose is 4x 200 mg tablets (800 mg) once daily.

8.2.11 Route of Administration

Rev. 2/15

Oral. Pazopanib/Placebo should be taken on an empty stomach either 1 hour before or 2 hours after food. The tablets should be swallowed whole with water and cannot be crushed or broken

Rev. 2/15

8.2.12 Potential Drug Interactions

In vitro data indicate that pazopanib is primarily metabolized by CYP3A4 isoenzyme. Potent CYP3A4 inducers and inhibitors are prohibited on pazopanib trials. Pazopanib is also a substrate for p-glycoprotein and breast cancer resistance protein (BCRP) transporters and concomitant administration of inhibitors such as lapatinib will result in increased plasma pazopanib concentrations.

Clinical studies indicate that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Use caution when combining pazopanib with CYP3A4, CYP2C8, and CYP2D6 substrates known to have a narrow therapeutic window.

In virtro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1. Pazopanib may increase concentrations of drugs primarily eliminated through these systems.

Avoid co-administration of pazopanib with medicines that increase gastric pH. If the concomitant use of a proton pump inhibitor (PPI) is medically necessary, pazopanib should be taken without food once daily in the evening with the PPI. If the concomitant administration of an H_2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H_2-receptor antagonist. Administer pazopanib at least 1 hour before or 2 hours after administration of short acting antacids.

Avoid co-administration of pazopanib with simvastatin. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevation. Data are not sufficient to assess the risk of concomitant administration of other statins and pazopanib.

Rev. 2/15

8.2.13 Precautions

Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Monitor ECGs and serum electrolytes (e.g., calcium, magnesium, potassium) at baseline and periodically and maintain within the normal range.

For patients who develop hepatic impairment, refer to the protocol document for appropriate dose modification or dose delay.

8.2.14 Side Effects

See Section 5.5.

8.2.15 References

GW786034 Investigator's Brochure.[22]

9. Statistical Considerations

9.1 Statistical Design

Patients will be randomized (1:1) to pazopanib or placebo. The primary endpoint of the study is disease-free survival, comparing pazopanib to placebo. Disease-free survival is defined as time from randomization to recurrence, development of second primary cancer, or death from any cause. Second primary cancer is defined as any cancer other than localized breast cancer, localized prostate cancer, or non-melanoma skin cancer. Patients who experience one of these cancers will continue to be followed for recurrence of renal cancer. Rising PSA following local therapy for prostate cancer will constitute metastatic disease and will be considered an event. Patients who have not recurred, died, or developed a second primary cancer will be censored at the date of last disease evaluation. Overall survival and toxicity are important secondary endpoints. Patients will be stratified for balancing purposes based on disease-free interval (less than vs. greater than 1 year), and number of resected metastatic sites (1 or more than 1).

Based on review of single-institution retrospective series and the anticipated mix of patients enrolled, the proportion of patients randomized to placebo who are alive and disease-free at 3 years is estimated to be 25%. We hypothesize that 3-year DFS will be 45% among patients randomized to pazopanib. This corresponds to a 42 percent reduction in the DFS event rate. In September 2014 the study's design was modified in light of an accrual rate that was slower than expected. Following are statistical properties of the study as redesigned.

Rev. 11/14

We assume accrual of 2 patients per month and total accrual of 128 patients, with 14 additional months of follow-up after the end of accrual. Using a one-sided stratified log rank test with Type I error of 5%, this design will provide about 81% power. Full information will exist when 90 events (death, recurrence, or qualifying second primary cancer) have occurred.

Interim efficacy analyses are planned for each semi-annual ECOG-ACRIN Data Safety Monitoring Committee (DSMC) meeting beginning at approximately 31% of full information. Significance levels at each analysis will be determined from a truncated O'Brien-Fleming error spending rate function. Boundaries for analyses prior to the information proportion of 0.50 will be truncated at 0.0005, with the significance levels at subsequent analyses adjusted to preserve the overall type I error rate. The error-spending plan is summarized in the following table. Because interim analyses are timed to coincide with meetings of the ECOG-ACRIN DSMC, the exact boundary value and its associated nominal significance will be based on the number of events at the time of the analysis.

Rev. 11/14

Analysis	Calendar Time (Months)	Information Proportion	Failures	Upper Boundary	Nominal Significance	Rejection Probability H0	Rejection Probability H1
1	36	0.31	28	3.09	0.0010	0.0010	0.0495
2	42	0.40	36	2.97	0.0015	0.0010	0.0519
3	48	0.50	45	2.59	0.0048	0.0036	0.1309
4	54	0.60	54	2.34	0.0096	0.0061	0.1544
5	60	0.71	64	2.14	0.0162	0.0085	0.1508
6	66	0.82	74	1.98	0.0239	0.0105	0.1279
7	72	0.92	82	1.88	0.0301	0.0102	0.0868
8	78	1.00	90	1.81	0.0351	0.0090	0.0564

Rev. 11/14
Rev. 2/15

The study will also be monitored for early stopping for harm and inefficacy. At 31% information, the DSMC may consider stopping the study for harm if the lower bound of a 90% confidence interval on the hazard ratio (pazopanib/placebo) is above 1.0. Interim inefficacy analyses are also planned. The approach to this monitoring plan, starting at 42.5% information, is described by Freidlin et al (43). The study will be stopped if there is not at least a small trend in favor of the alternative hypothesis starting at this time. Specifically, an inefficacy monitoring boundary will begin at this time at a hazard ratio greater than 1 and will gradually increase to 20% of the targeted benefit at full information, subject to the requirement that the two-sided 90% confidence interval for the log hazard ratio does not contain the design-alternative log hazard ratio of 0.576. This plan is summarized in the following table.

Rev. 11/14

Information Proportion	Cutoff (Hazard Ratio Scale)
0.60	1.00
0.71	0.97
0.82	0.94
0.92	0.92
1.00	0.90

If the hazard ratio exceeds the cutoff value at the corresponding information proportion, the Data Monitoring Committee may recommend that the study be terminated for inefficacy. Actual information times corresponding to the data cutoffs for the DMC meetings may vary; the critical value for the test statistic will be calculated for the actual information proportion.

Interim analyses for both efficacy and inefficacy will be timed to correspond to the semi-annual meetings of the ECOG-ACRIN Data Monitoring Committee using the information proportion as of the data cutoff date prior to the meeting. No interim analyses will be performed if there is not at least a 10% increment in the information proportion compared to the previous interim analysis.

9.2 Statistical Analysis Plan for Quality of Life **(QOL)**

Rev. 11/14

All randomized patients (n=128) will participate in the QOL component of the study.

Q-TWiST

We will use a quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) analysis to provide an integrated measure of clinical benefit, with the objective of comparing quality-adjusted survival between the two arms.

Overall survival for each treatment group will be partitioned into three health states: toxicity (TOX), time without symptoms of disease or toxicity (TWiST), and recurrence (REC).

TOX

Toxicity is defined as the time spent with grade 3 or 4 adverse events prior to disease recurrence. The start and end date for each adverse event will be captured. The number of days between randomization and disease recurrence with any adverse event of grade 3 or 4 will be counted. A day with multiple

qualifying adverse events will only be counted once. Adverse events occurring after disease progression will not be counted in the TOX state.

TWiST

Time without symptoms of disease or toxicity will be defined as the number of days prior to disease recurrence when no adverse events of grade 3 or 4 were experienced. Specifically, this is the time from randomization to recurrence or second primary cancer, or to death without recurrence, minus TOX. For patients alive without recurrence at the time of the Q-TWiST analysis, TWiST will be censored at the date of last disease assessment.

REC

The recurrence health state is defined as the time from disease recurrence or second primary cancer until death. Patients alive at last follow-up will be censored at the date of last contact.

For each of the above health states, a patient-reported utility weight will be assigned. The EQ-5D will be used to derive these weights. This brief instrument consists of five questions, related to mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, along with a question about global health which is rated from 0 (the worst health you can imagine) to 100 (the best health you can imagine). The EQ-5D will be administered at baseline and at the end of every cycle until the end of treatment, then every 3 months until disease progression. For each patient, EQ-5D assessments will be averaged during each of the health states. Specifically, EQ-5D scores for all visits during which a patient reports grade 3 or 4 adverse event will be averaged to form that patient's TOX utility score. Similarly, all EQ-5D scores for visits without either grade 3 or 4 adverse events or recurrence will be averaged to form the patient's TWiST utility score. All EQ-5D scores for visits after recurrence will be averaged to form that patient's REC utility score. The available EQ-5D (utility) scores for the TOX, TWiST, and REC states for each arm will then be compared.

Rev. 8/13

The mean amount of time in each state will be estimated using the method of Kaplan and Meier (1958). The areas between the curves represent the restricted mean duration of TWiST and REC as follows:

Duration of TWiST = mean RFS – mean time with toxicities

Duration of REC = mean OS – mean RFS

The quality-adjusted times (Q-TWiST) for each arm will be calculated using the following formula:

$Q\text{-TWiST} = (u_{TOX} \times TOX) + (u_{TWiST} \times TWiST) + (u_{REC} \times REC)$

Where u_{TOX}, u_{TWiST}, and u_{REC} represent the average group utility value for each state for that arm and TOX, TWiST and REC represent the mean duration of the state for that arm.

The null hypothesis of no difference between arms will be tested using a Z-test, with standard errors calculated by the bootstrap method. The bootstrap will be conducted by repeatedly sampling with replacement from the sample of patients included in the study, to obtain a new sample of the same size as the observed dataset. The means for the new sample will be calculated from the area under

Rev. 11/14

the Kaplan-Meier curve. This process will be repeated 1000 times. Based on the means obtained by the bootstrap, standard errors will be calculated. Assuming similar variability in our patients and assuming that 102 patients contribute information to the analysis, we will have 85% power to detect a difference of 3.4 weeks, using a two-sided test with 5% Type I error.

As an example of power that will exist, we consider differences similar to those observed by Wang et al in a Q-TWiST analysis of panitumumab in patients with metastatic colorectal cancer (39). In Table 2, they report a difference in mean duration of the TOX state of 2.37 weeks and from the p-value, we estimate a standard deviation within groups of 5.7 weeks. Assuming similar variability in our patients and assuming that 148 patients contribute information to the analysis, we will have 85% power to detect a difference of 2.8 weeks, using a two-sided test with 5% Type I error.

We have chosen the EQ-5D as a tool for assessing overall quality of life because of its previous use in this context (35,42,44,45). It is very short and easy to administer making it suitable for the frequent administration necessary to derive health utilities. It targets overall quality of life, rather than specific symptoms, which is our primary interest.

Fatigue

We are also interested in assessing specific patient-reported symptoms in this under-studied population, using tools that have been employed in other studies of patients with renal cell carcinoma. Evaluating fatigue in this otherwise healthy population will enable us to better understand the relative contributions of treatment and disease burden to the problem. We will assess fatigue at baseline, 6 months, and 15 months. The 6-month assessment will enable assessment of fatigue levels on-treatment, while the 15-month assessment will allow us to assess recovery following treatment for the subset of patients who are still free of disease at that time point.

Currently, validation of the PROMIS Fatigue instrument is ongoing using data from ASSURE. Until this analysis is complete, we propose using both PROMIS Fatigue and the FACIT Fatigue subscales to measure fatigue. Once the analysis is complete, we will remove the less-effective instrument from the battery and continue with only the more effective one in order to minimize burden to patients and staff.

As an example of power that will exist, we consider the FACIT Fatigue subscale. FACIT Fatigue scores are reported to have a standard deviation ranging from 9.4 to 13.6. Differences in the FACIT Fatigue mean change scores between the treatment arms from baseline to 6 months that can be detected with 80% power assuming a t-test with a two-sided significance level of 0.05 are shown in the following table.

Rev. 11/14

Rev. 11/14

Standard Deviation (SD)	Correlation	SD of Change	Difference between placebo and experimental arm in mean change score between randomization and Week 24	
			65% Adherence/Participation (42 per arm)	80% Adherence/Participation (51 per arm)
9.5	0.4	10.4	6.4	5.8
	0.6	8.5	5.3	4.8
11.0	0.4	12.0	7.4	6.7
	0.6	9.8	6.1	5.5
12.5	0.4	13.7	8.5	7.7
	0.6	11.2	6.9	6.3
14.0	0.4	15.3	9.5	8.6
	0.6	12.5	7.7	7.0

Kidney Symptom Index

The 15-item version of the Functional Assessment of Cancer Therapy-Kidney Symptom Index will be used to assess symptoms found in previous studies to be of concern among patients with kidney cancer. Since this study involves patients with no evidence of disease and is placebo-controlled, it will provide a unique opportunity to identify quality of life concerns attributable to treatment with pazopanib among patients with no disease-related symptoms. Patients are expected to have low symptom levels at baseline. Since about 80% of patients are expected to have ECOG performance status 0 at baseline, we estimate the mean score at baseline to be 50.0 (SD at one administration 5.2). Cella et al. indicated that a minimally important difference of 2 to 5 is appropriate for this scale. The following table shows differences in mean change scores between placebo and pazopanib-treated patients that will be detectable with 80% power assuming a t-test with a two-sided significance level of 0.05.

Rev. 11/14

Rev. 11/14

Standard Deviation (SD)	Correlation	SD of Change	Difference between placebo and experimental arm in mean change score between randomization and Week 24	
			65% Adherence/Participation (42 per arm)	80% Adherence/Participation (51 per arm)
5.2	0.4	5.70	3.53	3.19
	0.6	4.65	2.78	2.52

9.3 Study Monitoring

Rev. 11/14

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office.

Blinded safety data will be available for review using standard ECOG-ACRIN toxicity monitoring procedures. Adverse event rates for unblinded treatment arms will also be reviewed semiannually by the ECOG-ACRIN Data Monitoring Committee.

9.4 Safety Monitoring

Rev. 11/14

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required.

9.5 Gender and Ethnicity

Based on previous data from E2805 the anticipated accrual in subgroups defined by gender and race is:

Rev. 11/14

Racial Category	Ethnic Categories				Total
	Hispanic or Latino		Not Hispanic or Latino		
	Females	Males	Females	Males	
American Indian or Alaskan Native	0	0	0	0	0
Asian	0	0	0	2	2
Native Hawaiin or other Pacific Islander	0	0	0	0	0
Black or African American	0	0	3	3	6
White	2	5	36	77	120
Total	2	5	39	82	128

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Pathology Review

Formalin-fixed, paraffin-embedded tissues from the nephrectomy and metastatectomy procedures are to be submitted for central diagnostic review and classification. Additional materials, from consenting patients, are requested for banking for future research studies.

The submitting pathologist and clinical research associate should refer to Appendix II (Pathology Submission Guidelines) for guidelines and summary of submission requirements.

10.1 Pathology Submission

10.1.1 The materials required for this protocol are:

Forms:

Rev. 2/15

- A copy of the surgical pathology report
- Immunological study reports, if available
- STS-generated shipping manifest

Biological Material Submission

Submit within one month after randomization

- Representative tumor blocks from both primary nephrectomy and metastasectomy specimens

  AND

- Representative H&E slides from all tumor blocks

NOTE: During central review, ECOG-ACRIN CBPF may request additional or alternative materials selected by the review team to complete tumor submission requirements.

NOTE: Block from a core needle biopsy may be submitted if resected specimens are unavailable. If unable to submit the requested materials, contact ECOG-ACRIN CBPF (844-744-2420), email eacbpf@mdanderson.org to obtain description of alternative submission requirements.

Rev. 2/15

NOTE: If slides only are submitted for review, additional materials (blocks, cores and/or slides) are requested to be submitted from patients who answer "Yes" to "My coded samples and related coded information may be kept for use in research to learn about, prevent, find or treat cancer."

10.1.2 Shipping Procedures

Pathology materials are to be submitted at ambient within one month following patient randomization. If materials will be submitted with frozen blood samples, use the combination shipment guidelines in Section 11.1.2.1

Rev. 8/13

The shipping account information: THE FEDEX ACCOUNT FOR THE ECOG-ACRIN CBPF at MD Anderson Cancer Center is obtained

by logging into fedex.com using your account issued previously by the ECOG-ACRIN CBPF. This account is for all shipments to the ECOG-ACRIN CBPF on any designated ECOG-ACRIN trials. If your site has not yet obtained an account, to have an account created please contact the ECOG-ACRIN CBPF by email at

Rev. 2/15

eacbpf@mdanderson.org. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email.

Ship materials to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all sample submissions.

Rev. 2/15

10.1.3 Central Biorepository and Pathology Facility: Sample processing and Routing

Initial diagnostic materials will be forwarded to Dr. Michael Pins for review. The ECOG-ACRIN CBPF may request additional materials for review, as directed by Dr. Michael Pins to complete tumor submission requirements. Other than an H&E from the submitted block, other H&E and immunochemical stains submitted will be returned to the site.

Blocks and slides from consenting patients will be retained in the ECOG-ACRIN Repository for future research studies.

10.2 Histologic predictor of prognosis (Pins)

The following pathological parameters (beyond TNM assignment) have been demonstrated to have prognostic relevance in renal cell carcinoma. As such, uniform documentation of these parameters is essential in any study measuring outcomes. Other parameters of prognostic significance not listed below have also been reported (46):

1. RCC Subtypes: Only patients with tumors subclassified as clear cell renal cell carcinoma are eligible. While subclassification based upon rigorous application of histological criteria is usually straightforward, a significant subset of cases are problematic for the pathologist. The 2004 WHO classification system recognized over 50 different tumors of the kidney. For practical purposes, the carcinoma subtypes fall into five major categories, including clear cell, papillary, chromophobe, collecting duct, and renal cell carcinoma, unclassified. Increasingly, rarer subtypes, such as renal medullary carcinoma, translocation carcinomas (Xp11.2/TFE3 fusions, for example), mucinous tubular and spindle cell carcinoma, multilocular cystic renal cell

carcinoma, mixed epithelial stromal tumor and others are increasingly recognized. Each of these common and rarer subtypes have characteristic molecular genetic abnormalities, which in turn correlate with biological behavior and likely correlate with response to adjuvant therapy. Specific examples of tumors which may be misclassified include the occasional tumor with eosinophilic features, which may be classified as eosinophilic variant of clear cell carcinoma, papillary carcinoma (type 2), eosinophilic variant of chromophobe carcinoma, benign oncocytoma, or epithelioid angiomyolipoma. The correct subclassification is not only critical from a molecular-genetic standpoint, but also from a prognostic standpoint as several studies have demonstrated the prognostic significance of the tumor subtype (47-49).

2. Sarcomatoid component: The 2004 WHO classification discarded the term "sarcomatoid carcinoma" in favor of the term "[subtype] with sarcomatoid change" recognizing that most renal cell carcinomas with sarcomatoid elements have associated, conventional (clear cell, papillary, or chromphobe) subtypes. Those tumors that lack a conventional subtype are categorized as RCC, unclassified. Several studies have shown that presence of sarcomatoid change is associated with an unfavorable prognosis (50,51). It is currently accepted that the presence of any sarcomatoid component portends an unfavorable prognosis; however, the significance of the histopathological features of the sarcomatoid component or the relative amount of the sarcomatoid component has not been rigorously analyzed.
3. Fuhrman Grade: The Fuhrman system is the most widely used nuclear grading system for renal cell carcinoma of clear cell histology. The Fuhrman nuclear grade is widely accepted as a significant prognostic variable. Although the criteria for grades 1 to 4 are fairly rigidly defined, its reproducibility between pathologists appears to be low, with studies showing Kappa values ranging from 0.19 to 0.44, reflecting only poor to moderate reproducibility (52-54). In addition, renal cell carcinomas are often heterogeneous containing areas of tumor with more than one Fuhrman grade. By convention, the tumor is graded based upon the highest Fuhrman grade present; however, this approach has not been seriously validated; a tumor with a small focus of Fuhrman grade 4 very likely will not behave as badly as a tumor with mostly Fuhrman grade 4 - yet both would be classified as grade 4.
4. Necrosis: The presence of coagulative tumor necrosis has recently been shown to be an adverse prognostic variable (55). Similar to the presence of a sarcomatoid component, the amount of coagulative necrosis may also show prognostic significance.
5. Renal pelvic sinus invasion: The renal sinus is the fatty compartment that invests the collecting system and abuts the cortical columns of Bertin (56). Recent data suggests that the primary pathway by which renal cell carcinoma metastasizes is via the rich vascular network present within the kidney's renal sinus (57). Presence of sinus invasion correlated with tumor grade, size and subtype; however, follow-up data is currently not available. Prospective sampling of the renal pelvic-tumor interface is the optimal way to document sinus invasion; however, retrospective histopathological examination may be insightful.

6. TNM: Accurate assignment of TNM status is important in renal cell carcinoma. As such, tumor size, extension beyond the renal capsule (perinephric fat, Gerota fascia, adrenal, other), renal vein (or vena cava) invasion, renal sinus involvement, and lymph node (hilar, periaortic, distant, etc) involvement (if sampled by the surgeon or pathologist) must be documented in a uniform manner via Central Pathology Review.

10.3 ECOG-ACRIN Sample Tracking System

It is required that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Rev. 2/15

Important: Additionally, please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog-acrin.tst@jimmy.harvard.edu

Study Specific Notes

The Generic Specimen Submission Form (#2981) and Shipment Notification Form (faxed to the receiving laboratory) will be required only if STS is unavailable at time of sample submission. Indicate the appropriate Lab on the submission form:

Rev. 2/15

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Banking

Residual material from all specimens submitted on this trial will be retained at the ECOG-ACRIN Central Repository for possible use in future ECOG-ACRIN approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11. Correlative Studies

Plasma specimens are requested for pharmacokinetic studies (Section 11.2) and peripheral blood will be collected for future plasma and DNA studies to establish predictive and prognostic biomarkers associated with clinical outcome and toxicity.

Rev. 8/13

Patient-reported outcomes will be captured through a Quality of Life questionnaire, which will be administered at baseline, at the end of every cycle of study treatment, and during follow-up.

Specimen submissions are outlined in Section 11.1.

11.1 Specimen submissions

Kits for sample collection and shipment are requested by contacting the Zemotak-International. Complete the KIT ORDER FORM (Appendix VIII) and fax to (800)-815-4675.

All specimens submitted must be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 10.3).

LABELING: All samples are to be labeled with the ECOG-ACRIN protocol number E2810, the ECOG-ACRIN patient sequence number, date and time of collection, and type of material (e.g. EDTA peripheral blood, plasma EDTA).

11.1.1 Specimen Preparation Guidelines

A. PHARMACOKINETIC LABORATORY RESEARCH STUDIES

Submit from all patients who answer "Yes" to **"I agree to participate in the laboratory research studies that are being done as part of this clinical trial**". These samples will be used in the laboratory research defined in Section 11.2.

Blood samples are to be collected within 24 hours prior to start of treatment on Cycle 2 Day 1. It is requested that the patient bring their study drug to the clinic on the day of the draw and take the medication AFTER collection of the research specimen.

Ship Frozen →

Plasma: EDTA purple top tube

a. Draw peripheral blood into 2 vacutainers and gently invert 8-10 times.
b. Within 20 minutes of collection, centrifuge at 1500xg (2700-3000 rpm) for 15 minutes.
c. Pipette the plasma into **8 cryotubes** provided in the kit and store frozen, below –20ºC (-70 ºC preferred), until shipped
d. Remaining Cells: **EDTA purple top tube**
e. Replace the stopper on the EDTA tube containing the cells and ship ambient the day of collection

B. FUTURE RESEARCH STUDIES

Plasma and residual cells are to be submitted from patients who answer "Yes" to "**I agree to provide additional blood for research.**"

It is preferred that samples be collected at baseline (prior to treatment), however any time during the trial is acceptable.

Rev. 8/13 Ship Frozen →

Peripheral blood: ACD (yellow top) or EDTA (purple top)

a. Draw peripheral blood into ACD vacutainers and gently invert 8-10 times.

b. For glass vacutainers, pipette the whole blood into **the large cryotubes** provided in the kit and store frozen, below –20ºC (-70 ºC preferred), until shipped. Plastic vacutainers may be frozen directly.

NOTE: The peripheral blood may be shipped at ambient or frozen day of collection.

11.1.2 Shipping Guidelines

All blood samples are shipped via OVERNIGHT delivery using an airbill provided in the kit. The blood samples MUST be shipped on DRY ICE. Frozen specimens are to be shipped MONDAY through THURSDAY only. Do not ship on the day before a weekend or holiday.

Fixed, paraffin embedded tissue samples are to be packaged to prevent breakage and shipped no later than one month following randomization. If tissue samples are shipped with the frozen blood samples, use the combination shipment guidelines outlined in Section 11.1.2.1.

An STS-generated shipping manifest must be submitted with every shipment.

Rev. 2/15

SHIP TO:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

Rev. 2/15

NOTE: Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

11.1.2.1 **Combination Shipment:** Shipping Both Frozen and Ambient Samples Together.

For shipments with peripheral blood draws OR shipments performed Monday through Thursday ONLY.

- Line the styrofoam containers with enough absorbent material to absorb any contents that may leak.
- Each frozen sample must be in its own cryovial or sealed container. The frozen samples are then placed into a biohazard bag, sealed and placed into the large styrofoam container.
- Add DRY-ICE or Frozen Brick into large styrofoam. Use enough of DRY ICE to last 4 days. Cover the Styrofoam.

Rev. 8/13

- Place room temp samples, if applicable, into small styrofoam/cardboards provided. Fixed tissue blocks may be submitted with these samples.
- Place the styrofoam containers into large cardboard box.
- Affix IATA labels (UN3373, Biohazard, and DRY-ICE label if dry-ice is used) on the cardboard box. Sites outside of US borders must include CDCP permit label on shipment.
- Place documents (STS Shipping manifest or Material Submission Form) on top, then seal box.

11.2 Pazopanib Pharmacokinetics

Data obtained in prior clinical studies suggest that plasma pazopanib trough levels greater than 15 mcg/ml correlate with clinical response, toxicity (hypertension) and pharmacodynamic markers (circulating VEGFR) [21,22].

Day 28 pazopanib trough concentration and disease-free survival will be recorded as continuous variables. Spearman's Rank Correlation Coefficient will be calculated to test whether there is a relationship between pazopanib trough levels and DFS.

These studies will be performed by Dr. Jill Kolesar at the University of Wisconsin Cancer Center.

Because this is a blinded trial, the sample analysis will be performed as follows: All baseline and post cycle 1 samples received from pazopanib treated patients and from a subset of placebo treated patients will be batch analyzed after the study closes to accrual. The case listing will be generated by the ECOG-ACRIN statistician and provided to the ECOG-ACRIN Central Biorepository and

Rev. 2/15

Pathology Facility (CBPF), with no arm assignment or indication as to the percentage of placebo patients indicated. The CBPF will provide coded aliquots to Dr. Kolesar's laboratory, with no designation as to time point or ECOG-ACRIN patient ID or relatedness to another sample. The CBPF will provide the key for the coded samples, case numbers, and time points to the ECOG-ACRIN Operating Office - Boston and the ECOG-ACRIN statistician. Upon completion of

the analysis, Dr. Kolesar's laboratory will forward the data to ECC to be decoded by the statistician.

11.3 Banking

Residual material from the specimens submitted will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) for possible use in future ECOG-ACRIN approved studies. Any residual blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11.4 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operating Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operating Office - Boston.

11.5 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operating Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operating Office - Boston 1 week after these cut-off dates.

12. Electronic Data Capture

Please refer to the E2810 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operating Office - Boston to CTEP by electronic means.

12.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied,
  or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operating Office - Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin*. Sep-Oct 2010;60(5):277-300.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. 2010; Available from http://globocan.iarc.fr. Accessed August 27 2011.
3. Kane CJ, Mallin K, Ritchey J, Cooperberg MR, Carroll PR. Renal cell cancer stage migration: analysis of the National Cancer Data Base. *Cancer.* Jul 1 2008;113(1):78-83.
4. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. *J Clin Oncol.* Aug 1999;17(8):2530-2540.
5. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med.* June 3 2007;356(22):2271-2281.

6. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol.* Feb 20 2010;28(6):1061-1068.
7. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med.* Jan 11 2007;356(2):115-124.
8. Fyfe GA, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Long-term response data for 255 patients with metastatic renal cell carcinoma treated with high-dose recombinant interleukin-2 therapy. *J Clin Oncol.* Aug 1996;14(8):2410-2411.
9. McDermott DF, Regan MM, Clark JI, et al. Randomized phase III trial of high-dose interleukin-2 versus subcutaneous interleukin-2 and interferon in patients with metastatic renal cell carcinoma. *J Clin Oncol.* Jan 1 2005;23(1):133-141.
10. Yao M, Yoshida M, Kishida T, et al. VHL tumor suppressor gene alterations associated with good prognosis in sporadic clear-cell renal carcinoma. *J Natl Cancer Inst.* Oct 16 2002;94(20):1569-1575.
11. Nickerson ML, Jaeger E, Shi Y, et al. Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. *Clin Cancer Res.* Aug 1 2008;14(15):4726-4734.
12. Gnarra JR, Tory K, Weng Y, et al. Mutations of the VHL tumour suppressor gene in renal carcinoma. *Nat Genet.* May 1994;7(1):85-90.
13. Maxwell PH, Wiesener MS, Chang GW, et al. The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. *Nature.* May 20 1999;399(6733):271-275.
14. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol.* Feb 10 2005;23(5):1011-1027.
15. Wu LW, Mayo LD, Dunbar JD, et al. Utilization of distinct signaling pathways by receptors for vascular endothelial cell growth factor and other mitogens in the induction of endothelial cell proliferation. *J Biol Chem.* Feb 18 2000;275(7):5096-5103.
16. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med.* Jul 31 2003;349(5):427-434.
17. Lockhart AC, Rothenberg ML, Dupont J, et al. Phase I study of intravenous vascular endothelial growth factor trap, aflibercept, in patients with advanced solid tumors. *J Clin Oncol.* Jan 10 2010;28(2):207-214.
18. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med.* Jan 11 2007;356(2):125-134.
19. Rixe O, Bukowski RM, Michaelson MD, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. *The lancet oncology.* Nov 2007;8(11):975-984.
20. Motzer RJ, Escudier B, Oudard S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. *Lancet.* Aug 9 2008;372(9637):449-456.

21. Kumar R, Knick VB, Rudolph SK, et al. Pharmacokinetic-pharmacodynamic correlation from mouse to human with pazopanib, a multikinase angiogenesis inhibitor with potent antitumor and antiangiogenic activity. *Mol Cancer Ther.* Jul 2007;6(7):2012-2021.
22. Pandite L, Abissi, CBall H, et al. Investigator's Brochure for pazopanib (GW786034) for Oncology and Ophthalmic Indications, v.8: GlaxoSmithKline; 2011.
23. Hutson TE, Davis ID, Machiels JP, et al. Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* Jan 20 2010;28(3):475-480.
24. Clark JI, Atkins MB, Urba WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol.* Aug 15 2003;21(16):3133-3140.
25. Wood C, Srivastava P, Bukowski R, et al. An adjuvant autologous therapeutic vaccine (HSPPC-96; vitespen) versus observation alone for patients at high risk of recurrence after nephrectomy for renal cell carcinoma: a multicentre, open-label, randomised phase III trial. *Lancet.* Jul 12 2008;372(9633):145-154.
26. Pizzocaro G, Piva L, Colavita M, et al. Interferon adjuvant to radical nephrectomy in Robson stages II and III renal cell carcinoma: a multicentric randomized study. *J Clin Oncol.* Jan 15 2001;19(2):425-431.
27. Barney J, Churchill E. Adenocarcinoma of the kidney with metastasis to the lung: cured by nephrectomy and lobectomy. *J. Urol.* 1939;42:269.
28. Kavolius JP, Mastorakos DP, Pavlovich C, Russo P, Burt ME, Brady MS. Resection of metastatic renal cell carcinoma. *J Clin Oncol.* Jun 1998;16(6):2261-2266.
29. Zerbi A, Ortolano E, Balzano G, Borri A, Beneduce AA, Di Carlo V. Pancreatic metastasis from renal cell carcinoma: which patients benefit from surgical resection? *Annals of surgical oncology.* Apr 2008;15(4):1161-1168.
30. Adam R, Chiche L, Aloia T, et al. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg.* Oct 2006;244(4):524-535.
31. Piltz S, Meimarakis G, Wichmann MW, Hatz R, Schildberg FW, Fuerst H. Long-term results after pulmonary resection of renal cell carcinoma metastases. *Ann Thorac Surg.* Apr 2002;73(4):1082-1087.
32. Mitry E, Fields AL, Bleiberg H, et al. Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: a pooled analysis of two randomized trials. *J Clin Oncol.* Oct 20 2008;26(30):4906-4911.
33. Beaumont JL, Butt Z, Baladi J, et al. Patient-reported outcomes in a phase III study of everolimus versus placebo in patients with metastatic carcinoma of the kidney that has progressed on vascular endothelial growth factor receptor tyrosine kinase inhibitor therapy. *Oncologist.* 2011;16(5):632-640.
34. Cella D, Escudier B, Rini BI, et al. Patient-reported outcomes (PROs) in a phase III AXIS trial of axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC). *J. Clin. Oncol.* 2011;29 Suppl.:Abstract 4504.
35. Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. *Eur J Cancer.* Jun 18 2011.

36. Cella D, Michaelson MD, Bushmakin AG, et al. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. *Br J Cancer.* Feb 16 2010;102(4):658-664.
37. Cella D, Li JZ, Cappelleri JC, et al. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial. *J Clin Oncol.* Aug 1 2008;26(22):3763-3769.
38. Gelber RD, Goldhirsch A. A new endpoint for the assessment of adjuvant therapy in postmenopausal women with operable breast cancer. *J Clin Oncol.* Dec 1986;4(12):1772-1779.
39. Wang J, Zhao Z, Barber B, Sherrill B, Peeters M, Wiezorek J. A Q-TWiST analysis comparing panitumumab plus best supportive care (BSC) with BSC alone in patients with wild-type KRAS metastatic colorectal cancer. *Br J Cancer.* May 24 2011.
40. Brazier J, Jones N, Kind P. Testing the validity of the Euroqol and comparing it with the SF-36 health survey questionnaire. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* Jun 1993;2(3):169-180.
41. de Boer AG, van Lanschot JJ, Stalmeier PF, et al. Is a single-item visual analogue scale as valid, reliable and responsive as multi-item scales in measuring quality of life? *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* Mar 2004;13(2):311-320.
42. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Annals of medicine.* Jul 2001;33(5):337-343.
43. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials.* Jun 2010;7(3):197-208.
44. Sun H, King AJ, Diaz HB, Marshall MS. Regulation of the protein kinase Raf-1 by oncogenic Ras through phosphatidylinositol 3-kinase, Cdc42/Rac and Pak. *Curr Biol.* Mar 9 2000;10(5):281-284.
45. Zbrozek AS, Hudes G, Levy D, et al. Q-TWiST analysis of patients receiving temsirolimus or interferon alpha for treatment of advanced renal cell carcinoma. *PharmacoEconomics.* 2010;28(7):577-584.
46. Lohse CM, Cheville JC. A review of prognostic pathologic features and algorithms for patients treated surgically for renal cell carcinoma. Clinics in Lab Med. 25(2):433-64, 2005.
47. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol. 2003 May;27(5):612-24.
48. Patard JJ, Leray E., et al. Prognostic value of histologic subtypes in renal cell carcinoma: a multicenter experience. J Clin Oncol. 23(12):2763-71, 2005.
49. Frank I, Blute ML., et al. Independent validation of the 2002 American Joint Committee on cancer primary tumor classification for renal cell carcinoma using a large, single institution cohort. Journal of Urology. 173(6):1889-92, 2005.
50. de Peralta-Venturina M, Moch H., et al. Sarcomatoid differentiation in renal cell carcinoma: a study of 101 cases. Am J Surg Pathol. 25(3):275-84, 2001.

51. Cheville JC, Lohse CM. et al. Sarcomatoid renal cell carcinoma: an examination of underlying histologic subtype and an analysis of associations with patient outcome. Am J Surg Pathol. 28(4):435-41, 2004.
52. Lang H. Lindner V., et al. Multicenter determination of optimal interobserver agreement using the Fuhrman grading system for renal cell carcinoma: Assessment of 241 patients with > 15-year follow-up. Cancer. 103(3):625-9, 2005.
53. Ficarra V. Martignoni G., et al. Original and reviewed nuclear grading according to the Fuhrman system: a multivariate analysis of 388 patients with conventional renal cell carcinoma. Cancer. 103(1):68-75, 2005.
54. Al-Aynati M. Chen V., et al. Interobserver and intraobserver variability using the Fuhrman grading system for renal cell carcinoma. Arch athol Lab Med. 127(5):593-6, 2003.
55. Sengupta S. Lohse CM, et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. Cancer. 104(3):511-20, 2005.
56. Amis ES, Cronan JJ. The renal sinus: an imaging review and proposed nomenclature for sinus cysts. J Urol 1988;139:1151-9.
57. Bonsib SM. The renal sinus is the principal invasive pathway: a prospective study of 100 renal cell carcinomas. Am J Surg Pathol. 28(12):1594-600, 2004.

Rev. 8/13

58. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007).

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language)
[Deleted in Addendum #3]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix I was removed from the protocol document in Addendum #3 and is posted as a separate document on the ECOG-ACRIN website. This was removed from the protocol to comply with NCI formatting guidelines.

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix II
Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials
   (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E2810

Rev. 2/15

4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- ECOG-ACRIN Generic Specimen Submission Form (#2981)

Rev. 2/15

Instructions:

Rev. 2/15

1. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material to the appropriate pathologist. The ECOG-ACRIN Generic Specimen Submission (#2981) Form may be used as a reference to request the samples and a copy retained for their records.

Rev. 2/15

2. The pathologist should return the required pathology samples and surgical pathology reports. If any other reports are required, they should be obtained from the appropriate department at this time.
3. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)

   Pathology specimens submitted WILL NOT be processed by the Central Biorepository and Pathology Facility until all necessary items are received.
4. Mail pathology materials to:

Rev. 2/15

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506
Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone 844-744-2420 or by email eacbpf@mdanderson.org.

List of Required Material

E2810: Randomized Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Pre-Treatment

1. Institutional pathology report **(must be included with EVERY pathology submission)**.
2. STS-generated shipping manifest
3. Required path materials.
   (a) Representative tumor blocks from tumor or metastatic lesions

   OR

   (b) Representative H&E slides from all tumor blocks

Rev. 2/15

NOTE: Upon completion of slide review, ECOG-ACRIN CBPF will request paraffin blocks (or materials from the blocks) selected by Dr. Michael Pins to complete tumor submission requirements.

NOTE: Since blocks are being used for laboratory studies, in some cases the material may be depleted and, therefore, the block may not be returned.

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for E2810: Randomized Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy*

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for pathology review and future research studies.

Keep a copy of the submission for your records and return copies of the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility.

Rev. 2/15

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies. Paraffin blocks will be returned for purpose of patient management upon written request.

Please note: Since blocks are being *used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.*

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 844-744-2420 or eacbpf@mdanderson.org.

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address:_____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG-ACRIN web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Rev. 4/14

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix IV

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. If you forget, the missed pills will not be taken later.
3. Please bring the empty bottle along with any leftover tablets and your pill calendar to your next clinic visit.

Patient Pill Calendar

Patient ID #_____Patient Initials: _____ Cycle #:_____

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

DAY	Date Month Day Year			Time pills taken AM	 PM	Number of pills taken AM	 PM	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								
22								
23								
24								
25								
26								
27								
28								

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix V

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between GlaxoSmithKline (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(s) in this study:

Rev. 11/14

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 investigational 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 NIH, the design of the proposed combination protocol, and the existence of any obligations that 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 investigational 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 investigational 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 Collaborator(s) for Phase 3 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.

Rev. 11/14 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 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:

   Email: ncicteppubs@mail.nih.gov

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

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix VI

ECOG Performance Status

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

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix VII

Drugs Associated with QTc Prolongation

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism)*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix VIII

E2810 Collection and Shipping Kit Order Form

NOTE: Starter kits are not available. It is preferred that kit requests be made AFTER patient registration. At a minimum, the patient must have signed consent to participate in the trial and participate in the laboratory research studies.

FAX Completed form to Zemotak-International at (800) 815-4675

Date: _____

E2810 patient case number: _____

NOTE: Batch shipment on dry ice of baseline and day 28 blood samples preferred. Samples from multiple patients may be shipped together.

Kit is to be shipped to:

Institution Contact: _____

Phone number for contact: _____

Institution Address:

_____

_____

_____

Rev. 2/15

NOTE: Questions are to be directed to the ECOG-ACRIN CBPF,
Attn: Adekunle Raji
Tel: 844-744-2420
Email: eacbpf@mdanderson.org

Comments:

_____

_____

_____

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Appendix IX

Drugs Known to be Metabolized by CYP450 Isoenzymes

Rev. 8/13

The following table presents a list of drugs that may be substrates of CYP450 isoenzymes. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx[58]

CYP2C8/9

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	Trade Name	Generic Name	Trade Name	Generic Name	Trade Name
Antibiotics: e.g. Rifampin Sulfadiazine	 Rifadin --	Antifungals: e.g. Fluconazole Ketoconazole Miconazole Tioconazole	 Diflucan Nizoral Lotramin Monistat	Sedatives: e.g. Phenobarbiatl Primidone	 Luminal Mysoline
Misc. CV agents: e.g. Amiodarone Carvedilol	 Cordarone Coreg	Antimalarials: e.g. Pyrimethamine Quinine	 Daraprim Legatrin	Anticonvulsants: e.g. Carbamazapine Phenobarbital Phenytoin	 Tegretol Luminal Dilantin
Anti-asthmatics: e.g. Montelukast Zafirlukast	 Singulair Accolate	Anti-hyperlipidemics: e.g. Fluvastatin Gemfibrozil	 Lescol Lopid	Antibiotics: e.g. Rifapentine Rifampin	 Priftin Rifadin
Antidepressants: e.g. Fluoxetine Sertraline	 Prozac Zoloft	Antibiotics: e.g. Isoniazid Sulfadiazine Sulfamethoxazole Trimethoprim	 INH, Nydrazid -- Bactrim, Septra Primsol		
Anticonvulsants: e.g. Fosphenytoin Phenytoin	 Cerebyx Dilantin	Analgesics: e.g. Flurbiprofen Ibuprofen Indomethacin Mefenamic acid	 Ansaid Advil, Motrin Indocin Ponstel		
Anesthetics: e.g. Ketamine Propofol	 Ketalar Diprivan	Anti-ulceratives: e.g. Omeprazole Pantoprazole	 Prilosec Pantoloc		
Anti-diabetics: e.g. Glimepiride Rosiglitazone	 Amaryl Avandia	Antihypertensives: e.g. Irbesartan Losartan Nicardipine	 Avapro Cozaar Cardene		
Antihypertensives: e.g. Losartan Bosentan	 Cozaar Tracleer				
Paclitaxel	Taxol	Anti-diabetics: e.g. Pioglitazone Rosiglitazone	 Actos Avandia		
Alosetron	Lotronex	Amiodarone	Cordarone		
Torsemide	Demadex	Delavirdine	Rescriptor		
		Piroxicam	Feldene		
		Warfarin	Coumadin		
		Zafirlukast	Accolate		

When drugs classified as ‘substrates’ are co-administered with study agent, there is the potential for higher concentrations of the ‘substrate’. When study agent is co-administered with compounds classified as ‘inhibitors’, increased plasma concentrations of study agent is the potential outcome. The coadministration of ‘inducers’ would potentially lower plasma study agent concentrations.

Comprehensive list of drugs that may have potential interactions

Rev. 8/13

The following table presents a list of drugs may be inhibitors, inducers or substrates of CYP450 isoenzymes. Please note that this list is frequently updated. For the most current list of medications, users should be directed to the following website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx[58]

CYP2C8/9

Substrates			
Alosetron	Losartan	Rifampin	Tolbutamide
Amiodarone	Mephenytoin	Rosiglitazone	Torsemide
Bosentan	Mestranol	Selegiline	Trimethoprim
Carvedilol	Montelukast	Sertraline	Voriconazole
Fluoxetine	Nateglinide	Sulfadiazine	Warfarin
Fosphenytoin	Paclitaxel	Sulfamethoxazole	Zafirlukast
Glimepiride	Phenytoin	Sulfinpyrazone	Zopiclone
Glipizide	Pioglitazone	Sulfisoxazole	
Ketamine	Propofol	Tamoxifen	

Inhibitors			
Amiodarone	Felodipine	Modafinil	Sertraline
Amitryptiline	Fluconazole	Montelukast	Sildenafil
Amlodipine	Fluoxetine	Nateglinide	Simvastatin
Anastrozole	Fluphenazine	Nelfinavir	Sulconazole
Aprepitant	Flurbiprofen	Nicardipine	Sulfadiazine
Atazanavir	Fluvastatin	Nifedipine	Sulfamethoxazole
Azelastine	Fluvoxamine	Olanzapine	Sulfinpyrazone
Bortezomib	Gemfibrozil	Omeprazole	Sulfisoxazole
Candesartan	Ibuprofen	Ondansetron	Tamoxifen
Chloramphenicol	Imatinib	Orphenadrine	Teniposide
Cholecalciferol	Indinavir	Pantoprazole	Thioridazine
(Vitamin D3)	Indomethacin	Paroxetine	Ticlopidine
Cimetidine	Irbesartan	Pentamidine	Tioconazole
Clopidogrel	Isoniazid	Pioglitizone	Tolbutamide
Clotrimazole	Ketoconazole	Piroxicam	Tolcapone
Clozapine	Ketoprofen	Pravastatin	Tranylcypromine
Cyclosporine	Lansoprazole	Progesterone	Tretinoin
Delavirdine	Leflunomide	Propafenone	Triazolam
Dexmedetomidine	Losartan	Propofol	Trimethoprim
Diclofenac	Lovastatin	Propoxyphene	Valdecoxib
Diltiazem	Mefenamic acid	Pyrimethamine	Valproic acid
Dimethyl sulfoxide	Meloxicam	Quinidine	Valsartan
Disulfiram	Methimazole	Quinine	Verapamil
Drospirenone	Methoxsalen	Ritonavir	Voriconazole
Efavirenz	Metronidazole	Rosiglitazone	Warfarin
Entacapone	Miconazole	Saquinavir	Zafirlukast
Eprosartan	Midazolam	Selegiline	
Etoposide			

Inducers			
Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

Selected Potential Cytochrome P450 (CYP) Drug Interactions

CYP3A4

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Anti-neoplastics: e.g. Docetaxel Gefitinib Irinotecan	Taxotere Iressa Camptosar	Anti-arrhythmics: e.g. Amiodarone Diltiazem Quinidine	Cordarone, Pacerone Cardizem, Dilacor XR Cardioquin	Aminoglutethimide	Cytadren
Anti-virals: e.g. Amprenivir Rifampin	Agenerase Rifadin	Anti-virals: e.g. Amprenavir Indinavir Nelfinavir Ritonavir	Agenerase Crixivan Viracept Norvir	Antibiotics: e.g. Rifabutin Rifampin	Rifadin Mycobutin
Anxiolytics: e.g. Diazepam Sertraline	Valium Zoloft	Cimetadine	Tagamet	Anticonvulsants: e.g. Carbamazapine Phenytoin Pentobarbital Phenobarbital	Tegretol Dilantin Nembutal Luminal
Cyclosporine	Sandimmune	Cyclosporine	Sandimmune	Hypericum perforatum (2)	St. John's Wort
Anti-infectives: e.g. Erythromycin Tetracycline	Erythrocin Sumycin	Antibiotics: e.g. Ciprofloxacin Clarithromycin Doxycycline Enoxacin Isoniazid Telithromycin	Cipro, Ciloxan Biaxin Adoxa, Periostat Penetrex Nydrazid, INH Ketek		
Steroids: e.g. Estrogens, conjugated Estradiol Progesterone	Premarin Climara Crinone	Imatinib	Gleevec		
Haloperidol	Haldol	Haloperidol	Haldol		
Cardiovascular agents: e.g. Digitoxin Quinidine	Crystodigin Cardioquin	Diclofenac	Cataflam, Voltaren		
Anti-hypertensives: e.g. Nicardipine Verapamil	Cardene Calan, Chronovera	Vasodilators: e.g. Nicardipine Verapamil	Cardene Calan, Chronovera		
Anesthetics: e.g. Ketamine Lidocaine	Xylocaine Diprivan	Anesthetics: e.g. Lidocaine Propofol	Xylocaine Diprivan		
Nefazodone	Serzone	Anti-depressants: e.g. Nefazodone Sertraline	Serzone Zoloft		

Cocaine		Anti-fungals: e.g. Itraconazole Ketoconazole Miconazole	 Sporanox Nizoral Lotrimin, Monistat		
Ketoconazole	Nizoral	Caffeine			
Sildenafil	Viagra	Grapefruit juice (1)			
Albuterol	Ventolin				
Carbamazapine	Tegretol				
Lovastatin	Mevacor				

When drugs classified as 'substrates' are co-administered with study agent, there is the potential for higher concentrations of the 'substrate'. When study agent is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of study agent is the potential outcome. The coadministration of 'inducers' would potentially lower plasma study agent concentrations.

Comprehensive List of Drugs That May Have Potential Interactions

CYP3A4

Substrates			
Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate hydrochloride	Repaglinide
Amprenavir	Efavirenz	Levonorgestrel	Rifabutin
Aprepitant	Eletriptan	Lidocaine	Rifampin
Aripiprazole	Enalapril	Losartan	Ritonavir
Atazanavir	Eplerenone	Lovastatin	Saquinavir
Atorvastatin	Ergoloid mesylates	Medroxyprogesterone	Sertraline
Benzphetamine	Ergonovine	Mefloquine	Sibutramine
Bisoprolol	Ergotamine	Mestranol	Sildenafil
Bortezomib	Erythromycin	Methadone	Simvastatin
Bosentan	Escitalopram	Methylergonovine	Sirolimus
Bromazepam	Estradiol	Methysergide	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Miconazole	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Midazolam	Tamoxifen
Buspirone	Estrogens, conj., esterified	Miglustat	Tamsulosin
Busulfan	Estrone	Mirtazapine	Telithromycin
Carbamazapine	Estropipate	Modafinil	Teniposide
Cerivastatin	Ethinyl estradiol	Montelukast	Terbinafine
Chlordiazepoxide	Ethosuximide	Moricizine	Tetracycline
Chloroquine	Etoposide	Nateglinide	Theophylline
Chlorpheniramine	Felbamate	Nefazodone	Tiagabine
Cisapride	Felodipine	Nelfinavir	Ticlopidine
Citalopram	Fentanyl	Nevirapine	Tolterodine
Clarithromycin	Flurazepam	Nicardipine	Toremifene
Clobazam	Flutamide	Nifedipine	Trazodone
Clonazepam	Fosamprenavir	Nimodipine	Triazolam
Clorazepate	Fulvestrant	Nisoldipine	Trimethoprim
Cocaine	Gefitinib	Nitrendipine	Trimipramine
Colchicine	Halofantrine	Norethindrone	Troleandomycin
Cyclophosphamide	Haloperidol	Norgestrel	Vardenafil
Cyclosporine	Ifosfamide	Ondansetron	Venlafaxine
Dantrolene	Imatinib	Paclitaxel	Verapamil
Dapsone	Indinavir	Pergolide	Vinblastine
Delavirdine	Irinotecan	Phencyclidine	Vincristine
Diazepam	Isosorbide dinitrate	Pimozide	Vinorelbine
Digitoxin	Isosorbide mononitrate	Pioglitazone	Zolpidem
Dihydroergotamine	Isradipine	Primaquine	Zonisamide
Diltiazem	Itraconazole	Progesterone	Zopiclone
Disopyramide	Ketamine		

CYP3A4

Inhibitors			
Acetominophen	Diltiazem	Lovastatin	Progesterone
Acetazolamide	Disulfiram	Mefloquine	Propofol
Amioderone	Docetaxel	Mestranol	Propoxyphene
Amlodipine	Doxorubicin	Methadone	Quinidine
Amprenavir	Doxycycline	Methimazole	Quinine
Anastrozole	Drospirenone	Methoxsalen	Quinupristin
Aprepitant	Efavirenz	Methylprednisolone	Rabeprazole
Atazanavir	Enoxacin	Metronidazole	Risperidone
Atorvastatin	Entacapone	Miconazole	Ritonavir
Azelastine	Ergotamine	Midazolam	Saquinavir
Azithromycin	Erythromycin	Mifepristone	Selegiline
Betamethasone	Ethinyl estradiol	Mirtazapine	Sertraline
Bortezomib	Etoposide	Mitoxantrone	Sildenafil
Bromocriptine	Felodipine	Modafinil	Sirolimus
Caffiene	Fentanyl	Nefazodone	Sulconazole
Cerivastatin	Fluconazole	Nelfinavir	Tacrolimus
Chloramphenicol	Fluoxetine	Nevirapine	Tamoxifen
Chlorzoxazone	Fluvastatin	Nicardipine	Telithromycin
Cimetadine	Fluvoxamine	Nifedipine	Teniposide
Ciprofloxacin	Fosamprenavir	Nisoldipine	Testosterone
Cisapride	Glyburide	Nitrendipine	Tetracycline
Clarithromycin	Grapefruit juice	Nizatidine	Ticlopidine
Clemastine	Haloperidol	Norfloxacin	Tranylcypromine
Clofazimine	Hydralazine	Olanzapine	Trazodone
Clotrimazole	Ifosfamide	Omeprazole	Troleandomycin
Clozapine	Imatinib	Orphenadrine	Valproic acid
Cocaine	Indinavir	Oxybutynin	Venlafaxine
Cyclophosphamide	Irbesartan	Paroxetine	Verapimil
Cyclosporine	Isoniazid	Pentamidine	Vinblastine
Danazol	Isradapine	Pergolide	Vincristine
Delavirdine	Itraconazole	Phencyclidine	Vinorelbine
Desipramine	Ketoconazole	Pilocarpine	Zafirlukast
Dexmedetomidine	Lansoprazole	Pimozide	Ziprasidone
Diazepam	Lidocaine	Pravastatin	
Diclofenac	Lomustine	Prednisolone	
Dihydroergotamine	Losartan	Primaquine	

Inducers			
Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazapine	Oxcarbazepine	Primidone	
Fosphenytoin	Pentobarbital	Rifabutin	
St. John's wort	Phenobarbital	Rifampin	

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

(1) Malhorta *et al*. (2000). Clin Pharmacol Ther. 69:14-23

(2) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249

Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329

Rev. 8/13 (3) Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007)

Dihydropyridine calcium-channel blockers (DHP CCB)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd		10 mg po qd	CYP 3A4 substrate + inhibitor

Selective β blockers (BB)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	**No**
Acebutolol	100 mg po bid	200 mg-300 mg po bid	400 mg po bid	Yes(CYP450 unknown)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes(CYP450 unknown)

Angiotensin Converting Enzyme Inhibitors (ACEIs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Captopril	12.5 po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (CYP450 unknown)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	**No**
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (CYP450 unknown)
Rarely used:				
Perindopril	4mg po qd	none	8mg po qd	Yes but not CYP450
Quinapril	10mg po qd	20 mg po qd	40 mg po /qd	No

Angiotensin II Receptors Blockers (ARBs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Losartan	25 mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4 mg po qd	8-16 mg po qd	32 mg po qd	CYP 2C9 substrate
Irbesartan	75 mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	Yes but not CYP450
Valsartan	80 mg po qd	none	160mg po qd	Yes but not CYP450

α and β blocker

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate and inhibitor

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with pazopanib through CYP450.

Randomized, Double-Blind Phase III Study of Pazopanib vs. Placebo in Patients with Metastatic Renal Cell Carcinoma Who Have No Evidence of Disease Following Metastatectomy

Rev. 8/13, 4/14

Appendix X

Procedures for Reporting the Occurrence of Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on pazopanib/placebo, or within 28 days of the patient's last dose of pazopanib/placebo must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- 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.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operating Office - Boston. Please contact the ECOG-ACRIN Operating Office - Boston to ask for a conference call to be set up with the appropriate individuals.
- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Fetal Death

A fetal death is 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.*"

It must be reported via CTEP-AERS as Grade 4 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is 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. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to pazopanib/placebo must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*General disorders and administration - Other (neonatal loss)*"under the System Organ Class (SOC) "General disorder and administration".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm