

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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PROTOCOL UPDATE TO CALGB 90802

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**RANDOMIZED PHASE III TRIAL COMPARING EVEROLIMUS VERSUS EVEROLIMUS  
PLUS BEVACIZUMAB FOR ADVANCED RENAL CELL CARCINOMA PROGRESSING  
AFTER TREATMENT WITH TYROSINE KINASE INHIBITORS**

*NCI-supplied agent(s): Bevacizumab (NSC 704865, IND #113911)*

☒ **Update:**

☐ Eligibility changes

☐ Therapy / Dose Modifications / Study Calendar changes

☒ Informed Consent changes

☐ Scientific / Statistical Considerations changes

☐ Data Submission / Forms changes

☒ Editorial / Administrative changes

☒ Other: **Bevacizumab CAEPR Update**

☐ **Status Change:**

☐ Pre-Activation

☐ Activation

☐ Closure

☐ Suspension / temporary closure

☐ Reactivation

*The changes included in this update to CALGB 90601 have been made in response to the NCI Request for Amendment (RA) from Dr. Helen Chen dated May 09, 2014.*

*This update contains modifications to the risk information in the model consent form consistent with the new NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio and this information would have already been communicated to study participants in the previous version of the informed consent document. The Alliance does not require patient re-consent.*

*IRB review of this update is required within 90 days. Full Board review is recommended.*

*Please follow your local IRB guidelines.*

**UPDATES TO THE PROTOCOL:**

**Cover Page**

- “Vance E. Erese” replaces “Michele M. Seiler, MS” as Protocol Coordinator.

### **Section 16.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for bevacizumab (rhuMAb VEGF, NSC 704865)**

An updated CAEPR for bevacizumab (Version 2.3, August 1, 2013) has replaced the previous version. In this updated version, the following revisions have been made:

- Added New Risk:
  - Less Likely: **Dehydration; Wound complication**
  - Rare But Serious: **Infections and infestations – Other (necrotizing fasciitis)**
  - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Acidosis; Activated partial thromboplastin time prolonged; Agitation; Alopecia; Anxiety; Arachnoiditis; Arterial injury; Arthritis; Ascites; Ataxia; Atelectasis; Atrioventricular block complete; Atrioventricular block first degree; Back pain; Bladder spasm; Blood antidiuretic hormone abnormal; Blurred vision; Bone marrow hypocellular; Bone pain; Breast pain; Bruising; Burn; Carbon monoxide diffusing capacity decreased; Cardiac arrest; Cataract; CD4 lymphocytes decreased; Central nervous system necrosis; Cerebrospinal fluid leakage; Chelitis; Chest wall pain; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic stenosis; CPK increased; Cystitis noninfective; Death NOS; Depressed level of consciousness; Depression; Dermatitis radiation; Dry eye; Dry mouth; Dry skin; Dysesthesia; Dysphagia; Dysphasia; Ear and labyrinth disorders – Other (tympanic membrane perforation); Edema face; Edema limbs; Edema trunk; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Enterocolitis; Erectile dysfunction; Esophageal pain; Esophageal stenosis; Extraocular muscle paresis; Extrapyrimal disorder; Eye disorders – Other (blindness); Eye disorders – Other (conjunctival hemorrhage); Eye disorders – Other (corneal epithelial defect); Eye disorders – Other (floaters); Eye disorders – Other (ischemic CRVO); Eye disorders – Other (macular pucker); Eye disorders – Other (transient increased IOP > or = 30 mm Hg); Eye disorders – Other (vitreous hemorrhage); Eye pain; Facial nerve disorder; Facial pain; Fever; Fibrosis deep connective tissue; Flatulence; Flu like symptoms; Flushing; Forced expiratory volume decreased; Fracture; Gallbladder necrosis; Gallbladder obstruction; Gastrointestinal disorders – Other (peritonitis); Generalized muscle weakness; GGT increased; Head soft tissue necrosis; Hearing impaired; Hemolysis; Hepatic necrosis; Hot flashes; Hydrocephalus; Hypercalcemia; Hyperglycemia; Hyperhidrosis; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperthyroidism; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Hypotension; Hypothyroidism; Hypoxia; Injection site reaction; INR increased; Insomnia; Irregular menstruation; Joint effusion; Keratitis; Leukoencephalopathy; Libido decreased; Lipase increased; Localized edema; Lymphocele; Lymphocyte count decreased; Memory impairment; Multi-organ failure; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder – Other (polymyalgia rheumatic); Myocarditis; Nail loss; Nasal congestion; Neck pain; Nervous system disorders – Other (increased intracranial pressure); Optic nerve disorder; Oral pain; Pain in extremity; Pain of skin; Pancreatitis; Paresthesia; Pelvic pain; Pelvic soft tissue necrosis; Phlebitis; Photophobia; Photosensitivity; Proctitis; Psychosis; Pulmonary fibrosis; Purpura; Pyramidal tract syndrome; Rash acneiform; Rectal mucositis; Rectal stenosis; Renal and urinary disorders – Other (dysuria); Renal and urinary disorders – Other (ureterolithiasis); Renal hemorrhage; Respiratory failure; Respiratory, thoracic and mediastinal disorders – Other (dry nares); Respiratory, thoracic and mediastinal disorders – Other (pulmonary infarction); Restrictive cardiomyopathy; Retinal detachment; Retinal tear; Retinopathy; Right ventricular dysfunction; Serum amylase increased; Skin and subcutaneous tissue disorders – Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders – Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Soft tissue necrosis lower limb; Somnolence; Stevens-Johnson syndrome; Tinnitus; Tremor; Tumor

- pain; Typhlitis; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain; Vaginal discharge; Vasculitis; Vasovagal reaction; Watering eyes; Weight gain
- Increase in Risk Attribution:
    - Changed to Likely from Less Likely: Neutrophil count decreased
    - Changed to Less Likely from Reported But Undetermined: Platelet count decreased
  - Decrease in Risk Attribution:
    - Changed to Reported But Undetermined from Less Likely: **Vertigo**
  - Provided Further Clarification:
    - Supraventricular tachycardia is now reported as Cardiac disorders – Other (supraventricular arrhythmias) and the following footnote (#3) was added, “Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation and atrial flutter.”
    - Gastrointestinal anastomotic leak is now reported as Injury, poisoning and procedural complications – Other (anastomotic leak) and the following footnote (#10) was added, “Anastomotic leak may include Gastrointestinal anastomotic leak; Gastric anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.”
  - Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
    - Added: Dehydration; Platelet count decreased; Wound complication
  - Deleted Risk:
    - Also Reported on Bevacizumab Trials But With the Relationship to Bevacizumab Still Undetermined: Pneumonitis; Pneumothorax

## UPDATES TO THE MODEL CONSENT:

Beneath “**What side effects or risks can I expect from being in the study?**”

The risk list for “Group 2 (Everolimus and bevacizumab)” has been replaced with two risk lists, one for Everolimus and the NCI condensed risk profile\* for bevacizumab\*\*.

\* *Note that CTEP does not include laboratory abnormalities in the NCI condensed risk profiles (i.e. hypoglycemia, low thyroid hormone, etc.)*

\*\* Based on the revisions to the bevacizumab CAEPR described above, the NCI added the following risks to the NCI condensed risk profile:

- Occasional: Dehydration; Delay in healing of wounds or spontaneous opening of wounds
- Rare: Flesh-eating bacteria syndrome, an infection in the deep layers of skin

Based on the revisions to the bevacizumab CAEPR described above, the NCI removed the following risks from the NCI condensed risk profile:

- *Feeling of spinning or whirling*

**This protocol remains closed to accrual.**

**A replacement protocol and model consent have been issued.**

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**ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL**

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CALGB 90802

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BEVACIZUMAB FOR ADVANCED RENAL CELL CARCINOMA PROGRESSING AFTER  
TREATMENT WITH TYROSINE KINASE INHIBITORS**

*NCI-supplied agent(s): Bevacizumab (NSC 704865, IND #113911)*

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<b>Protocol-related questions may be directed as follows:</b>	
<b>Questions</b>	<b>Contact (via email)</b>
Questions regarding patient eligibility, treatment, and dose modification:	<b>Study Chair</b> , Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	<b>Data Manager</b>
Questions regarding the protocol and model informed consent documents:	<b>Protocol Coordinator</b>
Questions related to IRB review:	<i><a href="mailto:regulatory@alliancenctn.org">regulatory@alliancenctn.org</a></i>
Questions regarding CTEP-AERS reporting:	<i><a href="mailto:Tonya.Hanes,thaynes2@uchicago.edu">Tonya Hanes, thaynes2@uchicago.edu</a></i> 312-702-9814
Questions regarding specimens/specimen submissions:	<b>Alliance Biorepository at Ohio State University (OSU)</b>

**Document History**

Activation  
Update #01  
Update #02  
Update #03  
Closure  
Update #04  
Update #05

**Effective Date:**

September 15, 2010  
July 15, 2011  
December, 16, 2011  
February 15, 2012  
February 15, 2013  
May 15, 2013  
July 01, 2014

**CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION**

<b>To submit site registration documents:</b>	<b>For patient enrollments:</b>	<b>Submit study data directly to the Lead National Clinical Trial Network (NCTN) Group unless otherwise specified in the protocol:</b>
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section.	Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
<p>The <b>study protocol and all related forms and documents</b> must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <a href="https://www.ctsuo.org">https://www.ctsuo.org</a>. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.</p>		
<b><u>For patient eligibility or treatment-related questions</u></b> see the Protocol Contacts, Page 2.		
<p><b><u>For questions unrelated to patient eligibility, treatment, or data submission</u></b> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a>. All calls and correspondence will be triaged to the appropriate CTSU representative.</p>		
<p><b><u>For detailed information on the regulatory and monitoring procedures for CTSU sites</u></b> please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website <a href="https://www.ctsuo.org">https://www.ctsuo.org</a>.</p>		
<b>The CTSU Web site is located at</b> <a href="https://www.ctsuo.org">https://www.ctsuo.org</a> .		

The pharmacogenomic component of this study is conducted as part of the NIH Pharmacogenomics Research Network, which is funded through a separate U01 mechanism (see [http://www.nigms.nih.gov/pharmacogenomics/research\\_net.html](http://www.nigms.nih.gov/pharmacogenomics/research_net.html) for details).

# **RANDOMIZED PHASE III TRIAL COMPARING EVEROLIMUS VERSUS EVEROLIMUS PLUS BEVACIZUMAB FOR ADVANCED RENAL CELL CARCINOMA PROGRESSING AFTER TREATMENT WITH TYROSINE KINASE INHIBITORS**

## **ELIGIBILITY CRITERIA (see [Section 4.0](#))**

Stage IV, pathologically proven, metastatic renal carcinoma with clear cell component

Failure of at least 1 prior VEGFR TKI therapy defined as progressive disease or treatment intolerance.

No prior systemic therapy with a VEGF binding agent

No prior systemic therapy with any mTOR inhibitor

(e.g., sirolimus, temsirolimus, everolimus)

Prior cytokine therapy is allowed

Any systemic therapy must be completed at least 4 weeks prior to registration

≥ 2 weeks since any prior radiation (including palliative)

≥ 4 weeks since any major surgery and fully recovered (see [Sec. 4.2](#))

Measurable disease by RECIST criteria

No active brain metastases (effectively treated brain metastases are allowed, see [Sec. 4.4](#))

No serious non-healing wound, ulcer, or bone fracture

No arterial thrombotic events within 6 months of registration (see [Sec. 4.6](#))

Patients who have experienced a deep venous thrombosis or pulmonary embolus with the past 6 months must be on therapeutic anticoagulation

Patients receiving anti-platelet agents and prophylactic anticoagulation are eligible (see [Sec. 4.8](#))

Patients with history of hypertension must be well controlled (< 160/90)

No known severe impairment of lung function (see [Sec. 4.10](#))

No active or severe liver disease (e.g. acute or chronic hepatitis, cirrhosis) and no evidence of hepatitis B or C infections (see [Sec. 4.11](#))

No NYHA Class ≥ 2 congestive heart failure

No active bleeding or chronic hemorrhagic diathesis or increased risk for bleeding (see [Sec. 4.13](#))

No history of abdominal fistula, GI perforation or intra-abdominal abscess within 6 months (see [Sec. 4.14](#))

No ongoing immunosuppressive therapy including chronic systemic treatment with corticosteroids (≥10 mg/day prednisone equivalent)

Available archival tissue for submission (see [Sec. 4.16](#))

Not pregnant or nursing

Age ≥18 years

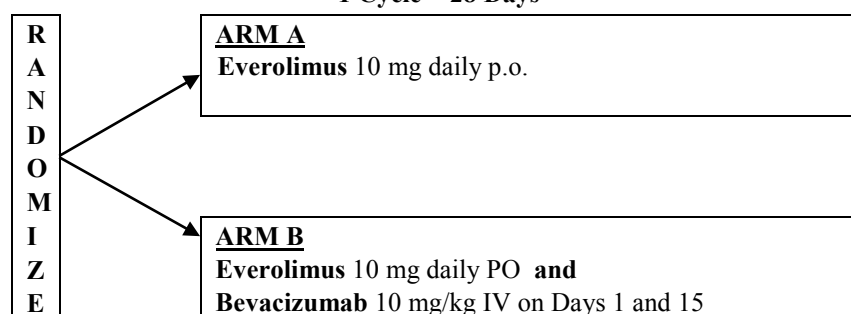
ECOG performance status 0-2 or Karnofsky score ≥ 60%

## **Required Initial Laboratory Values**

Granulocytes	≥ 1500/μL
Platelet Count	≥ 100,000/μL
Bilirubin	≤ 1.5 x ULN
AST	≤ 2.5 x ULN
Calc. Creatinine Clearance	≥ 30 mL/min
Fasting serum glucose	≤ 1.5 x ULN
Serum Cholesterol	≤ 300 mg/dL
Triglycerides	≤ 200 mg/dL
UPC Ratio < 1 or urine protein	≤ 1+

## **Schema**

**1 Cycle = 28 Days**



\* See [Section 8.0](#) for complete treatment details.

Treatment is to continue until disease progression or unacceptable toxicity.

## **Stratification Factors:**

- 1) Number of the following risk factors present: Karnofsky performance status < 80%; corrected serum calcium ≥ 10mg/dL; and Hb ≤ 13 for males and ≤ 11.5 for females.
  - a) Zero risk factors
  - b) One risk factor
  - c) Two or three risk factors
- 2) Total duration of prior VEGFR TKI therapy
  - a) < 12 weeks of therapy
  - b) ≥ 12 weeks of therapy

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## 1.0 INTRODUCTION

### 1.1 Biology and therapeutic targets in renal cell carcinoma (RCC)

Recent advances in understanding the genetics and biology of renal cell carcinoma have promoted the successful development of therapies directed at novel targets and pathways, including the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways (1, 2). Regarding VEGF, several lines of data support a unique dependency of renal cell carcinoma (RCC), in particular those of clear cell histology, on this growth factor for carcinogenesis and progression. Patients with a germline deletion in the von Hippel Lindau (VHL) gene frequently develop multiple clear cell RCC tumors in their kidneys at an early age. Similarly, biallelic loss of the VHL gene occurs in the majority of patients who develop sporadic clear cell RCC. VHL protein functions to regulate the transcriptional activity of hypoxia-inducible factor (HIF) and HIF regulated gene products including VEGF. VEGF binds to cell surface tyrosine kinase receptors (VEGFR) located on endothelial cells to promote tumor angiogenesis and progression.

mTOR is an intracellular signal transduction regulator critical for cellular growth and metabolism particularly in response to nutrient and hypoxic stress (3). In RCC, activation of the mTOR pathway is commonly detected in clinical specimens and RCC cell lines (4). Preclinically, mTOR inhibition demonstrates both antiproliferative and antiangiogenic effects (5). Particularly relevant to RCC, mTOR activation results in increased HIF mRNA and protein levels which are suppressed by mTOR inhibition (6, 7). In addition, mTOR inhibition reverses tumor vessel growth and permeability resulting in overall decreased tumor growth (8).

For VEGF pathway targeted therapy, all VEGF receptor tyrosine kinase inhibitor (VEGFR-TKI) and VEGF binding agents have demonstrated anti-tumor activity in renal carcinoma and several such as sunitinib (9), sorafenib (10), pazopanib, and the combination of bevacizumab and interferon (11, 12) have been found to be effective in phase III trials where a progression free survival advantage has been established leading to FDA approvals.

Rapamycin (sirolimus) is a naturally occurring inhibitor of mTOR that is the prototype for several clinically effective mTOR inhibitors. Rapamycin and related compounds bind with the intracellular chaperone FK506 binding protein-12 (FKBP-12) forming a complex that sequesters mTOR and blocks its phosphorylation and activation. Temsirolimus functions in a similar manner and in a phase III study of metastatic, untreated poor prognosis RCC patients, resulted in an overall survival advantage compared to interferon alfa (2). Furthermore, everolimus, an orally absorbed mTOR inhibitor, demonstrated a PFS advantage compared with placebo in patients previously treated with VEGFR targeted therapy (see below) (13).

### 1.2 Treatment of RCC patients after failure of initial VEGFR targeted therapy

Most patients diagnosed with metastatic or recurrent RCC today are treated first with a multi-targeted VEGFR-inhibitor such as sunitinib or sorafenib. Unfortunately, the vast majority of these patients will develop disease progression on one or both of these agents. In this context, a recent phase III study showed that everolimus dramatically improves progression free survival (PFS) over placebo in patients whose disease progresses after one or more multikinase VEGFR inhibitor therapies, establishing a new standard of care for patients in this setting (13). Median PFS was 4.0 months (95% CI 3.7–5.5) in the everolimus group and 1.9 months (1.8–1.9) for placebo. The probability of being progression-free at 6 months was 26% (95% CI 14–37) for patients receiving everolimus compared with 2% (95% CI 0–6) for patients in the placebo group. Overall tolerance of everolimus in this setting was very good; specifically,

grade 3/4 toxicities in  $\geq 5\%$  of patients, included only anemia, hyperglycemia and lymphopenia, suggesting there is an opportunity to build upon this monotherapy.

In RCC patients previously treated with a multikinase VEGFR inhibitor, preliminary data suggests lack of absolute cross-resistance to an alternate multikinase VEGFR inhibitor, and that continued inhibition of the VEGF/VEGFR pathway remains therapeutically relevant in such patients (14). Currently, it is not known whether any particular mechanism of VEGF pathway inhibition is superior to another in the clinical setting following disease progression on or after treatment with a multikinase VEGFR inhibitor.

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#### 1.4 Clinical Development of bevacizumab and everolimus

A phase I trial of bevacizumab (10 mg/kg IV every 2 weeks) and daily doses of either 5 or 10 mg of everolimus has been conducted in patients with advanced solid tumors (15). Adverse events in 14 patients were primarily grade 1 or 2 class-specific toxicities. One patient experienced a myocardial infarction at day 72 and one developed nephrotic syndrome at day 70. Seven of 14 patients had stable disease as best response and the 10 mg/day dose of everolimus was recommended for further clinical testing in combination with bevacizumab. A phase II trial of the combination of bevacizumab and everolimus in 59 RCC patients was also reported at the 2008 ASCO meeting (16). In 18 patients previously treated with sorafenib and/or sunitinib, 11% experienced a partial response, 72% stable disease, and the median progression free survival was 6 months. Updated results (Hainsworth JD, personal communication, submitted for publication) showed that in 30 previously treated patients, the overall objective response rate was 23%, median progression free survival was 7.1 months and the median overall survival was 14.5 months. The most common grade 3/4 toxicities were proteinuria (26%), mucositis (15%), fatigue (12%) and diarrhea (9%) but there were no episodes of symptomatic pneumonitis or serious cardiac events. Treatment was well tolerated overall but eleven patients (14% of entire cohort of 80 patients) discontinued treatment because of toxicity including proteinuria, pulmonary embolism, stomatitis or acute kidney injury.

The combination of bevacizumab and everolimus, both of which carry the capacity to modulate the VEGF pathway and have independently shown activity in RCC, is a rational mechanistic and clinical strategy for treatment of clear cell RCC. This is particularly relevant after failure of VEGFR TKI therapy where HIF modulation (17) and elevation of VEGF levels (18) may constitute a specific mechanism of resistance. Furthermore, non-overlapping toxicities and relative ease of administration improve the likelihood of successful long-term drug administration. This phase III study continues CALGB's successful exploration of rational combinations for the treatment of advanced renal cell carcinoma and advancing knowledge of the biologic basis for the disease and its therapy. Demonstration of efficacy for the proposed combination has the potential to establish a post-VEGFR TKI standard of care as well as a new comparator for testing the efficacy of other agents or combinations in this setting.

### 1.5 Risk assessment in second-line treatment of RCC

The stratification factors for overall survival to be used in this study ([Section 5.4](#)) are derived from 251 previously treated patients with advanced RCC participating in sequential clinical trials at the Memorial Sloan-Kettering Cancer Center (MSKCC) between 1975 and 2002 (19). The median survival of the post 1990 cohort was 12.7 months, and 42, 35 and 23% of all patients were in the good, intermediate and poor risk categories. Since these trials used mostly ineffective agents, the outcomes represent the natural history of previously treated advanced RCC. It should be noted in this context that although everolimus prolonged PFS in the RECORD-1 trial, no effect on OS has been established thus far. The median survival in the placebo arm of the second line phase III registration trial of sorafenib was 14.7 months among patients who had mostly been treated previously with immunotherapy.

In the VEGFR-TKI era, Choueiri (20) determined the outcomes of patients treated with a variety of VEGF-targeted therapies in clinical trials at a single institution. Of 120 patients, 75 (63%) were previously treated with non-VEGF targeted therapies (mostly immunotherapy) and the rest received first line VEGFR targeted therapies. However there was no difference in the PFS outcome for the two subgroups defined by prior therapy and the overall PFS was 13.8 months and OS was not defined. This multivariate prognostic model also contained serum calcium and ECOG PS as in the Motzer MSKCC model, but additionally included time from diagnosis, neutrophilia and thrombocytosis. The median PFS for good (53% of patients), intermediate (23%) and poor (25%) risk patients were 20.1, 13 and 3.9 months and overall survival data was unavailable. In both the MSKCC and Cleveland Clinic cohorts, about a quarter of patients were in the poor risk category.

The RECORD-1 study was an international trial in previously VEGFR-TKI treated advanced RCC patients and used the MSKCC stratification system. The trial cohort consisted of 29% good risk, 56% intermediate and only 15% poor risk patients. The median PFS in the everolimus arm of that study (which is the closest representation to the control arm of this study) was 4 months, and the median OS was 8.8 months for the placebo group and had not been reached for the everolimus arm.

In the phase II of bevacizumab plus RAD001 in 59 patients (21) 74% were designated as intermediate risk by the Motzer criteria and the PFS was 6 months (11 months at meeting presentation update) among 18 previously VEGFR-TKI treated patients; however OS was not described.

The CALGB conducted a trial of gemcitabine and capecitabine in 56 evaluable patients, 75% of whom received prior systemic therapy, with 34%, 43%, and 16% of patients in good, intermediate and poor risk groups respectively (22). The median overall survival was 14.5 months.

Overall, despite the wide variability in survival outcome for the discrete risk categories in advanced RCC, it is reasonable to expect that 15-25% accrued to a clinical trial of second line therapy in the cooperative group setting will represent a poor risk subset. Despite this, multiple lines of evidence support the contention that the median survival of the overall trial cohort will approximate one year in the control arm of this trial.

### **1.6 Protocol Update #3**

Since CALGB 90802 was activated on September 15, 2010, concerns have been raised that the placebo infusions present barriers to study activation at local institutions, patient enrollment and continued participation. In an effort to address concerns raised by local investigators and to lessen barriers to enrollment, the protocol study design has been amended to an open-label trial design. The primary endpoint, stratification factors and the total number of patients enrolled in this study will not change. The details of implementing this change are described on the Update #3 cover page.

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### **1.8 Tumor-based predictors of mTOR sensitivity**

Despite the clinical benefit associated with mTOR inhibition in RCC patients, little is known about why this disease is uniquely sensitive to monotherapy treatment with mTOR inhibitors (such as everolimus) or mechanisms of resistance to this class of agent. In order to investigate potential tissue predictors of response or resistance to everolimus-based therapy we propose to collect primary, and when available, metastatic paraffin-embedded tissue and to evaluate these tissues for predictors of response or resistance. The most common and important genetic alteration in RCC tumors occurs in the VHL gene and subsequent HIF modulation (26). Therefore, we propose to evaluate VHL mutational status by DNA sequencing and HIF expression levels, and to correlate these findings with clinical outcomes on everolimus-based treatment.

### **1.9 Inclusion of Women and Minorities**

Minorities will be eligible for this study without alteration in eligibility criteria. From prior knowledge, gender or race/ethnicity differences in the intervention effect are not expected. Based on previous data from advanced renal carcinoma patients enrolled on CALGB 90206, the accrual targets in individual cells are not large enough to perform subgroup analysis by the two treatment groups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets. However, we plan to perform exploratory analyses within gender, racial, and ethnic groups. Both men and women of all races and ethnic groups are eligible for this study.

Accrual Targets					
Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	15	+	45	=	60
Not Hispanic or Latino	189	+	451	=	640
<b>Ethnic Category: Total of all subjects</b>	204	+	496	=	700
Racial Category					
American Indian or Alaskan Native	3	+	4	=	7
Asian	5	+	18	=	23
Black or African American	11	+	30	=	41
Native Hawaiian or other Pacific Islander	2	+	3	=	5
White	183	+	441	=	624
<b>Racial Category: Total of all subjects</b>	204	+	496	=	700

## 2.0 OBJECTIVES

### 2.1 Primary Objective

**2.1.1** To compare the overall survival of patients receiving bevacizumab plus everolimus and everolimus alone among patients with advanced renal cell carcinoma progressing after first line VEGFR-TKI treatment.

### 2.2 Secondary Objectives

**2.2.1** To compare the progression-free survival and proportion who experience an objective response (defined as cCR + PR) in patients with advanced renal cell carcinoma receiving bevacizumab plus everolimus and everolimus alone.

**2.2.2** To compare grade 3 or higher toxicity in patients receiving each treatment regimen.

## 3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a “currently active” second malignancy other than non-melanoma skin cancers. Patients are not considered to have a “currently active” malignancy if they have completed therapy and are free of disease for  $\geq 3$  years.

- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study and for up to 6 months after discontinuation of study treatment due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
- Patients should not have anticipation for major surgical procedures during the course of the study.
- Strong inducers (e.g., rifampin, phenobarbital, phenytoin) and strong inhibitors (e.g., itraconazole, ketoconazole) of CYP3A4 should be avoided. A list of inhibitors and inducers can be found in Appendix III.

#### 4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility criteria should be directed to the CALGB Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

##### 4.1 Documentation of Disease

**4.1.1 Histologic Documentation:** Renal cell carcinoma with some component of clear cell histology

**4.1.2 Stage:** Metastatic or unresectable disease

##### 4.2 Prior Treatment

- Must have been treated with at least 1 prior VEGFR tyrosine kinase inhibitor treatment and have progressed or have been intolerant to treatment.
- No prior systemic therapy with a VEGF binding agent (e.g., bevacizumab)
- No prior systemic therapy with any mTOR inhibitor (e.g., sirolimus, temsirolimus, everolimus)
- Prior cytokine therapy is allowed
- Any systemic therapy must be completed at least 4 weeks prior to registration
- $\geq 2$  weeks since any prior radiation (including palliative)
- Patients must not have had a major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to study registration, and must have fully recovered from any such procedure.

The following are **not** considered to be major procedures: Thoracentesis, paracentesis, port placement, laparoscopy, thoracoscopy, bronchoscopy, endoscopic ultrasonographic procedures, mediastinoscopy, skin biopsies, incisional biopsies and routine dental procedures.

##### 4.3 Patients must have Measurable Disease by RECIST criteria

Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as  $\geq 2$  cm with conventional techniques or as  $\geq 1$  cm with spiral CT scan.



**4.4 No active brain metastases:**

**Patients with treated, stable brain metastases for at least three months are eligible as long as they meet the following criteria:**

Treated brain metastases are defined as having no ongoing requirement for steroids and no evidence of progression or hemorrhage after treatment for at least 3 months, as ascertained by clinical examination and brain imaging (MRI or CT). (Stable dose of anticonvulsants are allowed). Treatment for brain metastases may include whole brain radiotherapy (WBRT), radiosurgery (RS; Gamma Knife, LINAC, or equivalent) or a combination as deemed appropriate by the treating physician. Patients with CNS metastases treated by neurosurgical resection or brain biopsy performed within 3 months prior to Day 1 are not eligible.

Baseline brain imaging (MRI/CT) is required.

**4.5 No serious non-healing wound, ulcer, or bone fracture****4.6 No arterial thrombotic events within 6 months of registration:**

Including transient ischemic attack (TIA), cerebrovascular accident (CVA), peripheral arterial thrombus, unstable angina or angina requiring surgical or medical intervention in the past 6 months, or myocardial infarction (MI). Patients with clinically significant peripheral artery disease (i.e., claudication on less than one block), significant vascular disease (i.e., aortic aneurysm, history of aortic dissection), or any other arterial thrombotic event are ineligible.

**4.7 Deep venous thrombosis or pulmonary embolus:**

Patients who have experienced a deep venous thrombosis or pulmonary embolus within the past 6 months must be on stable therapeutic anticoagulation to be enrolled to this study.

**4.8 Anti-platelet agents and prophylactic anticoagulation:**

Patients receiving anti-platelet agents and prophylactic anticoagulation **are eligible**.

**4.9 No inadequately controlled hypertension:**

(defined as a blood pressure of  $\geq 160$  mmHg systolic and/or  $\geq 90$  mmHg diastolic on medication), or any prior history of hypertensive crisis or hypertensive encephalopathy

**4.10 No known severe impairment of lung function.**

No known severe impairment of lung function, defined as  $\geq$  grade 2 dyspnea or cough, or either:

- a) Requirement of supplemental oxygen, or
- b) in cases where pulmonary function or pulse oximetry tests have been obtained, FEV1 or FVC are  $< 50\%$  of predicted, or single breath DLCO is  $< 35\%$  of predicted or resting room oxygen saturation is less than 90%.

**4.11 No active or severe liver disease (e.g. acute or chronic hepatitis, cirrhosis).**

No positive serology for anti-HBC or anti-HCV antibodies. HBV seropositive patients (HBsAg positive) are eligible if they are closely monitored for evidence of active HBV infection by HBV DNA testing and agree to receive suppressive therapy with lamivudine or other HBV-suppressive therapy until at least 4 weeks after the last dose of everolimus.

**4.12 No NYHA Class  $\geq 2$  congestive heart failure**

**4.13 No active bleeding or chronic hemorrhagic diathesis or increased risk for bleeding:**

Including but not limited to history of major bleeding within 6 months (e.g. gastrointestinal, lung, CNS sites; or required transfusion support).

**4.14 No history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to the initiation of treatment.****4.15 No ongoing immunosuppressive therapy:**

Including chronic systemic treatment with corticosteroids ( $\geq 10$  mg/day prednisone equivalent).

**4.16 Archival tissue must be available for submission:**

Though it is optional patients to choose to participate in the correlative substudies or not.

**4.17 Patients who are pregnant or nursing are not eligible.**

Women of child bearing potential must have a negative serum or urine pregnancy test within 16 days prior to registration. This is because the effects of everolimus and bevacizumab on a developing fetus at the recommended therapeutic doses are unknown.

Women of child-bearing potential include:

- Any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea  $\geq 12$  consecutive months].
- Women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level  $> 35$  m IU/mL.
- Women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g., vasectomy).

**4.18 Age  $\geq 18$  years of age****4.19 Performance Status ECOG 0-2 or Karnofsky Score  $\geq 60\%$** **4.20 Required Initial Laboratory Values:**

Granulocytes	$\geq 1,500/\mu\text{L}$
Platelet count	$\geq 100,000/\mu\text{L}$
Calculated creatinine clearance	$\geq 30$ mL/minute (modified Cockcroft and Gault formula; see below)
Bilirubin	$\leq 1.5 \times$ upper limits of normal
AST	$\leq 2.5 \times$ ULN
Fasting serum triglycerides	$\leq 200$ mg/dL
Serum cholesterol	$\leq 300$ mg/dL
Fasting serum glucose	$\leq 1.5 \times$ ULN
Urine protein to creatinine ratio*	$< 1.0$ or Urine protein $\leq 1+$

\* See Appendix I for information regarding the calculation of UPC ratio.

**Cockcroft and Gault Formula for Estimated Creatinine Clearance ( $\text{CL}_{\text{cr}}$ )**

For Serum Creatinine Concentration ( $\text{Sr Cr}$ ) in mg/dL:

$$\text{Cl}_{\text{Cr}} (\text{mL}/\text{min}) = \frac{(140 - \text{age}) (\text{actual weight})^{\text{a}}}{(72) (\text{Sr Cr})}$$

a Age in years and weight in kilograms

**For females, use 85% of calculated Cl<sub>cr</sub> value**

## 5.0 REGISTRATION/RANDOMIZATION AND STRATIFICATION

### 5.1 Registration Requirements

**Informed Consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form are required.

### 5.2 Registration and randomization procedures

This study uses the CALGB Web-based Patient Registration system. Randomization will be accepted only through CALGB Main Member Institutions, selected affiliate institutions and CCOPs using the Web-based Patient Registration system. Registration must occur prior to the initiation of therapy.

Confirm eligibility criteria ([Section 4.0](#)). Complete the Registration Worksheet. Access the Web-based Patient Registration system via the Patient Registration tab on the CALGB Member Website at [www.allianceforclinicaltrialsnoncology.org](http://www.allianceforclinicaltrialsnoncology.org). If the study does not appear on the list of studies in the Patient Registration system, the registration must be performed by the CALGB Registrar via phone or fax. If the registering CRA requires assistance, he/she may consult the on-line help file at the bottom of the screen or call the IS Help Desk at 1-888-44CALGB. If further assistance is required, the registering CRA may call the CALGB Registrar (919)-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time. Enter the following information:

CALGB patient ID #, if applicable  
 Study  
 Name of group (CALGB)  
 Name of institution where patient is being treated  
 Name of treating physician  
 Name of person in contact with the patient record (responsible contact)  
 Protocol IRB approval date  
 Date of signed consent  
 Treatment Start Date  
 Date [of] HIPAA authorization signed by the patient  
 Patient's initials (L, F, M)  
 Patient's Social Security #, date of birth, hospital ID #, and survival status  
 Patient's gender  
 Patient's race  
 Patient's ethnicity  
 ECOG performance status  
 Patient's height (cm) and weight (kg)  
 Type of insurance (Method of Payment)  
 Patient's postal code  
 Disease, type and stage, if applicable  
 Eligibility criteria met (no, yes)  
 Companion studies (see [Section 5.3](#))

When the patient is registered, a CALGB patient identification number will be generated. Please write the number in your records. Registration to any mandatory or optional companion studies will be done at the same time as registration to the treatment study. Registration to both

treatment and companion studies will not be completed if eligibility requirements are not met for all selected trials (treatment and companions).

After registration is complete, the patient may be randomized. The patient is randomized according to the stratification factors indicated in [Section 5.4](#) below, which must be entered to obtain a treatment assignment. Treatment is to begin within 14 days of randomization.

The Main Member Institution and registering institution will receive a Confirmation of Registration and a Confirmation of Randomization. Please check both confirmations for errors. Submit corrections in writing to the data coordinator at the CALGB Statistical Center, Data Operations, 2424 Erwin Rd, Ste 802 Hock Plaza, Durham, NC 27705, or fax to 919-668-9397.

### 5.3 Registration to companion studies

There are two substudies within CALGB 90802. These substudies must be offered to all patients enrolled on CALGB 90802 (although patients may opt not to participate). The substudies included within CALGB 90802 are:

- Correlative science studies: CALGB 150907 ([Sections 10.1](#) and [10.2](#))
- Pharmacogenomic studies: CALGB 60903 ([Section 10.3](#))

If a patient answers “yes” to “I agree that my specimens may be used for the research studies described above.” (Question #1) in the Model Consent, s/he has consented to participate in the biomarker studies described in [Sections 10.1](#) and [10.2](#). The patient should be registered to CALGB 150907 at the same time that s/he is registered to the treatment trial (90802) and samples submitted per [Sections 6.2.2](#) and [6.2.3](#).

If a patient answers “yes” to “I agree that my blood may be used for the genetic research studies described above” (Question #2) in the Model Consent, s/he has consented to participate in the studies described in [Section 10.3](#). Patients should be registered to CALGB 60903 and samples should be submitted per [Section 6.2.4](#).

### 5.4 Stratification

**5.4.1 Number of risk factors present:** The risk factors are: Karnofsky performance status < 80%; corrected serum calcium  $\geq 10$ mg/dL; and Hb  $\leq 13$  for males and  $\leq 11.5$  for females.

- |                      |                              |
|----------------------|------------------------------|
| a) Zero risk factors | c) Two or three risk factors |
| b) One risk factor   |                              |

**5.4.2 Total duration of prior VEGFR TKI therapy**

- a) < 12 weeks of therapy
- b)  $\geq 12$  weeks of therapy

## 6.0 DATA AND SAMPLE SUBMISSION

### 6.1 Data Submission:

Forms should be submitted to the CALGB Statistical Center, Data Operations in compliance with the Data Submission schedule below. There are three options for submitting forms that use the Teleform barcode and cornerstones:

- The preferred method is to submit the forms electronically using the “Submit to CALGB” button located at the bottom of the last page of each form. Forms submitted electronically should not be submitted by fax or mail.

- The forms may be faxed at 919-416-4990. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- The forms may be mailed to the CALGB Statistical Center, Data Operations, Hock Plaza, 2424 Erwin Rd, Suite 802, Durham, NC 27705. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

For the most up-to-date data forms, please visit the CALGB or CTSU web site at [www.allianceforclinicaltrialsinoncology.org](http://www.allianceforclinicaltrialsinoncology.org) or [www.ctsu.org](http://www.ctsu.org).

**Data Submission Schedule:**

Form		Submission Schedule
Baseline		
C-1931	CALGB 90802 Registration Worksheet CALGB 90802 Eligibility Checklist CALGB 90802 On Study Form	Submit within 2 weeks after registration
C-2000	CALGB Solid Tumor Evaluation Form (RECIST)	
Reports	Copies of baseline metastatic pathology reports, Brain Imaging CT/MRI scans, Chest/abdomen/ pelvis MRI/CT scans*	
Treatment		
C-1934 C-1935 C-1936 C-1937 S-072	CALGB 90802 Treatment Form CALGB 90802 Adverse Event Form CALGB 90802 Supplemental Adverse Event Form (thromboembolic events)† CALGB 90802 Follow Up Form CALGB 90802 Patient Medication Calendar	Every cycle during protocol therapy.
C-1936	CALGB 90802 Adverse Event Form (Thromboembolic Events)†	Within 24 hrs of knowledge of ≥ grade 3 thromboembolic event.
C-2000 Reports	CALGB Solid Tumor Evaluation Form (RECIST) Copies of follow-up metastatic pathology reports, Brain Imaging CT/MRI scans, Chest/abdomen/ pelvis MRI/CT scans*	Every 2 cycles and at the end of protocol treatment.
Follow-up (after end of protocol treatment)		
C-1937	CALGB 90802 Follow Up Form	For patients who discontinue treatment for reasons other than progression: Every 8 weeks until progression. After progression for all patients: Every 6 months until 5 ½ years after registration to report survival and new primary or secondary malignancies.
C-2000 Reports	CALGB Solid Tumor Evaluation Form (RECIST) Copies of restaging metastatic pathology reports, Brain Imaging CT/MRI scans, Chest/abdomen/ pelvis MRI/CT scans**	Submit after each post-treatment restaging through progression.

\* Submit copies of all required reports to confirm eligibility and restaging results.

**Common Terminology Criteria for Adverse Events (CTCAE):** This study will utilize the Common Terminology Criteria for Adverse Events version 4.0 for toxicity and adverse event reporting.

## 6.2 Specimen Submission for Correlative Studies

All participating institutions must ask patients for their consent to participate in the correlative substudies planned for CALGB 90802, although patient participation is optional. Biomarker and pharmacogenomic studies will be performed. Rationale and methods for the scientific components of these studies are described in [Section 10.0](#). For patients who consent to participate, tissue, blood, and urine will be collected at the following time points for these

Time point	Pre-treatment	Every 2 cycles (i.e., before cycles 3, 5, 7, etc.)	Ship to
Tumor block <sup>1</sup>	X		PCO
EDTA plasma (Lavender top) <sup>2</sup>	1 x 6 mL	1 x 6 mL	PCO
Urine <sup>2</sup>	1 x 5 mL	1 x 5 mL	PCO
Citrate plasma (Light blue top) <sup>2</sup>	4 x 2.7 mL		PCO
Whole blood (Lavender top) <sup>3</sup>	1 x 10 mL		PCO

- 1 Archival paraffin-embedded tissue from primary and metastatic tissue (when available) to be used for correlative studies described in [Section 10.2](#) (150907).
- 2 Plasma and urine to be used for correlative studies described in [Section 10.1](#) (150907).
- 3 To be used for pharmacogenomic assays described in [Section 10.3](#) (60903).

### 6.2.1 Specimen Submission Instructions:

Use of the **Alliance Biospecimen Management System (BioMS)** is mandatory and all specimens must be logged and shipped via this system.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: <http://bioms.allianceforclinicaltrialsinoncology.org> using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or [Bioms@alliancenctn.org](mailto:Bioms@alliancenctn.org). For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or [Bioms@alliancenctn.org](mailto:Bioms@alliancenctn.org).

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (90802), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.



Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

All specimens should be sent to the following address:

CALGB Pathology Coordinating Office  
The Ohio State University  
Innovation Centre  
2001 Polaris Parkway  
Columbus, OH 43240  
Tel: 614-293-7073 Fax: 614-293-7967

### 6.2.2 Blood and urine sample submission

For patients who consent to participate, plasma and urine samples will be used for the biomarker analyses described in [Section 10.1](#).

**For EDTA plasma**, collect 6 mL of peripheral venous blood in one lavender top tube (K2EDTA anti-coagulant) prior to the initiation of treatment and every two cycles (i.e., prior to chemotherapy on Day 1 of Cycles 3, 5, 7, etc.).

Draw 1 x 6 mL of blood into lavender top vacutainer. Invert several times and centrifuge for 15 minutes at 2500 x g. Remove plasma and transfer to clean 5 mL tube. Repeat centrifuge at 2500 x g for 15 minutes. Aliquot 1.0 mL plasma into each cryovial.\* Label and freeze cryovials at -80°C. (If -80°C is not available, temporary storage at -20°C prior to shipment is acceptable.) Ship on dry ice to the CALGB PCO.

**For citrate plasma**, collect 10 mL of peripheral venous blood in 3 x 2.7 mL light blue top tubes (3.2% sodium citrate anti-coagulant) prior to the initiation of treatment.

Draw 4 x 2.7 mL of blood into light blue top vacutainer. Invert several times and centrifuge for 15 minutes at 2500 x g. Remove plasma and transfer to clean 5 mL tube. Repeat centrifuge at 2500 x g for 15 minutes. Aliquot 1.0 mL plasma into each cryovial.\* Label and freeze cryovials at -80°C. (If -80°C is not available, temporary storage at -20°C prior to shipment is acceptable.) Ship on dry ice to the CALGB PCO.

**For urine**, antiseptically collect 5 mL urine (mid-stream collection), voided directly into a sterile container. Specimens must be stored at  $\leq -20^{\circ}$  as soon as possible after collection. Ship on dry ice to the CALGB PCO.

Label samples with the following identification:

- 1) Procurement date
- 2) CALGB patient number
- 3) CALGB study number (i.e., 90802)
- 4) EDTA plasma, citrated plasma or urine.

\* Cryovial Choices: Some examples of acceptable 2.0 ml cryovials are: Nalgene (Cat #5012-0020), Fisher (Cat #05-669-57), Corning (Cat #430488), VWR (Cat #16001-102).

**6.2.3 Submission of paraffin blocks of archived renal tumors**

For patients who consent to participate, tumor blocks will be used for the analyses described in [Section 10.2](#).

Paraffin blocks of primary and, when available, metastatic tissue obtained from archival RCC tumor specimens should be sent to the CALGB Pathology Coordinating Office. Please specify the source of the tumor block (primary or metastatic site).

The CALGB has instituted special considerations for the small percentage of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be sent, please call the CALGB PCO at 614-293-7073 to obtain instructions for an adequate block alternative.

The goal of the PCO is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the PCO will be vacuum packed to prevent oxidation and will be stored at 4° C to minimize degradation of cellular antigens. For these reasons it is preferred that the PCO bank the block until the study investigator requests thin sections. Please contact the PCO if additional assurances with your hospital pathology department are required.

**6.2.4 Blood submission (for pharmacogenomic studies)**

For patients who consent to participate, whole blood samples will be used for the pharmacogenomic studies described in [Section 10.3](#). This sample should be collected prior to the initiation of protocol treatment.

Collect 10 mL of peripheral venous blood in an EDTA (lavender) tube. The tubes should be inverted several times to mix the EDTA and refrigerated until shipped on cool pack by overnight mail to the CALGB PCO. The samples should be shipped the same day that the blood is drawn.

## 7.0 REQUIRED DATA

### Pre-Study Testing Intervals

To be completed within 16 DAYS before registration:

- All laboratory studies, history and physical

To be completed within 28 DAYS before registration:

- Brain Imaging (MRI or CT), CT/MRI chest/abd/pelvis, and Bone Scan. PET scans are not allowed for tumor measurement.

To be completed within 42 DAYS before registration:

- Any baseline exams used for screening

	Prior to Registration*	Day 1 of each cycle	Post Treatment Follow up**
<b>Tests &amp; Observations</b>			
History and Progress Notes	X	X	
Physical Examination	X	X	X
Pulse, Blood Pressure	X	F	
Weight†	X	X	
Performance Status	X	X	
Tumor Measurements	X	PRN	PRN
Drug Toxicity Assessment		X	
<b>Laboratory Studies</b>			
CBC, Differential, Platelets	X	X	
Serum Creatinine,	X	X	
LDH, albumin, glucose	X	X	
AST, ALT, Alk. Phos., Bili	X	X	
Triglycerides, cholesterol	X	X	
Serum or Urine HCG	X***		
HBsAg, HBsAb, HB core antibody, HCV Ab	X		
HBV DNA testing	A	A	
UPC ratio/Dipstick	X	B	
<b>Staging</b>			
Brain Imaging (MRI or CT)	X	C	C
CT/MRI chest/abd/pelvis	X	D	X
Bone Scan	X	E	E
<b>Correlative studies‡</b>			
Tissue, Blood, and Urine Samples	See <a href="#">Section 6.2</a> .		

\* Pre-registration labs may be used for day 1 of cycle 1 tests if obtained within 16 days prior to Day 1 of Cycle 1. For subsequent cycles labs may be obtained within 72 hours prior to day of treatment.

\*\* Physical examination and staging scans must be repeated after the end of protocol treatment unless performed within the prior 4 weeks; then every 8 weeks until progression or until 5½ years after registration, whichever comes first.

\*\*\* For women of childbearing potential (see [Section 4.16](#)).

† The dose of bevacizumab need not be changed unless the calculated dose changes by  $\geq 10\%$ .

‡ For those patients who consent to participate in the substudies.

A HBV DNA testing should be performed at baseline and every 8 weeks during treatment with everolimus, and at 4 weeks after the last dose of everolimus, only if hepatitis B seropositive at baseline. In carriers of hepatitis B, lamivudine or other HBV suppressive therapy is required.

B All patients receiving bevacizumab will have a urinalysis or urine dipstick performed within 72 hours prior to every bevacizumab dose; if urine protein is  $\geq 2+$ , 24-hour urine collection or UPC ratio will be required (see [Section 9.10](#)).

C Required only if signs or symptoms suggestive of metastases develop.

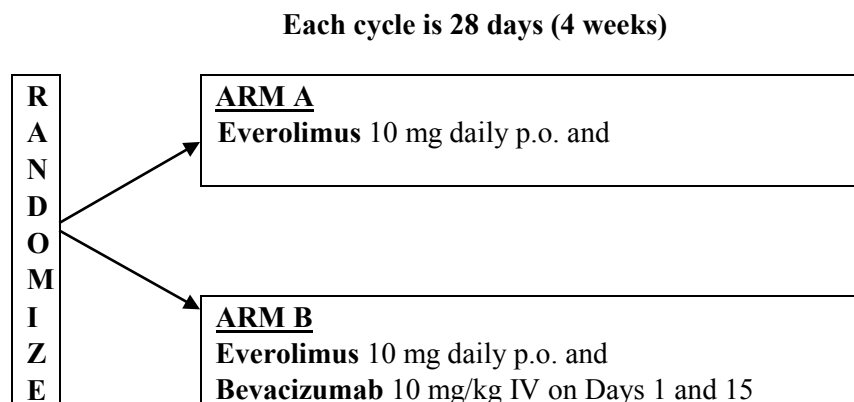
D CT scans/MRI are required every 2 cycles until evidence of progression or relapse. Scans may be done up to 10 days prior to beginning a cycle.

E Bone imaging (after baseline) is required only if indicative of metastases at baseline or if signs or symptoms suggestive of metastases develop.

F For patients receiving bevacizumab (Arm B), blood pressure is to be measured on Days 1 and 15 of every cycle for the first six months of protocol therapy, then on Day 1 only of every cycle. For patients receiving everolimus alone, blood pressure is to be measured on Day 1 of every cycle.

## 8.0 TREATMENT PLAN

Protocol treatment is to begin within 14 days of registration. Questions regarding treatment should be directed to the CALGB Study Chair.



All patients must be screened for hepatitis B before starting treatment. Carriers of hepatitis B should be closely monitored, including HBV DNA testing (see [Section 6.0](#)), for evidence of active HBV infection and hepatitis during and at four weeks after the last dose of everolimus treatment. For patients with evidence of prior HBV infection, lamivudine or other HBV suppressive therapy is required.

### 8.1 Bevacizumab:

10 mg/kg IV every 14 days. The initial dose is to be given over 90 minutes, second dose over 60 minutes, and all subsequent doses over 30 minutes if prior infusions are tolerated without infusion-associated adverse events (see [Section 11.5](#)).

### 8.2 Everolimus:

10 mg p.o. daily. Everolimus should be administered on an empty stomach or with a light, fat-free meal.

### 8.3 Duration of treatment:

Treatment with everolimus and bevacizumab will continue until disease progression or unacceptable toxicity.

## 9.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

- Missed doses for either agent will not be made up.
- Doses will not be re-escalated once reduced.
- If more than one dose modification applies, use the most stringent (i.e., the greatest dose reduction).

### 9.1 Dose Levels

#### Everolimus

- No dose reduction below dose level -2 for everolimus is allowed. If dose reduction below -2 is required, everolimus must be discontinued.

Dose Level	Everolimus
0	10 mg daily
-1	5 mg daily
-2	5 mg every other day

#### Bevacizumab

- There are no dose reductions for bevacizumab. Bevacizumab may be skipped or discontinued for toxicity as described below.

### 9.2 Hematologic toxicity

**9.2.1 For ANC 500-999/ $\mu$ L,** interrupt everolimus until ANC  $\geq 1000/\mu$ L, then resume with one dose level reduction of everolimus.

If everolimus is interrupted for > 4 weeks for ANC, discontinue everolimus. Continue bevacizumab if everolimus is interrupted or discontinued for ANC 500-999/ $\mu$ L.

**9.2.2 For ANC < 500/ $\mu$ L,** skip bevacizumab and interrupt everolimus. When ANC improves to 500-999/ $\mu$ L, resume bevacizumab.

When ANC improves to  $\geq 1000/\mu$ L, resume everolimus with one dose level reduction.

If everolimus is interrupted for > 4 weeks for ANC, discontinue everolimus (and discontinue bevacizumab if ANC < 500/ $\mu$ L).

**9.2.3 For platelets < 50,000/ $\mu$ L,** skip bevacizumab and interrupt everolimus until platelets  $\geq 50,000/\mu$ L, then resume bevacizumab and resume everolimus with one dose level reduction.

If platelets do not recover to  $\geq 50,000/\mu$ L within 4 weeks, discontinue everolimus and bevacizumab.

**9.2.4 Febrile neutropenia:** For febrile neutropenia (defined as temperature  $\geq 38.5^\circ$  C [ $101^\circ$  F] sustained for more than one hour concomitant with ANC < 500/ $\text{mm}^3$ ), interrupt everolimus until ANC  $\geq 1500/\mu$ L and fever has resolved. Resume everolimus at one lower dose level. If febrile neutropenia recurs, discontinue everolimus. Continue bevacizumab.

Febrile neutropenia should be evaluated as appropriate at the discretion of the treating physician.

### 9.3 Pulmonary toxicity

If everolimus is interrupted for  $\geq 4$  weeks for pulmonary toxicity, discontinue everolimus. If everolimus is interrupted or discontinued for pulmonary toxicity, continue bevacizumab.

**Grade 1:** Obtain CT scan with lung windows. Continue previous dose of everolimus.

**Grade 2:** Obtain CT scan with lung windows. Consider pulmonary function testing including spirometry, DLCO, room air O<sub>2</sub> saturation at rest, and bronchoscopy. Interrupt everolimus until toxicity improves to  $\leq$  grade 1, then resume everolimus with one dose level reduction. Steroids may be used at the discretion of the treating physician for relief of symptoms associated with pulmonary toxicity.

**Grade 3:** Obtain CT scan with lung windows and pulmonary function testing including spirometry, DLCO, and room air O<sub>2</sub> saturation at rest. Interrupt everolimus until recovery to  $\leq$  grade 1, then resume everolimus with one dose level reduction. Steroids should be used for relief of symptoms associated with pulmonary toxicity.

**For grade 3 pneumonitis** considered related to everolimus, continue everolimus only if there is evidence of antitumor activity. If there is a second episode of grade 3 pneumonitis, discontinue everolimus.

**Grade 4:** Obtain CT scan with lung windows and pulmonary function testing including spirometry, DLCO, room air O<sub>2</sub> saturation at rest, and bronchoscopy. Permanently discontinue everolimus. Steroids should be used for relief of symptoms associated with pulmonary toxicity.

### 9.4 Management of oral mucositis (see also [Section 12.5](#))

For grade 3 oral mucositis, interrupt everolimus until mucositis improves to  $\leq$  grade 1, then resume at one lower dose level. If everolimus is interrupted for mucositis for  $> 4$  weeks, discontinue everolimus.

For grade 4 oral mucositis, discontinue everolimus.

If everolimus is interrupted or discontinued for oral mucositis, continue bevacizumab.

See [Section 12.5](#) for recommendations for management of oral mucositis.

### 9.5 Hypertension

- **For hypertension controlled with medication (to  $< 160/90$ ):** Continue therapy.
- **For persistent or symptomatic hypertension despite antihypertensive therapy,** skip bevacizumab and adjust antihypertensive treatment. If treatment is skipped for two cycles ( $> 8$  weeks) due to uncontrolled hypertension, discontinue bevacizumab. Continue everolimus.
- **Grade 4 hypertension:** Discontinue of bevacizumab. Continue everolimus.

### 9.6 Suspected reversible posterior leukoencephalopathy syndrome (RPLS)

For signs and symptoms suggestive of RPLS (e.g., confusion headache, seizures, cortical blindness) skip bevacizumab. Suspected RPLS should be investigated with brain MRI as described in [Section 11.5](#). If diagnosis of RPLS is confirmed, bevacizumab should be permanently discontinued.

If RPLS is ruled out by MRI, the decision on resuming bevacizumab should be based on the nature of the signs/symptoms: For grade 4 events with likely relationship to bevacizumab, discontinue bevacizumab; for grade 3 events, bevacizumab may be resumed if toxicities

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1. The first step is to identify the problem. In this case, the problem is that the company is not meeting its sales targets.

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- **For grade 1 intracranial or pulmonary hemorrhage/bleeding:** For patients receiving full-dose anticoagulation, discontinue bevacizumab, but continue everolimus. For patients not receiving full-dose anticoagulation, hold bevacizumab until the bleeding has resolved, hemoglobin is stable, AND there is no bleeding diathesis or pathologic condition that would increase the risk of bleeding from bevacizumab therapy.
- **For grade 2 intracranial or pulmonary hemorrhage/bleeding,** discontinue bevacizumab. Interrupt everolimus until bleeding resolves to < grade 2, then resume everolimus.
- **For grade 3 or 4 hemorrhage/bleeding,** discontinue bevacizumab. Interrupt everolimus until bleeding resolves to < grade 3, then resume everolimus.

**For grade 3 or 4 congestive heart failure or LV dysfunction, discontinue bevacizumab; continue everolimus.**

**9.10 Fistula, perforation involving any organ, bowel obstruction, and wound dehiscence**

- **For any grade perforation of any organ, GI leak, or any fistula:** Discontinue all protocol therapy.
- **For any grade bowel obstruction requiring medical intervention:** Skip bevacizumab and interrupt everolimus until complete resolution, then resume. If surgery is required, protocol therapy may be resumed after full recovery from surgery (at least 4 weeks after surgery for bevacizumab) and after consultation with the Study Chair.
- **For wound dehiscence requiring medical or surgical intervention:** Discontinue all protocol therapy.

**9.11 Proteinuria**

Urine protein is to be measured within 72 hours prior to each bevacizumab dose. For 2+ proteinuria, the scheduled dose of bevacizumab may be given while awaiting the results of the UPC (urine protein to creatinine) ratio or 24-hour collection. The UPC ratio can be used in the place of a 24-hour urine protein collection.

For > 2+ proteinuria, omit bevacizumab while awaiting results of the UPC ratio or 24-hour urine collection. See Appendix I for information regarding the calculation of UPC ratio.

- For UPC Ratio < 2.0 or urine protein < 2 g/24 hours: Bevacizumab may be given as scheduled.
- For UPC Ratio  $\geq$  2.0 or urine protein  $\geq$  2.0 g/24 hours: Hold bevacizumab therapy until proteinuria resolves to UPC < 2.0 or urine protein < 2.0 g/24 hours. If bevacizumab treatment is delayed for more than one cycle (4 weeks) due to proteinuria, discontinue bevacizumab; continue everolimus.
- For UPC Ratio  $\geq$  4.0 or Nephrotic Syndrome: Discontinue bevacizumab; continue everolimus.

**9.12 Hepatotoxicity (CTCAE v. 4.0, Infections and infestations - hepatitis viral)****9.12.1 Hepatitis B:**

- Reactivation of hepatitis B in patients already receiving antiviral therapy is defined as an increase of 1 log in HBV DNA over baseline or the appearance of new measurable HBV DNA and ALT > 5 x ULN.

For reactivation of hepatitis B in patients already receiving antiviral therapy, interrupt everolimus until ALT improves to less than or equal to grade 1, and HBV DNA improves to less than or equal to baseline level, and add a second antiviral. When ALT and HBV DNA improve, resume everolimus with one dose level reduction.

- Reactivation of hepatitis B in patients not receiving antiviral therapy is defined as new appearance of measurable HBV DNA.

For reactivation of hepatitis B in patients not receiving antiviral therapy, interrupt everolimus until HBV DNA improves to less than or equal to baseline level, and add lamivudine (or other HBV-suppressive therapy). When HBV DNA improves, resume everolimus with one dose level reduction.

If everolimus is interrupted for > 4 weeks, discontinue everolimus.

Reactivation of hepatitis B is considered a grade 3 (or in the case of a life-threatening event, grade 4) event. Therefore, when everolimus is interrupted bevacizumab should be



skipped, or when everolimus is discontinued, bevacizumab should be discontinued (see also [Section 9.15](#)).

### 9.13 Hypersensitivity or bevacizumab infusion reactions

The initial bevacizumab dose should be administered over a minimum of 90 minutes. If no hypersensitivity or infusion reactions occur, the second dose should be administered over a minimum of 60 minutes. If no hypersensitivity or infusion reactions occur with the second dose, the third and subsequent doses should be administered over a minimum of 30 minutes. If infusion-related reactions occur, subsequent bevacizumab infusions should be administered over the shortest period that is well-tolerated. Patients may receive premedication with antihistamines prior to bevacizumab if they have previously experienced allergic reactions (grade 1 or 2).

For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

**For grade 1 or 2 hypersensitivity reactions**, bevacizumab infusion should be interrupted for subjects who develop dyspnea or clinically significant hypotension.

**For grade 3 or 4 hypersensitivity reactions**, discontinue bevacizumab; continue everolimus.

**For bronchospasm of any grade**, discontinue bevacizumab; continue everolimus.

### 9.14 Surgery

For patients who require surgery while on study, bevacizumab should be discontinued for at least 28 days prior to surgery whenever possible. Everolimus may be continued. Re-initiation of bevacizumab therapy should be discussed with the CALGB Study Chair.

### 9.15 Other non-hematologic toxicities

For all other  $\geq$  grade 3 non-hematologic toxicities not described above, hold all protocol treatment and monitor toxicity at least weekly. If toxicity resolves to  $\leq$  grade 1 within 4 weeks, treatment may be resumed, with everolimus at one lower dose level. Bevacizumab will not be dose-modified.

### 9.16 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by actual weight without any modification unless explicitly described in the protocol.** This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with calculating doses based on actual body weight should recognize that doing otherwise would be a protocol violation.

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## 10.1 Predictive significance of plasma and urine biomarkers in TKI-refractory RCC

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The image displays a sequence of 25 black and white photographs arranged in a 5x5 grid. Each photograph captures a different pose of a person, likely a dancer or performer, in a studio setting. The poses vary significantly, showing a range of movements from standing to crouching, with arms and legs in various positions. The background is a plain, light-colored wall, and the floor appears to be a dark, reflective surface. The overall composition is a visual study of human movement and form.

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## **10.2 Tumor-based predictors of mTOR sensitivity**

### **10.2.1 Background**

Despite the clinical success of mTOR-based strategies in RCC patients, little is known about why this disease is uniquely sensitive to monotherapy treatment with mTOR inhibitors (such as everolimus) or mechanisms of resistance to this class of agent. In order to investigate potential tissue predictors of response or resistance to everolimus-based therapy we propose to collect primary, and when available, metastatic paraffin-embedded tissue from patients enrolled onto treatment and to evaluate these tissues for predictors of response or resistance. The most common and important genetic alteration in RCC tumors occurs in the VHL gene. To date no correlations between the VHL gene and response to mTOR inhibition has been completed. In preclinical RCC models, silencing of VHL and resultant increase in HIF activation results in an mTOR sensitive phenotype (26). Therefore, we propose to evaluate VHL mutational status by DNA sequencing and HIF protein expression to correlate their status with clinical outcomes on everolimus-based treatment. To do so, submission of primary and/or metastatic tumor blocks from patients enrolled to this study, will be requested. Following completion of the study, these samples

will be used to sequence the VHL gene, assess protein levels of HIF as well as to perform a global CGH analysis and correlated with survival.

### 10.2.2 Objectives

- Evaluate the association between VHL mutational status and overall survival.
- Evaluate the association between pretreatment HIF protein expression and overall survival.

### 10.2.3 Methods

We propose to test whether the presence, type, and location of VHL mutations or promoter methylation predict overall survival in patients treated with everolimus with or without bevacizumab. The VHL status will be combined with clinical, pathologic, genomic, IHC, and plasma/urine VEGF levels. We expect that at least 560 samples treated with everolimus alone and with everolimus plus bevacizumab will be available. DNA will be extracted from paraffin sections and sequenced bi-directionally for the 3 exons of VHL (four amplicons). Patient DNA samples showing no mutations will be further characterized by methylation status of the VHL promoter.

#### DNA extraction

An H&E-stained section from each sample will be reviewed (at the CALGB Pathology Coordinating Office) to identify tumor content. Tumor cells will be manually microdissected from areas indicated to maximize tumor content to at least 70% tumor cells. DNA will then be isolated from three 10-micron sections using a 3-day proteinase K treatment. Following extraction, DNA will be purified and concentrated with Microcon YM-30 columns.

#### DNA Quantification, Amplification, and Sequencing

Purified genomic DNA will be quantified by Quantitative Microsatellite Analysis. PCR will be performed in 25 uL reaction mixtures consisting of 10 ng of template DNA, 0.2 uM of each primer pair, 4% DMSO, 1% Triton X-100, 0.1% gelatin, and 12.5 uL of AmpliTaq Gold PCR Master Mix (ABI). Reaction mixtures will be incubated at 95°C for 5' prior to 35 cycles of 2-step PCR (15s at 95°C, 60s at 62°C), followed by 7' at 72°C. Amplification products will be treated with ExoSAP-IT (USB) according to the manufacturer's instructions. Normal reference DNA will also be amplified and sequenced as a negative control for *VHL* mutation; RCC cell lines 769-p and 786-O will serve as positive controls for *VHL* mutation. Mutation analysis will be performed using Mutation Surveyor software (SoftGenetics).

#### VHL gene methylation status

Methylation status will be determined using *VHL* methylation-specific PCR primers after DNA bisulfite modification. Genomic DNA will be modified using the CpGenome™ DNA modification kit according to the manufacturer's protocol (Chemicon International, Temecula, CA). The product will then undergo PCR-based amplification using methylation-specific primers, and methylation status will be determined by gel electrophoresis of the PCR products.

## 10.3 Pharmacogenetic companion study

### 10.3.1 Background

In CALGB 80303, a phase III trial of gemcitabine plus bevacizumab or placebo in advanced pancreatic cancer, it was discovered that the rs763780 variant in the *IL17F* gene was a prognostic factor in advanced pancreatic cancer patients treated with chemotherapy

(Innocenti, *Proc ASCO* 2009). Germline DNA was isolated from peripheral blood on 352 patients, and was typed for more than 550,000 SNPs using the Illumina550 platform. The associations between overall survival (OS) and SNPs were investigated using the log-rank test. A review of the clinical data and ancestry genomic analysis identified 294 patients who were clinically eligible and determined to be genetically European, and this subset was used for the primary analysis.

For the analysis of OS, patients in both arms were pooled, and a nonsynonymous SNP in the *IL17F* gene (rs763780) with an allelic frequency of 3.9% (H161R,  $p < 2.7 \times 10^{-8}$ ) was associated with OS. Median OS was significantly shorter for the H/R heterozygotes (3.1 months, 95% CI 2.3-4.3,  $n=23$ ), as compared to the H/H homozygotes (6.8 months, 95% CI 5.8-7.3,  $n=271$ ). This association remained highly significant when the analysis was stratified by extent of disease or previous radiotherapy. There was no evidence of an interaction with bevacizumab, suggesting that this SNP is prognostic rather than predictive.

*IL17F* codes for interleukin-17F, a cytokine with the ability to induce several types of cells to secrete pro-inflammatory cytokines in various inflammatory diseases. In vitro functional experiments demonstrated that the 161R variant form of IL17F lacks the ability to activate the mitogen-activated protein kinase pathway, cytokine production, and chemokine production, unlike the wild-type 161H IL17F (48, 49). Wild-type 161H IL17F has also demonstrated a strong anti-angiogenesis effect in vitro by markedly inhibiting the angiogenesis of human endothelial cells and inducing them to produce IL2, TGF-beta, and monocyte chemoattractant protein-1 (Starnes et al., 2001). The variant 161R form of IL17F is a natural antagonist of the anti-angiogenic effects of wild-type IL17F.

Our hypothesis is that the angiogenesis potential of RCC patients with the variant 161R IL17F is higher than tumors with wild-type 161H interleukin-17F, conferring worse prognosis. As 1) the biology of RCC is dependent upon angiogenesis, 2) angiogenesis is a mechanism that is primarily host-mediated (50) and 3) the heritable variant 161R IL17F seems to have a prognostic effect (Innocenti *Proc ASCO* 2009), the prognosis of RCC patients might be affected by heritable variation in the IL17F gene.

In addition to IL17F, among several pro-angiogenic factors, VEGF appears to be a key regulator in neovascularization and enhanced vascular permeability. The VEGF family consists of VEGF-A (commonly referred to as VEGF), -B, -C, -D, -E, and PGF. The VEGF receptors are tyrosine kinases and are classified as VEGFR-1, -2, -3. VEGF and VEGFR-2 represent the most important ligand and receptor mediating the functions of endothelial cells during the process of tumor angiogenesis. SNPs in the VEGF gene are commonly found in Caucasian populations. In the *VEGF* gene, -634G>C (also referred to as +405G>C, rs2010963) has been found to be associated with increased overall survival (OS) in Korean HCC patients (34), similar to studies in NSCLC (35) and breast cancer (36). The -634C allele has been associated with lower VEGF levels in some studies (37, 38) but not in others (34).

Most pharmacogenetic analyses have taken a candidate gene approach that utilizes biological data to guide the selection of drug response genes in a pathway. This approach is limited by our knowledge of the mechanisms underlying the phenotypes. In the case of drug response phenotypes, most candidate gene studies have focused on drug metabolizing enzymes and transporters, thus limiting the chance of discovering causal SNPs not involved in mediating drug levels (52,53). In contrast, a genome-wide approach collects SNP data across the entire human genome and has significant power to detect common variants that confer a modest risk for a complex phenotype (54). Genome-wide studies capitalize on the large number of SNPs (more than 10 million available in dbSNP) that

have been localized and validated across the genome, a majority of which have resulted from the HapMap project (55). This valuable collection of publicly available, validated SNPs has provided the framework for performing genome-wide association studies. Recent technological advancements in genotyping platforms have also enabled the development of genome-wide associations. Searching the whole genome in an association study requires genotyping of anywhere between  $10^5$  to  $10^6$  markers across the genome (56-59). Until recently, this approach was fiscally prohibitive and impractical. However, new gene chip platforms from Affymetrix and Illumina have made large scale genotyping feasible and cost effective. This new capability represents a paradigm shift in the number of genotypes that can be evaluated in any given individual with one genotyping assay and provides a platform for the identification of novel genes involved in the response to and toxicity associated with the drug(s) of interest.

An increasing number of reports of significant findings from genome-wide association studies in cancer are being published. To date, these have all focused on SNPs associated with risk of developing cancer, and include studies in prostate (60-64), colorectal (65-67), lung (68) and breast cancer (69-71). The success of these studies illustrates the power and validity of this approach for identifying genetic causes of disease. To date, there are no published reports of genome wide association analyses in cancer pharmacogenetics. The relatively large size of CALGB 90802 and robust response and toxicity phenotype data make it an ideal sample set for whole genome analysis. The identification of SNPs that contribute to response and toxicity of the widely used drugs studied in CALGB 90802 will lead to additional studies to understand the mechanism for these associations and to investigate the application of genetic information for the optimization of cancer therapy.

### 10.3.2 Objectives

The primary objective of the pharmacogenetic companion is the investigation of the effect of IL17F on OS in the self-reported Caucasian population.

Secondary objectives include 1) a potential interaction between bevacizumab and the VEGFA -634G>C variant (rs2010963) with respect to OS in the self-reported Caucasian population, 2) the identification of additional markers of OS, PFS, and toxicity through a genome-wide association study (GWAS).

### 10.3.3 Methods

In the present study, the pharmacogenetic investigation will take place in germline DNA extracted from a single 5 to 10 ml peripheral whole blood sample collected using EDTA vacutainer tubes (lavender tops) prior to beginning the study treatment. Samples will be shipped to the CALGB Pathology Coordinating Office at Ohio State University. Genomic DNA will be extracted using a commercially available kit from Qiagen. The concentration and quality of DNA will be quantified by ultraviolet spectroscopy. All DNA samples will be stored in the DNA bank at the CALGB PCO. Aliquots of DNA will be sent to the laboratory responsible for the genotyping.

Genotyping for *IL17F* rs763780 and *VEGF* rs2010963 will be performed using previously published methods and assay conditions (35, 51). For genome-wide genotyping, the Illumina 610-Quad platform will be used. If more efficient alternative genotyping methods become available in the future, the PET committee will consider changing the genotyping approach to optimize resource utilization. The genotype information will be correlated with the clinical data.

## 11.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

### 11.1 Qualified personnel:

Who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

### 11.2 Discard unused portions:

Of injectable antineoplastic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

### 11.3 The total administered dose:

Of injectable antineoplastic agents may be rounded up or down within a range of 5% of the actual calculated dose.

### 11.4 Changes in weight:

It is not necessary to change the dose of bevacizumab due to changes in weight unless the calculated dose changes by  $\geq 10\%$ .

### 11.5 Bevacizumab (NSC #704865, IND #113911)

**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 the PMB via e-mail at [pmbafterhours@mail.nih.gov](mailto:pmbafterhours@mail.nih.gov).**

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator ([ibcoordinator@mail.nih.gov](mailto:ibcoordinator@mail.nih.gov)) or by calling the IB Coordinator at 240-276-6570.

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

#### *Availability*

Bevacizumab (NSC 704865) will be provided free of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Once this study has converted to the open label design, (Update #3) a supply of bevacizumab may be ordered by using the PMB Online Agent Order Processing (OAOP) application (<https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jsp>). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (<http://eapps-ctep.nci.nih.gov/iam/>) and the maintenance of an "active" account status and a "current" password.

Prior to the conversion to the open label design, continue to order patient specific supplies per the original blinded study design.



Open label bevacizumab will be supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400 mg (25 mg/mL – 16 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

**Drug Returns:** **Only unopened clinical supplies should be returned to the PMB.** When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment or expired vials recalled by the PMB), 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>).

**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 Drug Accountability Record Form (DARF) available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 240-276-6575.

**Note:** Supplies for the open label study design are study specific (one DARF for the study). Supplies for the blinded study design continue to be patient specific, requiring a separate DARF for each patient as long as the blinded design is in effect.

### *Storage and Stability*

Bevacizumab is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in a refrigerator (2° to 8° C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry. Solutions diluted for infusion may be stored in the refrigerator for up to 8 hours.

### *Preparation*

Vials contain no preservative and are intended for single use only. **Place the calculated dose in 100 mL of 0.9% Sodium Chloride for Injection.** Once diluted in 0.9% Sodium Chloride for Injection, the bevacizumab solution must be administered within 8 hours.

### *Administration*

Bevacizumab is administered as an intravenous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

### *Toxicities*

**Hypertension:** Hypertension has been commonly seen in bevacizumab clinical trials to date and oral medications have been used to manage the hypertension when indicated. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS). RPLS may include signs and symptoms of headache, altered mental function, seizures, and visual disturbances/ cortical blindness and requires treatment, which should include control of hypertension, management of specific symptoms, and discontinuation of bevacizumab.

**Reversible posterior leukoencephalopathy syndrome (RPLS)** or similar leukoencephalopathy syndrome: RPLS or clinical syndromes related to vasogenic edema of the white matter have

been recently reported in association with bevacizumab therapy. These syndromes have been seen in < 1% of patients to date. Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyperintensity in T2 and FLAIR images and hypointensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

**Neutropenia:** When combined with chemotherapy, bevacizumab is reported to increase the risk of neutropenia over that of chemotherapy alone. Grade 3 – 4 neutropenia, febrile neutropenia, or increased rate of infection were increased in studies in which bevacizumab with chemotherapy (IFL, paclitaxel and carboplatin) was compared to chemotherapy alone.

**Proteinuria:** Proteinuria ranging from asymptomatic abnormal urinalysis to nephrotic syndrome, has been described in 10% or more of patients receiving bevacizumab. Proteinuria is managed with dose modifications as described in [Section 9.12](#).

**Thromboembolic Events:** Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer (CRC) trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials. In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events that was not statistically significant in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). There was also a higher rate of arterial TE events (3% vs. 1%) such as myocardial infarction, transient ischemia attack, cerebrovascular accident/stroke and angina/unstable angina. A pooled analysis of the rate of arterial TE events from 5 randomized studies (1745 patients) showed that treatment with chemotherapy plus bevacizumab increased the risk of having an arterial TE event compared with chemotherapy alone (3.8% vs. 1.7%, respectively). Furthermore, subjects with certain baseline characteristics (age  $\geq$  65 years and/or a history of a prior arterial TE event) may be at higher risk of experiencing such an event.

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin  $\leq$  325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similar retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005. Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

**Gastrointestinal perforation:** Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory process and gastrointestinal perforation to bevacizumab has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with

bevacizumab. Gastrointestinal perforation has been reported in trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, and breast) and may be higher in incidence in some tumor types.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (Bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-associated hemorrhage was observed in phase I and phase II bevacizumab studies. Six serious events, of which four had fatal outcome, were observed in a phase II trial of patients with non-small cell lung cancer receiving bevacizumab. These events occurred suddenly and presented as major or massive hemoptysis in patients with either squamous cell histology and/or tumors located in the center of the chest in close proximity to major blood vessels. In five of these cases, these hemorrhages were preceded by cavitation and/or necrosis of the tumor. Tumor-associated hemorrhage was also seen rarely in other tumor types and locations, including central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases and continuous oozing of blood from a thigh sarcoma with necrosis.

Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Congestive heart failure: CHF has been reported in bevacizumab clinical trials and may be increased in incidence in patients with prior exposure to anthracyclines or prior irradiation to the chest wall. In a phase III trial (AVF2119g) of capecitabine with or without bevacizumab for metastatic breast cancer, 7 subjects (3.1%) who received capecitabine plus bevacizumab developed clinically significant CHF compared with 2 subjects (0.9%) treated with capecitabine alone; of note, all subjects in this trial had had prior anthracycline treatment. In addition, 2 subjects had a left ventricular ejection fraction < 50% at baseline and 2 others had prior left chest wall irradiation. A recently published phase II study in subjects with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or decreases to <40% in left ventricular ejection fraction) of 48 subjects treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but one of these subjects had significant prior exposure to anthracyclines as well. Other studies are ongoing in this patient population.

Osteonecrosis of the jaw: There are several reports in the literature suggesting that bevacizumab increases the likelihood of osteonecrosis of the jaw in patients receiving bisphosphonates, and that bevacizumab may cause osteonecrosis of the jaw in patients not receiving bisphosphonates. This effect is thought to be related to inhibition of angiogenesis.

**For a comprehensive list of adverse events and potential risks (CAEPR), see [Section 16.3](#). Also refer to the bevacizumab Investigator's Brochure for additional information about toxicities.**

## **11.6 Everolimus (RAD-001, NSC #733504)**

Please refer to the FDA-approved package insert for everolimus for complete product information.

### *Availability*

Everolimus is commercially available, supplied as 5 mg and 10 mg tablets in cartons containing four blister packs with 7 tablets per pack.

### *Administration*

Everolimus will be administered orally by the patient once daily. The dose may be administered with or without food.

### *Storage and Stability*

Everolimus tablets should be stored and dispensed in the original container. Blister packs should be protected from light and moisture. Commercial preparations are labeled with an expiration date.

### *Toxicities*

Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, fatigue, headache, anorexia, nausea, vomiting, and diarrhea. Non-infectious pneumonitis has also been observed. The majority of these AEs have been of mild to moderate severity (CTC grade 1-2). Overall, the most frequently observed laboratory abnormalities include reduced blood counts, hyperlipidemia mostly reported as hypercholesterolemia and/or hypertriglyceridemia.

Stomatitis: The principal DLT in Phase 1 trials has been Grade 3 stomatitis. For guidance on management of stomatitis refer to [Section 12.5](#).

Hyperlipidemia was reported as a serious adverse reaction. It is a recognized side-effect of rapamycins. Use of lipid-lowering drugs should be associated with dietary recommendations. Monitoring of blood lipid levels requires patients to be fasting so that this aspect must be verified when interpreting results. For guidance on management of hyperlipidemia refer to [Section 12.6](#).

Hyperglycemia was reported as a serious adverse reaction. Similarly, the fasting state of patients should be verified when interpreting results. For guidance on management of hyperglycemia refer to [Section 12.7](#).

Pneumonitis is a recognized adverse effect of rapamycins (sirolimus, temsirolimus, and everolimus). Numerous case reports in the literature suggest that rapamycin-associated pneumonitis is relatively unaggressive, limited in extent, and reversible upon drug discontinuation. The term 'pneumonitis' is used here to describe non-infectious, non-malignant infiltration in the lungs which is evident radiologically. More precise diagnosis should follow histocytological examination following lung biopsy, generally during bronchoscopy.

In oncology studies with everolimus, severe pneumonitis suspected as drug-related has been reported as a serious adverse event on 13 occasions and additionally in the following associated preferred terms including acute respiratory distress syndrome (n=2), alveolitis (n=1) and allergic alveolitis (n=1), interstitial lung disease (n=10), lung infiltration (n=23), cryptogenic organizing pneumonia, lung consolidation, pulmonary alveolar haemorrhage, pulmonary toxicity and pulmonary fibrosis (n=1, each). One fatal case of drug-related

pneumonitis was reported for a patient with metastatic infiltrating ductal carcinoma of the breast treated with 10 mg/day, which developed approximately two months after starting everolimus. Cytology for both the pleural and pericardial fluids was positive for malignancy. The death was considered possibly related to the underlying late stage tumor and study drug. Additionally, one patient treated with 10 mg/day died due to severe acute respiratory distress syndrome and septic shock. Thoracic CT scan demonstrated condensation in the majority of the left lower lobe and frosted glass appearance in the left upper lobe, lingula, and right lung.

Along with the cases of non-infectious pneumonitis, serious opportunistic infections have also been reported in cancer patients treated with everolimus: mycobacterium, aspergillus, and fatal candidal sepsis, and fatal pneumocystis carinii in particular. Because everolimus, as other rapamycins, inhibits proliferation of activated lymphocytes and reduces neutrophil counts, treatment with everolimus must be considered as predisposing patients to the risk of infection. This risk will be higher in patients severely immunocompromised because of their underlying disease and/or co-medications. Outcome may be fatal in case of serious infections.

Hematologic toxicity: A reduction in blood cell counts is frequent when everolimus therapy is initiated. Without clinical significance and infrequently, anemia and thrombocytopenia have been reported. In heavily pretreated patients with aggressive lymphoma, the incidence of grade 3 anemia, neutropenia, and thrombocytopenia was reported to be 11%, 16%, and 30%, respectively. Serious, suspected drug-related hemorrhages have been exceptional. Nevertheless, everolimus should be considered as predisposing patients to hemorrhage, potentially fatal, should they develop severe drug-related thrombocytopenia.

Hepatic toxicity: Discrete, reversible changes in liver enzymes have been seen in patients in oncology trials, and in patients with rheumatoid arthritis. As noted above, opportunistic infections have been associated with everolimus. Opportunistic infections result from the immunosuppressive activity of everolimus. Among these opportunistic infections, reactivation of hepatitis B virus has been described. Hepatitis B reactivation may lead to hepatic failure, which can be fatal. Antiviral prophylaxis with lamivudine (or other HBV-suppressive therapy) is required as described in [Section 4.11](#).

Renal failure: Renal failure has been reported in oncology patients, as well as in transplant patients. In the transplant setting, mTOR inhibitors such as everolimus potentiates the nephrotoxicity seen with calcineurin inhibitors. In the oncology patients, additional factors may have contributed to the development of renal failure.

Hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia: Laboratory abnormalities including hypophosphatemia, hypomagnesemia, hyponatremia and hypocalcemia have been reported in patients receiving everolimus as a single agent, in combination with cytotoxic chemotherapy, and in patients previously treated with agents also known to cause these abnormalities. Occasionally, severity grade 3 or 4 abnormalities have been seen.

#### *Drug Interactions*

Everolimus is metabolized by CYP3A4. Strong inhibitors of CYP3A4 may increase everolimus exposure with the potential for toxicity. Several studies have documented increased exposure of everolimus in the presence of CYP3A4 inhibitors, but no adverse effects as a result of the combination were seen in healthy subjects. Rifampin, a potent inducer of CYP3A4 resulted in increased clearance, but highly variable changes in AUC of everolimus. It is recommended that both strong inducers (e.g., rifampin, phenobarbital, phenytoin) and strong inhibitors (e.g., itraconazole, ketoconazole) be avoided.

## 12.0 ANCILLARY THERAPY

### 12.1 Patients should receive full supportive care:

Including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on Form C-260.

### 12.2 Treatment with hormones or other chemotherapeutic agents:

May not be administered except for steroids given for adrenal failure, suspected drug induced pneumonitis or other allergic reactions; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic, or to treat cough associated with everolimus pneumonitis. See also [Section 4.14](#).

### 12.3 Palliative radiation therapy may not be administered while the patient is on study treatment.

A symptomatic lesion or one which may produce disability (e.g., unstable femur) may be irradiated before study initiation, provided other measurable or evaluable disease is present and radiation therapy is completed  $\geq 2$  weeks before start of therapy. All eligibility criteria must still be met. Any other indications for radiotherapy after protocol treatment has begun will constitute disease progression, and the patient will stop protocol treatment.

## 12.4 CALGB Policy Concerning the Use of Growth Factors

### 12.4.1 Epoetin (EPO)

The use of EPO is permitted; however, its use is discouraged according to the current guidelines.

### 12.4.2 Filgrastim (G-CSF) and sargramostim (GM-CSF)

1. Filgrastim (G-CSF), pegfilgrastim and sargramostim (GM-CSF) treatment for patients is discouraged.
2. Filgrastim/pegfilgrastim and sargramostim may not be used:
  - a. to avoid dose reductions, delays or to allow for dose escalations specified in the protocol,
  - b. prophylactically because of concern about myelosuppression
3. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported on Form C-260.
4. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

### 12.5 Recommendations for management of oral mucositis:

(see also [Section 9.5](#) for recommended dose reductions)

For grade 1 oral mucositis, the manufacturer recommends the use of alcohol-free mouthwash or saline mouthwash 3-4 times daily. For  $\geq$  grade 2 oral mucositis, consider topical anesthetics or topical steroids.

**12.6 Recommendations for management of hyperlipidemia:**

That is present at baseline or developing during treatment include a statin or other lipid-lowering agent as well as diet.

**12.7 Recommendations for management of hyperglycemia:**

Grade 3 hyperglycemia has been observed in patients receiving everolimus therapy, particularly in patients with an abnormal fasting glucose at baseline. Optimal glucose control should preferably be achieved before starting a patient on everolimus and should be monitored and treated promptly during everolimus therapy. Everolimus dose reduction or interruption is not required.

**13.0 CRITERIA FOR RESPONSE AND PROGRESSION**

For the purposes of this study, disease should be reevaluated every 4 weeks by physical examination and every 8 weeks by imaging studies. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response. This study uses RECIST criteria version 1.1.

**13.1 Target Lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should be chosen based on their suitability for accurate repetitive measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible repeated measurements in which case the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

**13.1.1 Complete Response:** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

**13.1.2 Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

**13.1.3 Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

**13.1.4 Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.

**13.2 Non-target Lesions**

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

- 13.2.1 Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- 13.2.2 Non-complete response (non-CR)/Non-progression (non-PD):** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- 13.2.3 Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of non-target lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed later on by the review panel (or Study Chair).

### 13.3 Cytology and Histology

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

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

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

### 13.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see [Section 13.6.1](#)).



**For Patients with Measurable Disease (i.e., Target Disease)**

Target Lesions	Non-target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥ 4 wks confirmation*
CR	Non-CR/Non-PD	No	PR	≥ 4 wks confirmation*
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 wks from baseline*
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

\* Only for non-randomized trials with response as the primary endpoint.

\*\* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration” on the Off-treatment Form (C-300) under “other.” Every effort should be made to document the objective progression even after discontinuation of treatment.

**For Patients with Non-measurable Disease (i.e., Non-target Disease)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

\*‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

**13.5 Guidelines for Evaluation of Measurable Disease**

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

**13.5.1 Clinical Lesions** will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

**13.5.2 Chest X-ray:** Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

**13.5.3 Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. **If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).** Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

**13.5.4 Ultrasound (US):** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

**13.5.5 Endoscopy and Laporascopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**13.5.6 Tumor markers** alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

## **13.6 Confirmation Measurement/Duration of Response**

### **13.6.1 Confirmation**

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

### **13.6.2 Duration of Overall Response**

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive

disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

### 13.6.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

## 14.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

### 14.1 Duration of Treatment

**14.1.1 CR, PR, or SD:** Continue treatment at the highest tolerable dose until the appearance of disease progression or unacceptable toxicity per [Section 9.0](#).

**14.1.2 Disease Progression:** Give a minimum of 2 cycles of therapy. Remove from protocol therapy any patient with rapid disease progression. Document details, including tumor measurements, on data forms.

**14.2 Extraordinary Medical Circumstances:** If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on Form C-1934.
- Follow the patient for survival or secondary malignancy and new primaries for a minimum of 5 1/2 years following registration.

## 15.0 STATISTICAL CONSIDERATIONS

### 15.1 Endpoints

The primary endpoint is overall survival (OS). Secondary endpoints will be progression-free survival (PFS), objective response rate (defined as confirmed CR plus PR), and toxicity. OS will be measured from date of randomization to date of death due to any cause. PFS will be measured from the date of randomization to date of progression or death due to any cause, whichever occurs first. Progression and response will be defined using the RECIST criteria.

### 15.2 Randomization and Stratification

Randomization will be stratified on the number of negative prognostic features (0, 1, 2-3) based on the variables: Karnofsky performance status < 80%, corrected serum calcium  $\geq 10$  mg/dl and hemoglobin levels  $\leq 13$  for males and  $\leq 11.5$  for females and prior VEGFR-TKI therapy (< 12 weeks of therapy,  $\geq 12$  weeks of therapy). Assignment to treatment arm will be performed centrally at the CALGB Statistical Center following determination of eligibility. The CALGB Statistical Center will use a randomized permuted block randomization method.

### 15.3 Power Considerations

This is a randomized, prospective phase III trial in which 700 patients will be randomized with equal probability to one of two possible treatment regimens: everolimus alone or everolimus plus bevacizumab.

The following calculations assume a monthly accrual rate of about 23 patients/month accrued over a 30-month period, post accrual period of 34 months after study closure and a two-sided alpha level of 0.05. Survival time is assumed to follow an exponential distribution. With 632 deaths, the power to detect a hazard ratio of 1.30 or a 24% decrease in hazard rate (equivalent to an increase in median OS from 12 months to about 15.6 months as was observed by Motzer, et al. is 90%.

#### 15.4 Interim Analysis

Efficacy (overall survival) results will be conducted on semiannual basis to coincide with the semiannual meetings of the CALGB Data and Safety Monitoring Board (DSMB). Under the alternative hypothesis, six hundred thirty two events (deaths) are expected at the end of the follow-up period. The first interim analysis for OS will be performed at about 23% of the full information (approximately 18 months after study activation). Other interim analyses will be performed at 37% of the full information (approximately 24 months), at 54% (approximately 30 months), at 69% of the total information (approximately 36 months), at 79% (approximately 42 months), at 88% (approximately 48 months), and at 100% (approximately 64 months after study activation). To help insure complete data on which to base the interim analyses, institutions will be asked to submit survival status on their patients on a semi-annual basis (April 1 and September 1 of each year when the trial is being monitored by the DSMB).

A Lan-Demets spending function analogue of a one-sided O'Brien-Fleming will be used to stop the trial early to reject the null hypothesis. Assuming the above percent information available at each look and a one-sided type I error rate = 0.025, the z-score boundaries for stopping for superiority for OS endpoint and the z-score boundaries for stopping for futility under the alternative hypothesis using Friedlin, et al. (73) futility guidelines presented in the table below. Should any boundary be crossed, accrual to the trial may be stopped. These rules have a negligible impact on the type I and II error rates of this trial.

		<b>One-sided Boundaries for Interim Analysis for the OS endpoint</b>	
	<b>Percent information (Number of deaths)</b>	<b>For Superiority</b>	<b>For Futility</b>
1	23% (145)	4.340	-1.645
2	37% (236)	3.400	0.003
3	54% (340)	2.834	0.120
4	69% (433)	2.510	0.252
5	79% (502)	2.331	0.353
6	88% (553)	2.222	0.452
7 (Final)	100% (632)	2.077	1.960

**Table 2**

In addition, this trial incorporates a phase II PFS-based decision rule and will be evaluated after the first 100 patients have been followed for 4 months. The phase II rule will be implemented as follows: the PFS rate at 4-month will be estimated and reported to the CALGB DSMB. The trial will remain open if the observed PFS rate at 4-month in the experimental arm is at least 6% higher than what is observed in the control arm. The trial will remain open while the phase II rule is evaluated.

### 15.5 Data Analysis

An intent-to-treat approach will be used in this phase III study to analyze OS and PFS. Patients who withdraw consent for treatment or withdraw from the study due to toxicity will continue to be followed for overall survival, even if they begin another therapy. The stratified log-rank statistic will be the primary analysis to compare the two treatment arms on OS and PFS adjusting on the stratification factors (number of negative prognostic factors (0, 1, 2-3) and prior VEGFR-TKI therapy (< 12 weeks, ≥ 12 weeks).

PFS will be defined as the time from randomization to disease progression or death from any cause. For patients who do not experience disease progression or death at the time of analysis their PFS will be censored at the time of the last tumor assessment (or, if no tumor assessments were performed after the baseline visit, at the time of randomization plus 1 day). In addition, we will perform sensitivity analyses based on the PFS endpoint. For patients who receive non-protocol-specified anti-cancer therapy prior to experiencing documented disease progression, their PFS will be censored at the time of the last tumor assessment prior to receiving the non-protocol-specified therapy. In addition, for patients who die more than 90 days following their last dose of study drug and are not found to have progression prior to death, PFS will be censored at the date of their last tumor evaluation.

The Kaplan-Meier product-limit estimator will be used to estimate the OS, and PFS distributions. In addition, the proportional hazards model will be used to assess the importance of the treatment arm adjusting on patient characteristics, stratification variables and other important covariates in predicting OS and PFS.

Furthermore, the Cochran-Mantel-Haenszel test will be used to compare the two arms on the proportion of patients who experience an objective response (defined as either a confirmed CR or a PR) adjusting on the stratification factors (number of negative prognostic features and prior VEGFR-TKI therapy. In addition, the Fisher exact test will be used to compare the two treatment arms on the proportion of patients with unacceptable treatment related grade 3 or higher toxicity.

### 15.6 Accrual Rate

Based on previous data from patients enrolled on CALGB 90206, the accrual rate was 40 patients per month. Assuming an accrual rate of 23 patients/month, accrual is expected to be completed in about 30 months within study activation. All patients will be followed for a maximum period of 5 ½ years after randomization.

### Statistical considerations for correlative sciences studies

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## 15.7.2 Data Analysis

The Kaplan-Meier product-limit estimator will be used to estimate the overall and survival distribution by the median value of each biomarker. In addition, the log-rank test will be used to compare OS between the two groups (low and high levels). Furthermore, the proportional hazards model will be used to assess the importance of VEGF levels in predicting OS adjusting for important clinical and stratification factors including Memorial Sloan Kettering risk factors, which are a stratification factor as well. Moreover, quartiles and continuous measures of VEGF levels will be used in the proportional hazards model. In addition, exploratory statistical methods will be used to find different (than the median) cut points for each biomarker that may identify a biologically significant subgroup.

For the second objective, we will be testing whether changes in biomarkers at 8 weeks (2 cycles of treatment) from baseline will predict survival time. Landmark analyses will be performed at 8 weeks from randomization to minimize “lead time bias.” Furthermore, the Kaplan-Meier product-limit estimator will be used to estimate the overall survival distribution by median change in each biomarker level at 8 weeks from baseline. In addition, the log-rank test will be used to compare OS between the two groups. Moreover, the proportional hazards model will be used to assess the importance of change at 8 weeks from baseline in biomarker levels in predicting OS adjusting for important clinical and stratification factors. We will test whether change in biomarkers at 8 weeks from baseline is a surrogate for OS if the treatment is statistically significant using Prentice’s criteria.

In addition, exploratory statistical methods will be used to find different (than the median) cut points for change in biomarker levels at 8 weeks from baseline. Statistical methods based on exact asymptotic distributions will be used to find a cutpoint (other than the median) for change in each biomarker at 8 weeks from baseline.

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### 15.8.1 Power Justification

Power computations are computed based on objective 1 ([Section 10.2.2](#)) and are presented assuming that 80% (n = 560) of the samples will be available and useable. The median survival for the control arm is 12 months. The hypothesized median for the experimental arm is 15.6 months. Based upon previous analyses we expect approximately 60% of the patients to display evidence of a VHL gene inactivation (either a gene mutation or methylation).

Table 4 below presents the minimum HR that can be detected assuming OS follows exponential distribution, 0.80 power, a two-sided test of 0.025, and events rates of 70-90% of the 560 patients.

Proportion of patients with VHL levels	Proportion of events observed among 560 patients with anticipated plasma		
	70% events	80% events	90% events
0.60	1.33	1.31	1.29

**Table 4**

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### 15.8.3 Data Transfer

Once the SNPs data analyses have been generated, files with the unadjusted expression data (CEL files) will be sent to the CALGB Bioinformatics Unit for Quality control and data analysis.

## 15.9 Statistical considerations for pharmacogenetics studies (60901)

### 15.9.1 Candidate Gene Analysis

The primary objective for this candidate marker study is to validate the *IL17F* SNP (rs763780) as a prognostic marker for overall survival.

A total of 700 patients are to be randomized to the study. It is assumed that 85% of these patients will provide consent and usable samples for this pharmacogenomic companion study. The analysis population will consist of those self-reported as Caucasian on the CRF form. The expected proportion for this population is 0.85. As such, the companion study will be powered based on a sample size of 506 ( $=700 \times 0.85 \times 0.85$ ). According to the clinical design, the assumed time to death distributions for the two arms are hypothesized to be exponential with medians of 12 and 15.6 months respectively. The follow-up distribution is assumed to be uniform on the interval (34,30+34) months.

Based on the CALGB 80303 genome-wide association study (GWAS), the relative genotypic frequencies for this SNP were 0.92, 0.08 and 0 for AA, AG and GG respectively. We will power the analyses for the dominant (in the G allele) model assuming relative frequencies of 0.92 and 0.08 for the {AA} and {AG, GG} groups, respectively. For the power calculations, it will be assumed that the OS distribution for the control arm is expressible as a mixture of exponential laws of the form  $P(T_1 > t) = 0.92 \times \exp[-\lambda_{1,0} \times t] + 0.08 \times \exp[-\lambda_{1,0} \times D \times t]$  where  $D \geq 1$  is the hazard ratio. Similarly for the experimental arm, the OS distribution will be expressed as  $P(T_2 > t) = 0.92 \times \exp[-\lambda_{2,0} \times t] + 0.08 \times \exp[-\lambda_{2,0} \times D \times t]$ . In the power calculations, we will set  $P(T_1 > t) = 0.5$  for  $t = 12$ ,  $P(T_2 > t) = 0.5$  for  $t = 15.6$  and then solve for  $\lambda_{1,0}$  and  $\lambda_{2,0}$ .

Under the above assumptions, the power of the two-sample log-rank test, at the one-sided 0.05 level, is 0.89 and 0.97 for hazard ratios of 1.6 and 1.8, respectively. The power was approximated using  $B = 10,000$  simulation replicates. It is noted that the estimated hazard ratio, within a proportional hazards framework, was 3.3 (95%CI = 2.1,5.1) for CALGB 80303.

It is also noted that this is a hypothesis of association (gene by outcome) and not a hypothesis of interaction (gene by drug with respect to outcome). Any potential interaction will be investigated using a log-linear multiplicative logistic model.

A secondary objective is to investigate if VEGFA variant rs2010963 is a predictive maker for OS. Specifically, we will investigate if there is a genotype by bevacizumab interaction with respect to OS. To this end, a log-linear multiplicative Cox model will be used.

The addition of other important clinical and demographic co-variables will be considered. Multivariable models, with molecular, clinical and demographic variables, will be constructed using conditional inference trees and random forests. The primary objective will be tested at the one-sided level of 0.05. All secondary and exploratory objectives will be tested at an unadjusted two-sided level of 0.05. Secondary analyses will also look into



additional candidate genes of treatment outcomes, including PFS and toxicity of chemotherapy. (39)

In addition to the candidate markers rs763780 and rs2010963, we may consider genotyping other markers. We may obtain the genotypes directly or by imputation from the platform used for the GWAS ([section 15.9.2](#)), or by candidate marker typing (e.g., PCR).

### **15.9.2 Genome-Wide Association Study**

The primary objective for the Genome-wide Association Study (GWAS) is to identify prognostic SNPs for overall survival. Secondary objectives are to correlate SNPs with the progression-free survival, as well as the occurrence of toxicity from treatment.

### **15.9.3 Computing Environment**

For pre-processing (quality control and genotype calls) the Illumina chips, we will use the commercial program Bead Studio, developed by Illumina. Although Illumina does not provide a Linux port of Bead Studio, one can run the software on VirtualBox running on a Linux host. A two CPU dual core (four cores) AMD Operation Socket F workstation, with 16GB of RAM, will be available for this purpose. The statistical analyses will be carried out on a Linux server with 8 dual core Operation Socket F CPUs (16 cores) with 64GB of RAM (expandable to 128GB if needed).

### **15.9.4 Analyses to assess genotyping quality and population stratifications**

Initial quality studies will be conducted to identify SNPs that have generated sufficiently poor quality genotype data that should be removed from analyses. Call rate, patterns of missing data, and departures from Hardy-Weinberg equilibrium (HWE) using an exact test will all be scrutinized to identify markers that will not be used in analysis.

The study will be designed with intra- and inter-plate intended duplicates and CEPH trio controls. The technical replicates and CEPH controls will be verified by cross-tabulating the genotypes. Among each set of technical replicates, the sample with the highest call rate will be retained.

Once the duplicates and controls are removed, we will remove any samples with extremely low call rates ( $< 0.1$ ) and then based on the remaining samples and SNPs with extremely low call rate ( $< 0.1$ ). Next, we determine, based on SNPs on the X chromosome, the genetic gender for each sample. Samples for which the genetic gender differs from the self-reported gender, may be removed. In the next step we exclude SNPs with low minor relative allele frequencies ( $MAF < 0.01$ ), any samples or SNPs with call rates lower than 0.95. Next we exclude any samples with high autosomal heterozygosity (HET) followed by any samples with high IBS (based on 2000 randomly selected autosomes). The latter may indicate the presence of unintended duplicates. These could be because of mismanagement of the samples or the presence of related samples. Although we do not expect to have closely related individuals included in this sample, only one member of any set of first-degree relatives will be included in subsequent analysis. We then repeat the MAF, call rate, HET and IBS filters iteratively until no samples or SNPs are in need of elimination. This procedure can be implemented in by the `check.marker` function in the R extension package GenABEL.

Population structure that is not appropriately recognized and accommodated can lead to both false positive and false negative results in association studies. We will conduct studies using structure (41) to estimate ancestry proportions using 10,000 SNPs chosen for having no pairwise LD with unrelated individuals from the HapMap CEU, YRI and

CHB+JPT samples used to model the ancestral populations. Substantial previous research has shown this to be a rapid and effective approach to defining historical geographic ancestry. Although self-identified race/ethnicity is usually highly correlated with estimated historical geographic ancestry (this has been confirmed by the GWA studies carried out for CALGB 80303, 40101 and 90401), there are often a few individuals who appear to be misclassified with self-defined labels, and it is the genetically defined ancestry that is critical to correctly accommodate to insure robust results from association studies.

Each individual will then have estimates of European, African and Asian ancestry. For individuals with high ancestry proportion for a single group (>98%), we will conduct further analyses with eigenstrat (42) using all SNPs to determine whether there are additional important sources of variation among individuals leading to detectable stratification by allele frequencies (reflecting, for example, differences in ethnic make-up within individuals of European descent from different U.S. cities from which subjects for the trial were obtained). Primary analyses, described below, will be conducted within groups defined by historical geographic ancestry. Secondary analyses will be conducted using logistic regression with ancestry proportions (and any additional stratification identified using eigenstrat) as covariates.

This principal component analysis will be based on the set of SNPs and samples that passed the initial set of QC filters. Once the set of genetic European samples has been determined, the iterative QC procedure described above, will be repeated restricted to the European samples and SNPs that passed the initial filter. At this step, any SNPs with significant deviation from HWE ( $P\text{-value} < 10^{-8}$ ) will be removed as well. The resulting set of samples and SNPs will be used in the association analyses.

Other QC steps will be carried out as well. Non-random patterns of missing data are sometimes encountered in data generated on high-throughput genotyping platforms; the most common non-random missing data problem is that heterozygous genotypes are more likely to be assigned as missing than either homozygous genotype. We will perform analyses using blind duplicates as well as analyses assessing the relationship between heterozygous call rates and missing data to identify any SNPs in which data are clearly not missing at random. Depending on the number and degree of difficulty observed, we will either remove problematic SNPs from analysis, or assign quality scores to reflect the extent of the non-random missing data.

### 15.9.5 Feature discovery

The association between the genotype call (say AA, AB or BB) for each autosomal SNP and OS will be carried out using a univariable Cox model. Let  $\lambda_{00}[t]$ ,  $\lambda_{01}[t]$  and  $\lambda_{02}[t]$ , denote the hazard rate at time  $t$  conditional on having 0, 1 or 2 copies of the B allele.

For the power calculations we will assume that the SNPs satisfy HWE and that the OS distribution for the control arm is expressible as a mixture of exponential laws of the form  $P(T_1 > t) = (1-q)^2 \exp[-\lambda_{1,0} * t] + 2*q*(1-q) \exp[-\lambda_{1,1} * t] + q^2 \exp[-\lambda_{1,2} * t]$  where  $q$  denotes the relative frequency of the B allele and  $\lambda_{1i}$  the exponential hazard rate specified in the clinical protocol. Similarly for arm 2, we will assume a mixture distribution of the form  $P(T_2 > t) = (1-q)^2 \exp[-\lambda_{2,0} * t] + 2*q*(1-q) \exp[-\lambda_{2,1} * t] + q^2 \exp[-\lambda_{2,2} * t]$ . In the power calculations, we will set  $P(T_1 > t) = 0.5$  for  $t = 12$ ,  $P(T_2 > t) = 0.5$  for  $t = 15.6$  and then solve for  $\lambda_{1,0}$  and  $\lambda_{2,0}$ .

We will power the study for the additive genetic model with no drug interaction. In other words, for some  $D > 1$ ,  $P(T_1 > t) = (1-q)^2 \exp[-\lambda_{1,0} * t] + 2*q*(1-q) \exp[-\lambda_{1,0} * D * t] + q^2 \exp[-\lambda_{1,0} * D^2 * t]$  and  $P(T_2 > t) = (1-q)^2 \exp[-\lambda_{2,0} * t] + 2*q*(1-q) \exp[-\lambda_{2,0} * D * t] + q^2 \exp[-\lambda_{2,0} * D^2 * t]$  for some  $0 < \lambda_{2,0} < \lambda_{1,0}$ .

A total of 700 patients are to be randomized to the study. It is assumed that 85% of these patients will provide consent and usable samples for this companion study. The analysis population will consist of those determined to be genetically European based on the SNP data. The expected proportion for this population is 0.85. As such, the companion study will be powered based on a sample size of 506 ( $=700*0.85*0.85$ ).

According to the clinical design, the assumed times to death distributions for the two arms are hypothesized to be exponential with medians of 12 and 15.6 months respectively. The follow-up distribution is assumed to be uniform on the interval (34,30+34) months.

A feature (SNP) will be considered significant if the corresponding nominal unadjusted two-sided P-value is less than  $0.05/K$ , where  $K$  is number of features which pass the pre-processing step. Needless to say, this approach may be conservative. It does however guarantee strict type I error control. It is expected that these samples will be genotyped on the Illumina 610Quad platform. The power, at the two-sided 0.05/600000 level (i.e., assuming  $K = 600,000$  autosomal SNP markers pass through the pre-processing step), is illustrated in Table 3. The Cox statistics, coding the genotypes AA, AB and BB as 0, 1 and 2 is used. Each case is based on 10,000 simulation replicates. In addition to the additive model, we provide power calculations for the recessive (i.e.,  $\lambda_{m0}=\lambda_{m1}, \lambda_{m2}=\lambda_{m0}*D$ ) and dominant (i.e.,  $\lambda_{m1}=\lambda_{m2}=\lambda_{m0}*D$ ) models if the test based on the additive model is used.

Hazard Ratio (D)										
q	mod	1.6	1.8	2	2.2	2.4	2.6	2.8	3	3.2
0.1	additive	0.1705	0.5305	0.8362	0.9646	0.9943	0.9990	1.0000	1.0000	1.0000
	dominant	0.0909	0.3356	0.6583	0.8777	0.9649	0.9931	0.9987	0.9998	0.9998
	recessive	0.0000	0.0001	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
0.2	additive	0.6247	0.9523	0.9978	0.9999	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.2207	0.6260	0.9052	0.9847	0.9983	0.9998	1.0000	1.0000	1.0000
	recessive	0.0000	0.0000	0.0000	0.0000	0.0003	0.0003	0.0005	0.0010	0.0011
0.3	additive	0.8479	0.9956	0.9999	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.2093	0.6001	0.8837	0.9796	0.9974	0.9998	1.0000	1.0000	1.0000
	recessive	0.0002	0.0010	0.0021	0.0060	0.0119	0.0187	0.0323	0.0443	0.0587
0.4	additive	0.9195	0.9985	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.1144	0.4042	0.7290	0.9183	0.9816	0.9962	0.9990	0.9997	1.0000
	recessive	0.0023	0.0141	0.0470	0.1061	0.1971	0.3011	0.4135	0.5245	0.6078
0.5	additive	0.9290	0.9990	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0366	0.1670	0.3901	0.6434	0.8270	0.9255	0.9702	0.9890	0.9960
	recessive	0.0186	0.1011	0.2872	0.5237	0.7337	0.8630	0.9443	0.9729	0.9880
0.6	additive	0.8999	0.9980	0.9999	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0046	0.0288	0.0918	0.1934	0.3563	0.5012	0.6421	0.7527	0.8359
	recessive	0.0783	0.3277	0.6721	0.8865	0.9724	0.9936	0.9983	0.9999	1.0000
0.7	additive	0.7853	0.9874	0.9995	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0005	0.0021	0.0044	0.0169	0.0349	0.0630	0.1047	0.1559	0.2008
	recessive	0.1546	0.5175	0.8476	0.9738	0.9972	0.9999	1.0000	1.0000	1.0000
0.8	additive	0.4726	0.8848	0.9886	0.9992	1.0000	1.0000	1.0000	1.0000	1.0000
	dominant	0.0000	0.0000	0.0000	0.0004	0.0007	0.0010	0.0014	0.0025	0.0042
	recessive	0.1402	0.5046	0.8254	0.9646	0.9947	0.9994	1.0000	1.0000	1.0000
0.9	additive	0.0647	0.2949	0.6079	0.8282	0.9420	0.9818	0.9954	0.9987	0.9996
	dominant	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	recessive	0.0291	0.1658	0.4194	0.6899	0.8591	0.9473	0.9816	0.9942	0.9976

**Table 5: Power illustration for SNP by OS association testing**

Here q denotes the relative frequency for the risk allele. A log-additive genetic risk model is assumed. D denotes the hazard ratio.

#### 15.9.6 Submission of molecular data

The laboratory of Dr. Yusuke Nakamura will submit the Illumina\*.idat image file using secure means to the CALGB Statistical Center. The lab will also submit a table along with this transmission, which at the minimum will provide the following information for each sample received from the repository.

The lab ID number provided by the repository.

- The experimental ID, a concatenation of the plate, well and replicate information, generated by the lab.
- The idat file names (the file string name will contain Lab ID).
- The md5sum signature of the idat files to ensure data integrity.

- The date the specimen was received from the repository.
- The date the sample was analyzed by the RIKEN laboratory.

Additionally, the lab will also provide the complete results from any quality control measures carried out. If a sample had to be redone (e.g., defective or poor quality array), the lab will provide all replicate idat files and add an appropriate column to the supplementary table. The molecular data generated for this aim may not be shared with other investigators or used for any analysis not specified in the protocol until a formal approval from the CALGB Statistical Center is obtained.

### 15.9.7 Secondary objectives

Other clinical endpoints such as overall-survival and toxicity are of interest. The definitions for these will coincide with those of the clinical protocol. Note that due to small sample size, we are primarily focusing on finding prognostic features. From a pharmacogenetic point of view, what is of greater interest is to validate existing or find novel predictive markers. This will be done in the context of multiplicative two-way ANOVA log-linear Cox (logistic) for censored (binary) outcomes. Logistic regression models and conditional inference trees (or more generally conditional random forests) will be used to construct multi-variable models based on the SNPs identified as interesting. These models also allow for inclusion of other potentially relevant clinical demographic variables. The Illumina HumanHap610 Quad contains 4,300 SNPs in regions with common copy number variants (CNVs). Given the complex structure of CNVs, it is not always clear how to define the genotype of a CNV. Instead of categorizing copy numbers into genotypes, we will estimate relative genomic abundance probe intensities. This approach allows for the consideration of other CNVs beyond deletions, including duplications and combinations of both. For notational brevity, we shall refer to these as CNV markers. For each objective, the association between each CNV marker and the clinical AE endpoint, will be assessed using the Wilcoxon two-sample test. The family-wise error rate will be controlled at the 0.05 level using permutation resampling (based on B=10,000 replicates).

Regression methods, as in the case of the SNP markers, will be employed to construct multivariable models based on the CNV markers. Secondary relevant clinical endpoints include other adverse events (e.g., proteinuria, hypertension, and other common side effects of study drugs) and overall survival. For censored time-to-event outcomes, the stratified log-rank test will be primarily used for assessment of significance. A risk analysis will be carried out by comparing the genotypic distributions of the SNPs from the CALGB 80802 data to those from controls (thought to not have cancer). The SNP data from the controls will be obtained from public databases. In addition to conducting analyses on all features directly assessed on the high-throughput platform used in these studies, we will also interrogate all additional HapMap SNPs that are not in strong pairwise LD with any genotyped SNP, but for which there is sufficient multi-locus LD to SNPs on the high-throughput platform. Testing Untyped Alleles (TUNA) is a robust approach for conducting such analyses that provides inexpensive *in silico* follow up to the initial analysis and allows us to more efficiently design any follow up genotyping studies (43, 44). For example, use of Illumina HumanHap300 enables direct testing of 270K-450K SNPs, and indirect testing of 750K-1.5M additional SNPs (i.e., these SNPs are so highly correlated with SNPs that are directly tested for association that testing them would provide little additional information). The ranges given above, bracket the expectations for different human populations, with European populations at the high end of the range, and populations of recent African descent at the lower end. Use of TUNA enables interrogation of an additional 100K-250K SNPs that are neither on the platform nor highly

correlated with any individual SNP on the platform. Note that use of TUNA will facilitate comparisons to genome-wide association studies on potentially related phenotypes (e.g., clinical trials of the same or related drugs) conducted using other high-throughput platforms or candidate gene studies utilizing SNPs not directly genotyped on the high-throughput platform chosen for our studies.

Finally, we note that the methodology field for the analysis of genome-wide SNP data is in its infancy. We will consider the employment of “newer” methods if they are deemed to be statistically sound and enable us to better interrogate, and more importantly, understand the data.

### 15.9.8 Statistical software

The R statistical environment (45) and Bioconductor (46) packages will be used for all of the primary statistical analyses relating features to phenotypes. Specialized statistical genetics software, including PLINK (47) structure (41), eigenstrat (42) and TUNA (43, 44) will be used for some of the quality or secondary analyses, and R will be used for logistic regression analyses allowing for ancestry covariates.

## 16.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the CALGB Central Office, the Study Chair, and their Institutional Review Board (IRB) if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

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 web site (<http://ctep.cancer.gov>). All reactions determined to be “reportable” in an expedited manner must be reported using the CTEP Adverse Event Reporting System (CTEP-AERS).

Reporting of cases of secondary AML/MDS should be done using the NCI/CTEP Secondary AML/MDS Report Form. New primary malignancies should be reported using Study Form C-1001.

In the rare occurrence when Internet connectivity is lost, an adverse event report may be submitted using CTEP’s Adverse Event Expedited Report – Single Agent or Multiple Agent paper template (available at <http://ctep.cancer.gov>) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 240-276-6575, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an adverse event report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

**CALGB requires investigators to route all adverse event reports (AERs) through the Central Office for CALGB-coordinated studies.**

The reporting of adverse events described in the table below is in addition to and does not supplant the reporting of adverse events on study-specific adverse event forms (see [Section 6.1](#) for required CALGB forms).

### 16.1 CALGB 90802 Reporting Requirements:

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of Treatment

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 <sup>2</sup>	Grades 4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
<b>Unrelated Unlikely</b>	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hrs; 5 Calendar Days	10 Calendar Days
<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment require reporting as follows: CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for: <ul style="list-style-type: none"> <li>Grade 4 and Grade 5 unexpected events</li> </ul> CTEP-AERS 10 calendar day report: <ul style="list-style-type: none"> <li>Grade 3 unexpected events with hospitalization or prolongation of hospitalization</li> <li>Grade 5 expected events</li> </ul> <sup>2</sup> Although a CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.									

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**Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.**

- Expedited AE reporting timelines defined:
  - “24 hours; 5 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - “10 calendar days” - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
- The CTEP-AERS reporting system can be accessed via the CTEP home page: <https://eapps-ctep.nci.nih.gov/ctepaers>.

## 16.2 Additional Instructions or Exclusions from CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- CALGB 90802 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (either treatment arm) in this trial.
- For the purposes of expedited adverse event reporting, the CAEPR (which includes expected adverse events) for bevacizumab may be found in [Section 16.3](#), below. Expected adverse events for everolimus may be found in [Section 11.6](#) or in the everolimus product literature. Note: The ASAEL column of the CAEPR has been replaced with the specific

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- Update #05

NCI Version Date 06/20/14









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**APPENDIX I: UPC (URINE PROTEIN TO CREATININE) RATIO**

The UPC (urine protein to creatinine) ratio directly correlates with the grams of protein found in a 24 hr urine. The UPC ratio can be used in the place of a 24-hour urine.

**Procedure for Obtaining a Urine Protein/Creatinine Ratio:**

1. Obtain at least 4 mL of a random urine sample in a sterile container (does not have to be a 24-hour urine sample).
2. Determine protein concentration (mg/dL).
3. Determine creatinine concentration (mg/dL).
4. Divide #2 by #3 above:

**UPC Ratio =**

$$\frac{\text{Protein Concentration (mg/dL)}}{\text{Creatinine Concentration (mg/dL)}}$$

## APPENDIX II: COLLABORATIVE AGREEMENT PROVISIONS

The agents used in this protocol are provided to the NCI under Collaborative Agreements (CRADA, CTA) between Genentech Inc. (hereinafter referred to as “Collaborator”) and Novartis Pharmaceuticals (hereinafter referred to as “Provider”) 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” (at <http://ctep.cancer.gov/industry>) contained within the terms of award, apply to the use of bevacizumab in this study:

1. Agents may not be used for any purpose outside the scope of this protocol, nor can it be transferred or licensed to any party not participating in the clinical study. Collaborator’s and Provider’s data for agents are confidential and proprietary to Collaborator and Provider and shall be maintained as such by the investigators. The protocol documents for this study 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 in which 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 and Provider 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, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. 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 or Provider for this phase III study must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for the clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group Office for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator 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 intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator 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:

Regulatory Affairs Branch, CTEP, DCTD, NCI  
Executive Plaza North, Suite 7111  
Bethesda, Maryland 20892  
FAX 301-402-1584  
Email: [anshers@ctep.nci.nih.gov](mailto:anshers@ctep.nci.nih.gov)

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

## APPENDIX III: INHIBITORS AND INDUCERS OF CYP3A4

Table 6-1 Clinically relevant drug interactions

SUBSTRATES	
<u>ANTIBIOTICS:</u> clarithromycin* erythromycin telithromycin*	<u>CALCIUM CHANNEL BLOCKERS:</u> amlodipine diltiazem felodipine nifedipine nisoldipine nitrendipine verapamil
<u>ANTIARRHYTHMICS:</u> quinidine	<u>HMG COA REDUCTASE INHIBITORS:</u> cerivastatin lovastatin simvastatin
<u>BENZODIAZEPINES:</u> alprazolam diazepam midazolam triazolam	<u>MISCELLANEOUS:</u> aripiprazole buspirone gleevec* haloperidol methadone pimozide quinine sildenafil tamoxifen trazodone vincristine aprepitant
<u>IMMUNE MODULATORS:</u> cyclosporine tacrolimus (FK506)	
<u>HIV Protease Inhibitors:</u> indinavir* ritonavir* saquinavir*	
<u>PROKINETIC:</u> cisapride	
<u>ANTIHISTAMINES:</u> astemizole chlorpheniramine	
INDUCERS	
Carbamazepine, Phenobarbital, Phenytoin*, Rifabutin*, Rifampin*, St John's wort, Troglitazone,	
INHIBITORS	
Amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluvoxamine*, Grapefruit juice, Seville orange, Indinavir, itraconazole*, ketoconazole*, voriconazole*, posaconazole*, mibefradil, nefazodone*, nelfinavir*, ritonavir*, troleandomycin, verapamil	
<p>* Strong inhibition/induction can cause <math>\geq 5</math>-fold increase in AUC or <math>\geq 80\%</math> decrease in clearance of sensitive CYP substrates</p> <p>Moderate inhibitor (can cause 2 to 5-fold increase in AUC values or 50-80% decrease in clearance of sensitive CYP substrates).</p> <p>Ingelman-Sundberg M, Human drug metabolising cytochrome P450 enzymes: properties and polymorphisms, Naunyn-Schmiedeberg's Arch Pharmacol. 2004 Jan;369(1):89-104.  <a href="http://www.medicine.lupui.edu/Flockhart/cinlist.htm">http://www.medicine.lupui.edu/Flockhart/cinlist.htm</a></p>	