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A Phase II Study of Bevacizumab and Erlotinib in Subjects with Advanced Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) or Sporadic Papillary Renal Cell Cancer

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Commercial Agents: Bevacizumab, Erlotinib

PRÉCIS

Background

- Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC) is a familial cancer syndrome characterized by a propensity for developing renal cancer, and uterine and cutaneous leiomyomas. The kidney cancer associated with HLRCC is clinically aggressive and is characterized by unique histopathologic features that are sometimes described as type 2 papillary RCC.
- Germline mutations in the fumarate hydratase (FH) gene are the genetic hallmark of HLRCC. Mutational inactivation of FH has been shown to result in VHL-independent upregulation of hypoxia inducible factor (HIF) and its downstream transcriptional targets.
- The recognition that HIF upregulation may play an important role in the formation and propagation of renal cancer associated with HLRCC suggests that interventions directed against components of this pathway, such as VEGF and TGF-α/EGFR, may be of benefit in this patient population.
- We propose to test the hypothesis that dual VEGF/EGFR blockade with bevacizumab/erlotinib is likely to be clinically active in patients with HLRCC associated RCC as well as those with sporadic papillary sporadic RCC.

Objective

Primary Objective

- To determine the overall response rate (RECIST) in patients with 1) metastatic RCC associated with HLRCC and 2) metastatic sporadic/non-HLRCC papillary renal cancer treated with a combination of bevacizumab and erlotinib

Eligibility

- Diagnosis of advanced RCC associated with HLRCC (cohorts 1 and 3) or sporadic/non-HLRCC papillary RCC (cohort 2 and 4)
- ECOG PS 0-2
- Measurable disease, as outlined in RECIST 1.1
- No history of major bleeding, recent or active myocardial ischemia, GI perforation, cerebrovascular accidents or other significant intercurrent illness
- No coagulopathy or bleeding diathesis
- No recent surgery (< 4 weeks or inadequately healed surgical scars)
- Adequate organ function
    - Adequate liver function (total bilirubin ≤ 1.5 mg/dL or < 3 x upper limit of normal (ULN) in subjects with Gilbert's disease, and AST (SGOT) / ALT (SGPT) ≤ 2.5 x ULN
    - Adequate renal function (creatinine ≤ 2.0 x ULN or creatinine clearance > 30 mL/min

  - Neutrophils >1500/μL and platelets >100,000
- No brain metastases
- No more than 2 prior regimens containing a VEGF-pathway inhibitor; no prior therapy with bevacizumab
- Ability to understand and sign informed consent

Design

- Patients will receive a fixed starting dose of bevacizumab (10mg/kg IV every 2 weeks) and erlotinib (150mg/day p.o.). Dose reductions and drug interruptions for unacceptable toxicity will be allowed.
- Patients will be evaluated for response every 8 weeks using RECIST criteria
- The study is based on an open label Simon two-stage minmax design in two cohorts, 1) cohort 1- patients with HLRCC, and 2) cohort 2- patients with sporadic papillary RCC. In each cohort, 13 patients will be accrued in the first stage and will accrue a maximum of 20 patients. Accrual into and analysis of the two cohorts will be independent.
- Following completion of accrual to cohorts 1 and 2, the study was expanded to include two additional cohorts- Cohort 3 (HLRCC patients and Cohort 4 (patients with sporadic/non HLRCC papillary RCC) to better estimate the overall response rate and to perform additional exploratory biomarker analyses. Up to 20 additional evaluable patients will be included in each of these cohorts.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Objective

- To determine the overall response rate (RECIST) in patients with 1) metastatic RCC associated with HLRCC and 2) metastatic sporadic/non-HLRCC papillary RCC, treated with a combination of bevacizumab and erlotinib

1.1.2 Secondary Objective

- To assess progression-free survival, duration of response and overall survival

1.1.3 Exploratory Objectives

- To investigate the effect of bevacizumab/erlotinib on circulating endothelial cells and endothelial progenitor cells and to explore the utility of these markers as surrogates of angiogenesis inhibition
- To investigate the effect of bevacizumab/erlotinib on potential biomarkers of angiogenesis in plasma such as VEGF and soluble VEGFR2
- To evaluate the prevalence of somatic FH mutations/inactivation in patients with sporadic papillary RCC
- To determine the extent of TGF-α upregulation and/or EGFR expression/ pathway activation in leiomyomas/ RCC tumor tissue (when available)

- To evaluate modulation of HIF, VEGF and EGFR pathways in cutaneous leiomyomas (in patients with HLRCC) and in renal tumors (when tumors are accessible for biopsy) following therapy
- To assess the effect of therapy on HLRCC associated skin leiomyomas

1.2 Background and Rationale

1.2.1 HLRCC and Papillary RCC

Hereditary Leiomyomatosis and Renal Cell Cancer is a familial syndrome in which affected individuals are at increased risk for the development of papillary renal cell cancer as well as cutaneous leiomyomas. Linkage analysis studies have led to the identification of germline mutations in the Krebs' cycle enzyme fumarate hydratase (FH) as the genetic event underlying this inherited syndrome.

The most common clinical features associated with this syndrome are cutaneous leiomyomas. Cutaneous leiomyomas are highly penetrant, and develop early (median age at presentation was 25 years in one study). Cutaneous leiomyomas most often occur on the trunk or extremities, and are often symptomatic. Wei et al. reported that 81% of HLRCC patients had cutaneous lesions, and 90% of these had sensitivity to light touch of the lesions.(1)

Although renal cell cancer occurs less frequently than leiomyomas (approximately one third of patients with HLRCC seen at the National Cancer Institute had renal cell cancer), it is usually associated with an aggressive clinical course and poor outcome. Unlike other well described hereditary renal carcinoma syndromes where multiple bilateral renal tumors are the norm, most HLRCC patients tend to have solitary renal lesions; however, bilateral, multifocal lesions have been described in some patients. HLRCC patients also develop renal cysts. Lehtonen et al. found that 42% of germline FH mutation-positive patients had renal cysts on radiologic review.(2) The clinical significance of these cysts is unclear and their malignant potential remains to be determined.

Renal cell cancer associated with HLRCC is characterized by distinct histopathologic features and clinical course. These tumors are often clinically aggressive, and tend to metastasize early with a predilection for regional and distant lymph nodes, liver and bone. There are currently no standard treatment options available for patients with advanced or unresectable disease, with the majority of these patients dying due to metastatic disease. In the past, HLRCC-associated renal tumors have been histologically described as resembling papillary type II or collecting duct tumors. In a recent report, Merino *et al.* have described the distinctive histopathologic features of HLRCC-associated renal tumors based on a review of forty tumors.(3) These tumors have characteristic large orangiophilic nuclei and a clear perinuclear halo, with a variety of architectural patterns such as papillary, tubulo-papillary, tubular, solid or mixed. There is currently no well described sporadic counterpart to HLRCC-associated kidney cancer and no conclusive evidence that somatic FH mutations play a significant role in sporadic kidney cancer tumorigenesis. However, we (investigators in the UOB/NCI) have evaluated several patients with papillary histology whose tumors histologically resemble that of HLRCC-associated renal cancer, with no accompanying family history, germline FH mutation or other sequelae of this syndrome. Most pathologists currently offer vague descriptions of these tumors, often characterizing them as papillary type 2 RCC or collecting duct tumors. Evaluation of these non-familial cases of papillary

RCC variants for evidence of somatic inactivation of FH is ongoing.

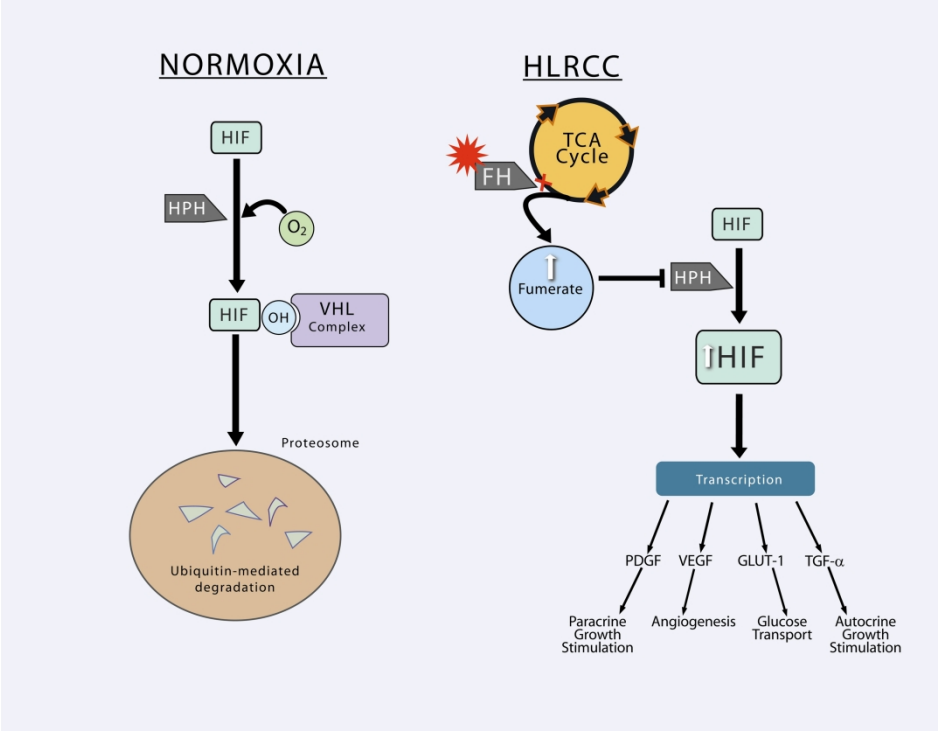
Genetic and Biochemical Basis of Renal Oncogenesis in HLRCC

Patients with HLRCC have a germline mutation localized to the long arm of chromosome 1 (1q42.3-q43). The gene responsible for HLRCC was identified through linkage analysis, and encodes fumarate hydratase (FH), a Krebs cycle enzyme. In addition to the germline loss/mutation of one FH allele, functional inactivation of the remaining copy of FH has also been found in most HLRCC associated renal tumors, cutaneous leiomyomas, and uterine leiomyomas. Correspondingly, tumors in HLRCC patients have been found to have extremely low or absent FH activity. Thus, the *FH* gene appears to act as a tumor suppressor gene, following Knudson's "two hit" model of carcinogenesis. Germline mutations are generally due to missense, frameshift, nonsense, or splice site mutations, and are distributed throughout the gene.

While the exact biochemical mechanism by which loss of FH activity leads to tumorigenesis is still under investigation, several lines of evidence suggest that generation of a pseudohypoxic state may play a role. This is supported by the demonstration by Pollard *et al*. (by immunochemistry and immunoblotting) that there was strong hypoxia inducible factor-1 (HIF-1) expression in kidney tumors from HLRCC patients.(4) Similarly, Isaacs *et al*. demonstrated increased expression of both HIF-1∝ and HIF-2∝ in renal tumors from patients with HLRCC compared to normal, matched renal tissue from the same patient.(5) In addition, there is also evidence of increased expression of downstream tumorigenic and pro-angiogenic transcriptional targets of HIF. For instance, the observed increase in microvessel density correlated with an increase in expression of *VEGF* mRNA. Furthermore, as described by Pollard *et al*., increased microvessel density is seen in leiomyomas from HLRCC patients, when compared to matched normal myometrium (6).

A recent publication from our group elucidates one potential mechanism by which FH inactivation can lead to upregulation of HIF. FH is an essential cellular enzyme catalyzing the conversion of fumarate to malate in the mitochondrial tricarboxylic acid (TCA) or Krebs cycle, which is the primary eukaryotic cellular pathway for the aerobic metabolism of glucose. Loss of FH activity results in the overaccumulation of its substrate fumarate. Isaacs et al. demonstrated that inactivation of FH and consequent excess intracellular fumarate accumulation lead to inhibition of HIF propyl hydroxylase (HPH), a critical enzymatic regulator of intracellular HIF levels, through competitive inhibition.(5) This interferes with hydroxylation of HIF at key proline residues and its subsequent recognition by the VHL complex, thus preventing VHL-dependent proteosomal degradation of HIFs. The resulting accumulation of HIF leads to transcriptional overexpression of proangiogenic factors such as VEGF as well as other genes such as transforming growth factor- α (TGF- α), platelet derived growth factor (PDGF) and GLUT-1. (**Figure 1**) Overexpression of VEGF (and PDGF) is likely responsible for enhanced tumor angiogenesis and the highly vascular renal tumors seen in HLRCC, while TGF- α overexpression may activate tumor growth pathways via its receptor (epidermal growth factor receptor, EGFR). Activation of components of the HIF pathway such as Glut-1 may also explain the avid FDG uptake of HLRCC-associated renal tumors demonstrated by PET imaging (Unpublished data).

Figure 1: **Normoxia: In the presence of oxygen, HIF is hydroxylated by HIF prolyl hydroxylase (HPH), which allows the VHL complex to recognize and target it for ubiquitin-mediated degradation in the proteosome. HLRCC: Loss of FH shunts the TCA cycle to produce excess fumarate. Fumarate stabilizes HIF through competitive inhibition of HPH, preventing HIF hydroxylation and degradation. Elevated HIF drives transcription products involved with angiogenesis (VEGF), glucose transport (GLUT-1), and growth stimulation (TGF-α, PDGF).**



1.2.2 Bevacizumab

1.2.2.1 Bevacizumab: Background

Bevacizumab is a recombinant humanized monoclonal IgG1 antibody that binds to and inhibits the biologic activity of human VEGF. Bevacizumab contains human framework regions and complementarity-determining regions of a murine antibody that binds to VEGF. Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from human IgG1, and approximately 7% of the sequence is derived from the murine antibody. Bevacizumab is approved by the Food and Drug Administration as first-line treatment of patients with metastatic carcinoma of the colon and rectum in combination with intravenous 5-fluorouracil-based chemotherapy, with oxaliplatin based chemotherapy for metastatic colon and rectal cancers, and with carboplatin and paclitaxel for non-small cell cancers of the lung. Bevacizumab binds VEGF and prevents its binding to cognate receptors (Flt-1 and KDR) on the surface of endothelial cells.

1.2.2.2 Bevacizumab: Preclinical Data

In cynomolgus monkeys, twice weekly IV treatments with bevacizumab (2, 10, and 50 mg/kg) for 4, 13, or 26 weeks were well tolerated, with no overt signs of acute toxicity.8, 9 Animals with open growth plates showed physeal dysplasia, as well as focal to diffuse

chondroid necrosis and linear fissuring of the cartilaginous growth plate. Females treated with 10-50 mg/kg twice weekly had decreased ovarian and uterine weights, which were associated with the absence of corpora lutea. These findings were expected considering the role of VEGF in the formation of the corpora lutea and the growing bone.10 In a further study using a similar treatment regimen, the recovery period of the physeal dysplasia and the ovarian and uterine changes induced by bevacizumab VEGF were partially reversible. No antibodies against bevacizumab were detected.

1.2.2.3 Bevacizumab: Phase I Clinical Studies

Two phase I studies have been performed. Study AVF0737g was a dose escalation trial of single and multiple intravenous (IV) administration of rhuMAb in patients with advanced malignancies. Five dose levels were evaluated (0.1, 0.3, 1.0, 3.0, and 10 mg/kg). rhuMAb VEGF was administered as a 90-minute infusion on days 0, 28, 35 and 42.(7) The second study, AVF0761g, evaluated multiple doses of rhuMAb VEGF 3 mg/kg weekly for up to 8 weeks in combination with one of three cytotoxic chemotherapy regimens (5-fluorouracil/leucovorin, carboplatin/paclitaxel, or doxorubicin) in subjects with advanced solid malignancies.(8) rhuMAb VEGF was administered weekly at 3 mg/kg for eight doses. In both studies, rhuMAb VEGF appeared to be well tolerated. In AVF0737g, 3 of 25 patients treated experienced tumor-related hemorrhagic events, possibly related to the administration of rhuMAb VEGF. In two cases the event was considered serious: an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and bleeding at the tumor site in a 38-year-old woman with a slowly progressing sarcoma of the thigh. No patient in AVF0761g reported serious bleeding. No dose limiting toxicity was reached in either study. No antibodies to rhuMAb VEGF were detected after therapy in either study.

1.2.2.4 Bevacizumab: Pharmacokinetics

The PK profile of bevacizumab was assessed using an assay that measures the total serum concentrations (i.e., the assay did not distinguish between freely circulating molecules of bevacizumab and those bound to a VEGF ligand). Based on a population PK analysis of 491 patients receiving bevacizumab 1−20 mg/kg weekly, every 2 or 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range, 11-50 days). The predicted time to reach a steady state was 100 days. The accumulation ratio following bevacizumab (10 mg/kg) every 2 weeks was 2.8. The clearance rate for bevacizumab varied according to body weight, gender, and tumor burden. After correcting for body weight, males had a higher clearance rate (0.262 L/day vs. 0.207 L/day) and a larger volume of the central compartment (Vc; 3.25 L vs. 2.66 L) than females. Patients with higher tumor burden (at or above median value of tumor surface area) had a higher bevacizumab clearance rate (0.249 L/day vs. 0.199 L/day) than patients with tumor burdens below the median. However, in a randomized study of 813 patients, there was no evidence of lesser efficacy (HR for overall survival) in males or patients with a higher tumor burden treated with bevacizumab compared with females and patients with a low tumor burden.

1.2.2.5 Bevacizumab: Phase II/III Clinical Studies

1.2.2.5.1 Phase II Clinical Studies:

Bevacizumab has been shown to be effective in the therapy of metastatic renal cell carcinoma. Yang et al.(9) completed a randomized, double-blind, phase 2 trial comparing

placebo to bevacizumab at doses of 3 and 10 mg/kg given every 2 weeks. There was a statistically significant increase in time to progression with the high-dose group compared to placebo.

1.2.2.5.2 Phase III Clinical Studies

In a clinical trial conducted by Hurwitz et al (10), the addition of bevacizumab- to fluorouracil-based combination chemotherapy (irinotecan, bolus fluorouracil, and leucovorin [IFL]) resulted in statistically significant and clinically meaningful improvement in survival among patients with metastatic colorectal cancer. The median duration of survival was 20.3 months in the group given IFL plus bevacizumab, as compared with 15.6 months in the group given IFL plus placebo, corresponding to a hazard ratio for death of 0.66 ($p < 0.001$). The median duration of progression-free survival was 10.6 months in the group given IFL plus bevacizumab, as compared with 6.2 months in the group given IFL plus placebo (hazard ratio for disease progression, 0.54; $p < 0.001$). The corresponding rates of response were 44.8% and 34.8% ($p = 0.004$). In a recent phase III study, the addition of bevacizumab to conventional chemotherapy (paclitaxel plus carboplatin) in the treatment of selected patients with advanced non-small cell lung cancer resulted in a significant survival benefit (hazard ratio for death, 0.79; $p = 0.003$) with the risk of increased treatment-related deaths.(11) Rates of clinically significant bleeding were 4.4% (bevacizumab arm) vs 0.7% (control arm; $p < 0.001$). There were 15 treatment-related deaths in the chemotherapy-plus bevacizumab group, including 5 from pulmonary hemorrhage.

The most recent report to be added in metastatic renal cell carcinoma (mRCC) is that of Escudier and colleagues, who randomized patients between bevacizumab plus interferon and interferon alone. This trail was conducted in first-line treatment for mRCC. This study demonstrated improved progression free survival from 5.4 months to 10.2 months with the addition of bevacizumab; data for overall survival have not yet been reported.(12)

1.2.2.6 Bevacizumab: Toxicities/Adverse Events

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common Grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea, and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation, congestive heart failure, primarily in breast cancer patients and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies. Increased rates of severe neutropenia have been observed in patients treated with some chemotherapy regimens plus bevacizumab. Other SAEs observed with bevacizumab therapy include hypertensive crisis, nephrotic syndrome and reversible posterior leukoencephalopathy syndrome.

The following is a description of major adverse events associated with bevacizumab therapy.

1.2.2.7 Hemorrhage

An increased incidence of bleeding events was observed in patients treated with bevacizumab as compared to control treatment arms. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence rate of NCI-CTC Grade ≥ 3 bleeding events ranged from 0.4-5%, compared to 0-2.9% in control treatment arms. The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

Life threatening hemorrhage was seen in a Phase I trial (AVF0737g) in the form of an intracranial hemorrhage (at an occult cerebral metastasis) in a patient with hepatocellular carcinoma and in the Phase II study (AVF0757g) in the form of massive hemoptysis or hematemesis.

Tumor-associated hemorrhage - Major or massive pulmonary hemorrhage/hemoptysis has been observed primarily in patients with NSCLC. In a Phase II study in NSCLC, 6 cases of life-threatening (4 fatal) hemoptysis were reported among 66 patients treated with bevacizumab and chemotherapy;(13) squamous cell histology was identified as the risk factor. In the Phase III trial in non-squamous NSCLC (E4599), the rate of Grade ≥ 3 pulmonary hemorrhage was <1% in the control arm (carboplatin/paclitaxel) versus 2.3% in the chemotherapy plus bevacizumab arm (10/427 patients, including 7 deaths).

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either pre-existing or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit.

Gastrointestinal hemorrhages, including rectal bleeding and melena have been reported in patients with colorectal cancer, and have been assessed as tumor-associated hemorrhages. In the pivotal Phase III trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; Grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious tumor associated bleedings have also been observed in patients with pancreatic cancer, gastric cancer, CNS metastases, hepatoma, or varices treated with bevacizumab.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, and included a case of central nervous system (CNS) bleeding in a patient with hepatoma with occult CNS metastases, and another patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneous hemorrhage - Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC 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.

1.2.2.8 Thrombosis

In Study AVF0780g in metastatic colorectal cancer, venous and arterial thrombosis were seen more frequently in patients treated with rhuMAb VEGF plus 5-FU/leucovorin than in

patients treated with 5-FU/leucovorin alone: 3 of 35 patients in the control arm, 9 of 35 patients in the 5 mg/kg rhuMAb VEGF arm and 4 of 32 patients in the 10 mg/kg rhuMAb VEGF arm. One event was fatal (a pulmonary embolism in the 10 mg/kg arm) and three events required study discontinuation (a pulmonary embolism and a superior mesenteric vein occlusion in the 5 mg/kg arm and a cerebrovascular event in the 10 mg/kg arm).

Cancer patients are known to be at high risk for thromboembolism owing to a number of factors including intrinsic tumor pro-coagulant activity, immobilization, indwelling catheters and the pro-thrombotic effects of chemotherapy. The incidence of thrombosis among patients with breast cancer receiving chemotherapy is approximately 5-10% being higher in patients on tamoxifen and in patients with metastatic disease.

In the first 59 patients with metastatic breast cancer treated with rhuMAb VEGF monotherapy, two patients have developed a subclavian/axillary deep venous thrombosis on the side of the indwelling central line. In the AVF2107 study, there was a 1% incidence of arterial thromboembolic (TE) events (which include myocardial infarction, transient ischemic attack, cerebrovascular accident/stroke, and angina/unstable angina) in the IFL + placebo arm versus 3% in the ILF + bevacizumab arm. A pooled analysis of the rate of arterial TE events from 5 randomized studies showed that treatment with bevacizumab increased the risk of these events two- to three-fold (up to 5%). Furthermore, certain baseline characteristics, specifically age > 65 years and prior arterial TE event, conferred additional risk.

Arterial Thromboembolic Events (ATE): The risk of arterial thromboembolic events is increased with bevacizumab therapy; such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction (MI) and other peripheral or visceral arterial thrombosis. A pooled analysis of five randomized studies showed a twofold increase in these events (3.8% vs. 1.7%). ATE led to a fatal outcome in 0.8% patients with bevacizumab (vs. 0.5% without bevacizumab). The rate of cerebrovascular accidents (including TIA) was 2.3% vs. 0.5%, and the rates of MI 1.7% vs. 0.7%. Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.(14)

In patients > 65 years treated with bevacizumab and chemotherapy, the rate of ATE was approximately 8.5%. Aspirin is a standard therapy for primary and secondary prophylaxis of ATE in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and ATE events, retrospective analyses of the ability of aspirin to affect the risk of ATE were inconclusive. Further analyses of the effects of concomitant use of bevacizumab and aspirin are ongoing.

Venous thromboembolism (VTE) *(including deep venous thrombosis, pulmonary embolism and thrombophlebitis)*: In the Phase III pivotal trial in metastatic CRC, there was a slightly higher rate of VTE in patients treated with chemotherapy + bevacizumab compared with chemotherapy alone (19% vs. 16%). The incidence of NCI-CTC Grade≥ 3 VTEs in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%).

In clinical trials across all indications the overall incidence of VTEs ranged from 2.8% to 17.3% in the bevacizumab-containing arms compared to 3.2% to 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the

risk of VTE compared with chemotherapy alone. However, patients with mCRC who receive bevacizumab and experienced VTE may be at higher risk for recurrence of VTE.

1.2.2.9 Hypertension

Hypertension has been seen in all rhuMAb VEGF clinical trials to date. Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% (all grades) across trials, with a mean increase of +5.5mmHg to +8.4mmHg for systolic pressure, or +4.1mmHg to +5.4mmHg for diastolic pressure. Incidence of Grade 3 (hypertension requiring initiation of or increase in hypertensive medications) ranges from 7.8 to 17.9%. Grade 4 hypertension (hypertensive crisis) occurred in up to 0.5% of bevacizumab-treated patients. Hypertension associated with bevacizumab can generally be controlled with routine oral drugs while the treatment is continued. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab. Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

There has been one reported case of hypertensive encephalopathy in a patient receiving 3 mg/kg of rhuMAb VEGF on study AVF0776g. In addition, there are 2 reports of reversible posterior leukoencephalopathy syndrome (RPLS) (Ozcan et al., 2006; Glusker et al., 2006). In study 0776g 12 other patients developed either new hypertension (7 patients) or worsening existing hypertension (5 patients) and 10 of these patients required medical therapy (3 patients in the 3 mg/kg rhuMAb arm (n = 18) and 7 in the 10 mg/kg (n = 41), no data available from the 20 mg/kg arm). After 10 weeks of treatment, the mean change in blood pressure for all subjects compared with baseline was as follows (mean systolic change/mean diastolic change): 3 mg/kg rhuMAb VEGF + 10.5 mmHg/+8.5 mmHg and 10 mg/kg rhuMAb VEGF +18.5 mmHg/+8.2 mmHg. In Study AVF0780g (colorectal cancer), using NCICTC Grade 3 or 4 events, there were four events in the control arm (n = 35), four events between 2 patients in the 5 mg/kg rhuMAb VEGF (n = 35) and nine events among 5 subjects in the 10 mg/kg rhuMAb VEGF (n = 32). The most commonly used therapies to treat this hypertension have been angiotensin converting enzyme inhibitors and calcium channel blockers. VEGF has been shown to induce nitric oxide-mediated vasodilatation and hypotension.(15) In a recent study, VEGF has been shown to govern endothelial nitric oxide synthase expression via a KDR/flk-1 receptor and protein kinase C signaling pathway, which suggests a possible mechanism for rhuMAb VEGFs induction of hypertension.(16)

1.2.2.10 Proteinuria

Proteinuria by dipstick analysis has been seen in all rhuMAb VEGF clinical trials and has ranged in severity from mild asymptomatic increase in urine protein (incidence of about 38%) to rare instances of Grade 3 proteinuria (> 3.5 g/24 hour urine) (3%), or nephrotic syndrome (1.4%). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. The risk of proteinuria may be higher in patients with advanced RCC or history of hypertension. There is also evidence that the rate of proteinuria may be dose related.

In study AVF0776g, 8 of 59 (12%) subjects treated with 3 mg/kg or 10 mg/kg have developed some degree of proteinuria (detected by dipstick) during the study. Three of these patients also developed hypertension. Two patients were discontinued from study because of proteinuria; one patient (10 mg/kg arm) had > 2.5g/24hr which decreased to 0.7 mg/24hr within 4 weeks with a normal serum creatinine and a second patient in the 20 mg/kg arm who developed > 5g/24hr. Another patient (3 mg/kg arm) developed hypertensive encephalopathy, which was followed by the development of nephrotic syndrome (5 g/24hr). This patient died of progressive disease soon thereafter and renal biopsy was not performed. A recent study has shown that VEGF mediates glomerular repair, which suggested a possible mechanism for rhuMAb VEGF-associated proteinuria.(17)

1.2.2.11 Congestive Heart Failure

The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In Phase III controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab+capecitabine arm compared to 2 (1%) in the capecitabine-only arm. 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. Patients receiving anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA or ECHO with a normal ejection fraction.

Two patients with metastatic breast cancer in study AVF0776g who had been treated previously with doxorubicin developed congestive heart failure while on rhuMAb VEGF, one patient after one year at 10 mg/kg and the second patient after two doses at 20 mg/kg.

1.2.2.12 Perforation

GI perforations/fistula were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal Phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or co-morbid GI conditions such as diverticulitis and gastric ulcer. GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain or rectal/abdominal abscess.

A Genentech sponsored trial of bevacizumab in recurrent ovarian cancer was terminated early due to a greater than expected incidence of bowel perforations (11%). Patients were dosed at 15 mg/kg q3wks as compared to our planned dosing of 10 mg/kg q2wks. Previous studies of bevacizumab in colon cancer had an incidence of bowel perforation of between 4 - 6%. At the recent January 2006 GOG meeting, an analysis of all ovarian cancer patients receiving bevacizumab in CTEP sponsored trials, approximately 150 patients, had only a 4.8% perforation/ fistula rate, approximating much closer the incidence seen in colon cancer. Further analysis is ongoing to ascertain the true risk of bowel perforation in ovarian cancer patients receiving bevacizumab.(18)

1.2.2.13 Fistula

Fistula formations, including events resulting in death, have been observed in patients receiving bevacizumab in clinical studies and postmarketing reports. Fistulae in the GI tract are common (1-10% incidence) in patients with metastatic colorectal cancer, but uncommon (0.1-1%) or rare (0.01-0.1%) in other indications. In addition, fistulae that involve areas other than the GI tract have also been observed (e.g., tracheoesophageal, bronchopleural, urogenital, biliary). For example, life-threatening or fatal tracheoesophageal fistula has been reported in patients with small cell lung cancer treated with concurrent chemoradiation and bevacizumab. In a Phase II trial of irinotecan + carboplatin + RT and bevacizumab followed by maintenance bevacizumab that accrued 25 patients, there have been two confirmed cases of tracheoesophageal (TE) fistula (one fatal) and a third case of fatal upper aerodigestive tract hemorrhage, with TE fistula suspected but not confirmed. All three events occurred during the bevacizumab maintenance phase (1.5 to 4 months after completion of chemoradiation). While pulmonary fistula (including TE fistula) has also been observed in advanced NSCLC or SCLC patients receiving bevacizumab and chemotherapy (without radiation), the incidence was extremely low.

1.2.2.14 Wound Healing Complications

Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. Across metastatic CRC trials, at least 28 days must have elapsed following major surgery before bevacizumab could be initiated; data suggested initiation of bevacizumab 29-60 days following surgery did not appear to increase the risk of wound healing complications compared to those treated with chemotherapy alone. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined, although at least 4 weeks should be required between the last dose of bevacizumab and elective surgery. In the pivotal study in CRC, among patients who underwent major surgery while on study therapy, there was an increased rate of significant postoperative bleeding or wound healing complications in the IFL + bevacizumab arms vs. IFL alone [10% (4/40) vs. 0% (0/25)].(19) Decisions on the timing of elective surgery should take into consideration the half life of bevacizumab (average 21 days, range 11-50 days). If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4–8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

1.2.2.15 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or similar leukoencephalopathy syndrome

RPLS or clinical syndromes related to vasogenic edema of the white matter have rarely been reported with bevacizumab therapy (< 1%). 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 (hyper-intensity in T2 and FLAIR images and hypo-intensity 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 altered mental status change, visual disturbances, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of blood pressure and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage.

1.2.2.16 Infusion-Related Reactions

Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

1.2.2.17 Fertility and Pregnancy

Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. Ovarian failure, which is defined as amenorrhea lasting 3 or more months, FSH level greater than or equal to 30 mIU/mL and a negative serum β-HCG pregnancy test, was prospectively evaluated in a subset study of 179 women receiving mFOLFOX alone (N= 84) or mFOLFOX with bevacizumab (N=95) as part of the NSABP C-08 trial for adjuvant stage II and III colorectal cancer, a use for which bevacizumab is not approved. New cases of ovarian failure were identified in 34% (32/95) of women receiving bevacizumab in combination with chemotherapy compared with 2% (2/84) of women receiving chemotherapy alone [relative risk of 14 (95% CI 4, 53)]. After discontinuation of bevacizumab treatment, recovery of ovarian function was demonstrated in 22% (7/32) of these women. Additionally, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. Bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures (hormonal or barrier method of birth control; abstinence) and women should avoid breast feeding.

1.2.2.18 Immunogenicity

As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

1.2.2.19 Neutropenia

Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone (Sandler et al. 2006).

1.2.2.20 Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients receiving bevacizumab, but not

bisphosphonates, in the postmarketing setting. The pathogenesis of the osteonecrosis is unclear.

1.2.2.21 Changes in Blood Chemistries

Hypophosphatemia and hypoalbuminemia have been seen in patients taking bevacizumab.

1.2.2.22 Changes in Thyroid Hormone Levels

Hypothryoidism has been seen in patients taking bevacizumab

1.2.3 Erlotinib

1.2.3.1 Erlotinib: Background

Epidermal Growth Factor Receptor Expression and Significance in Cancer

The control of cell growth is mediated by a complex network of signaling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF (or other ligands) to the cell surface EGF receptor (EGFR), stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Subsequent investigations revealed EGFR to be one of a family of closely related receptors that includes EGFR (HER1), HER2, HER3, and HER4.

EGFR and other HER family members are considered to be important in the development, progression, and aggressive behavior of human epithelial malignancies and to be relevant therapeutic targets. A number of human malignancies are associated with aberrant or over-expression of EGFR.(20) Stimulation of tumor cells via the EGFR is important for both tumor growth and tumor survival in vivo. Over-expression of EGFR in certain human tumors, including non–small cell lung carcinoma (NSCLC), has been correlated with both chemo-resistance and poor prognosis. (21-32) Inhibitors of EGFR tyrosine kinase activity have been in development for a number of years, and although earlier compounds lacked specificity and potency, newer compounds have proven active in nonclinical and clinical studies.

Erlotinib (previously known as OSI-774) is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Early clinical data with erlotinib indicate that the compound is generally safe and well tolerated at doses that provide the targeted effective concentration based on nonclinical experiments. A recently completed, randomized, double-blind, placebo-controlled trial has shown that erlotinib as a single agent significantly improves the survival of patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease.(33)

1.2.3.2 Erlotinib: Preclinical Data – Toxicology

Toxicology studies have been performed in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least one species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular dilatation), lacrimal glands (atrophy), salivary glands (atrophy),

mandibular lymph nodes (inflammation), spleen (hematopoiesis), gastrointestinal tract (delayed gastric emptying and diarrhea), and embryo-fetal toxicity. Red blood cell parameters were decreased, and white blood cells (primarily neutrophils) were increased. There were treatment-related increases in ALT, AST, triglyceride and bilirubin and decreases in albumin; increases in bilirubin were likely caused by a treatment-related impairment of bilirubin metabolism.

1.2.3.3 Erlotinib: Phase I Clinical Studies

Phase I trials of erlotinib explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound given as a single agent. A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily.

Cigarette smoking has been shown to reduce erlotinib exposure by 50-60%. The MTD of erlotinib in NSCLC patients who currently smoke cigarettes was 300mg. Efficacy and long term safety of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes. Smokers should be advised to stop smoking.

The primary toxicities of single-agent erlotinib consisted of rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. When given daily, dose-limiting toxicity (diarrhea) was observed at 200 mg/day. At 150 mg/day, diarrhea was manageable with the addition of loperamide therapy; this dose was considered the maximal tolerated dose.

Rash (variously referred to as dermatitis, acneiform rash, or maculopapular rash) has been variable in onset, duration, and severity, but typically appears on the face, neck, scalp, chest, and back starting after ~1 week of treatment. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated inflammatory cell infiltrate and mild epidermal hyperproliferation. In some cases, the rash gradually improved despite continued dosing and, in general, resolved without sequelae following erlotinib discontinuation. The rash did not result in study discontinuation in patients with cancer in the Phase I trials. Laboratory abnormalities observed infrequently with single-agent erlotinib involved primarily liver function tests, including elevation of ALT, AST, and/or bilirubin.

Selection of the 150 mg/day dose of erlotinib for subsequent single-agent studies was based on pharmacokinetic parameters, as well as the safety and tolerability profile of this dose in Phase I trials in heavily pretreated patients with advanced cancer. Drug levels seen in patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy.

1.2.3.4 Erlotinib: Pharmacokinetic Studies and metabolism

Erlotinib, a quinazoline, directly and reversibly inhibits the human EGFR tyrosine kinase with an IC50 of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC50 of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase both in assays assessing the effects of

erlotinib on a variety of other isolated tyrosine kinases and in cellular bioassays designed to isolate this functional pathway. Erlotinib is designed to inhibit EGF dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression in the G1 phase.

Data on drug exposure and anti-tumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of erlotinib associated with anti-tumor activity. Based on these efficacy models, the minimum steady-state plasma concentration targeted for clinical activity in humans is projected to be 500 ng/mL.

Oral erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 3 hours after oral dosing of 150 mg/dL at steady state. A study in healthy subjects provided an estimate of bioavailability of 59% (95% CI: 55%, 63%). The time to reach steady-state plasma concentration was ~5 days. The accumulation ratio with daily dosing of erlotinib was estimated to be 2.0. From a population pharmacokinetic analysis of 708 patients, the median trough concentration (C_{min}) 24 hours following the previous dose was 1041 (±697) ng/mL. Median AUC achieved during the dosing interval at steady state was 19,801 ng • hr/mL. Exposure after an oral dose is increased by food.

There is extensive binding of erlotinib and metabolites to both serum albumin and AAG (alpha-1-acid glycoprotein), with total plasma protein binding for erlotinib and OSI-420 of ~95% and 91%, respectively. Erlotinib is extensively metabolized in the liver by the hepatic cytochromes in humans–primarily by CYP3A4 and to a lesser extent by CYP1A2. The primary metabolite of erlotinib, OSI-420, has potency comparable to that of erlotinib, but is present at levels that are < 10% of erlotinib levels. Erlotinib is excreted predominantly via the feces (> 90%). The elimination half-life after a 150-mg oral dose is ~30 hours. In population-based data analyses, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, sex, ethnicity, or creatinine clearance.

1.2.3.4.1 Erlotinib Drug Interactions

Erlotinib is both protein bound (92%–95%) and metabolized by hepatic cytochromes CYP3A4 and CYP3A5 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug–drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors/inducers. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of erlotinib (AUC) by 46% and the maximum concentration (C_{max}) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of erlotinib and hence its bioavailability.

The exposure to erlotinib (AUC) increased to a moderate extent, by 39%, and the maximum concentration (Cmax) by 17%, when erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2.

Co-administration of erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole, 200 mg po BID for 5 days) resulted in increased exposure to erlotinib as measured by an 86% increase in median erlotinib AUC and a 69% increase Cmax, compared with administration of erlotinib alone.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, compared with

administration of erlotinib alone. However, the effect of rifampin on C_{max} was negligible. In another study, rifampicin pretreatment followed by co-administration of rifampicin with a single 150 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg erlotinib dose in the absence of rifampicin treatment. Therefore, a potential for drug-drug interaction exists when erlotinib is co-administered with drugs that are highly protein bound or that are potent CYP3A4 inhibitors or inducers.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients while on erlotinib alone and in combination with other chemotherapeutic agents, and concomitant NSAIDS or anticoagulants, including warfarin.

Please refer to **Appendix C** for a listing of interacting drugs.

1.2.3.4.2 Erlotinib Use in Hepatic and Renal Impairment

The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of erlotinib is not yet known. However, erlotinib is cleared predominately by the liver, and caution should be used when administering erlotinib to patients with hepatic dysfunction. Erlotinib is also a strong inhibitor of the UDP-glucuronosyltransferase UGT1A1 enzyme responsible for the glucuronidation of bilirubin. Hyperbilirubinemia appears most often to be a side effect related to genetic polymorphisms of UGT1A1. Rare cases of hepatic failure (including fatalities) have been reported during the postmarketing use of erlotinib. Confounding factors for severe hepatic dysfunction have included pre-existing liver disease such as cirrhosis, viral hepatitis, hepatocellular carcinoma, hepatic metastases, or concomitant treatment with potentially hepatotoxic drugs.

A study comparing the pharmacokinetics of erlotinib in patients with moderately impaired hepatic function with patients with normal hepatic function showed no significant difference in exposure suggesting that no dose modification is necessary for moderately hepatic-impaired patients. Caution, however, may need to be exercised in these patients as authors of an independent study performed by a collaborative group recommended an erlotinib dose of 75 mg daily in patients with hepatic dysfunction.

Rare cases of myocardial infarction (including fatalities) have been reported during the postmarketing use of erlotinib. No clinical studies have been conducted in patients with compromised renal function since erlotinib and its metabolites are not significantly excreted by the kidneys.

1.2.3.5 Erlotinib: Phase II / III Clinical Studies

Multiple Phase II trials evaluating the safety, tolerability, and antitumor activity of erlotinib have been conducted in patients with advanced, refractory malignancies including cancer of the head and neck, lung, aerodigestive tract, ovary, breast, central nervous system (glioma), and others. Erlotinib has been evaluated both as a single agent and administered concurrently with conventional chemotherapy agents using various doses and schedules.

Evidence of activity has been observed in squamous cell carcinoma of the head and neck, ovarian, breast and pancreatic carcinoma, non–small cell lung cancer (NSCLC), and

glioblastoma multiforme (GBM). Patients received 150 mg/day of erlotinib in all of these studies except the GBM study where dose escalation was allowed until limited by rash and where a higher starting dose was tested in subjects receiving concomitant enzyme inducing anti-epileptic drugs. Dose reduction was allowed in all studies in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents.

Patients receiving erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events (AEs) as with either agent alone.

The first randomized placebo controlled trial to demonstrate a survival advantage for an EGFR inhibitor was the Phase III study, BR21. This international trial, conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG), included 731 patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease. Patients randomized in a 2:1 ratio to single-agent erlotinib 150 mg/day obtained a 42.5% improvement in median survival over placebo, from 4.7 to 6.7 months. The one-year survival increased significantly (from 22% to 31%) as did the median and 6 month PFS, response rate, and the time to deterioration of tumor related symptoms of pain, cough, and dyspnea.(33)

In BR-21, of the 727 patients evaluable for safety (485 erlotinib, 242 placebo), the most common AEs in the erlotinib arm were rash (75% erlotinib, 17% placebo), diarrhea (54% erlotinib, 18% placebo) and stomatitis (17% erlotinib, 18% placebo) events. The majority of these events were mild to moderate in severity. The incidence of interstitial lung disease (ILD) reported was the same in the placebo and erlotinib groups at 0.8% in each arm.

Two large, Phase III, randomized studies in first-line NSCLC patients evaluated erlotinib in combination with platinum-based two-drug combination chemotherapy. A total of 1079 previously untreated patients received carboplatin/paclitaxel with either erlotinib or placebo in the TRIBUTE trial (OSI2298g) conducted in the United States. An additional 1172 patients received cisplatin/gemcitabine plus either erlotinib or placebo in the TALENT trial (BO16411) conducted in 27 countries in Europe and other ex-U.S. locations. Neither study met its primary endpoint of improved overall survival or a secondary endpoint of improved time to disease progression or overall response rate. Overall, the number of adverse events and serious adverse events were well balanced between the two arms of each study, with two exceptions. As expected, rash and diarrhea occurred more frequently in the erlotinib arms. In the TRIBUTE study, more serious adverse events resulting in death were seen in the erlotinib arm compared with the placebo arm (53 vs. 27). Most of the apparent imbalance was due to events reported as pneumonia or progression of underlying cancer.(34, 35)

The efficacy of erlotinib as a single agent in previously untreated NSCLC patients with somatic EGFR mutations was evaluated in a randomized study in Europe. Patients were randomized to receive either erlotinb (N=86) or a standard chemotherapy doublet (n=88). Patients treated with erlotinib had a significantly better PFS (10.4 vs 5.2 months, HR= 0.34, CI0.23-0.49) and higher overall response rate (65% vs 16%). Based on these data, erlotinib has been approved by the US FDA for first line treatment of NSCLC bearing EGFR mutations (Del exon 19, or L858R mutations).

1.2.3.6 Erlotinib: Toxicities/Adverse Events

Common adverse events associated with erlotinib administration include rash and diarrhea. Other common adverse events include nausea/vomiting, mucositis/ stomatitis, headache, and fatigue.

a) Rash: A rash occurred in 75% of erlotinib-treated NSCLC patients enrolled in BR.21. Similar incidences of rash have occurred when erlotinib was administered concurrently with chemotherapy including gemcitabine, paclitaxel/carboplatin, and gemcitabine/cisplatin. A papular, pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. Other dermatologic manifestations reported in clinical studies or postmarketing use of erlotinib include nail changes, paronychia, painful fissures or cracking of the skin on the hands and feet, and hair growth abnormalities (alopecia, thinning hair, eyelash/eyebrow changes, hirsutism). Bullous and exfoliative skin disorders, including fatalities, have been reported, albeit rarely.

b) Although the rash may resemble acne, it is histopathologically different. The skin reaction commonly occurs on the face, upper chest and back, but may be more generalized with desquamation. Associated symptoms may include itching, tenderness and/or burning, or dry skin. The following agents have been used to treat rash: alcohol-free emollient cream, diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline) with anti-inflammatory properties. The median time to onset of skin rash was 8 days.

c) Ocular: Contact lens use while receiving erlotinib therapy is not recommended due to potential ocular effects such as conjunctivitis, keratoconjunctivitis sicca, corneal ulceration and perforation.

d) Diarrhea: The incidence of diarrhea in BR.21 was 54% of erlotinib-treated NSCLC patients. The median time to occurrence of first diarrheal symptom was 9 days.

e) Pulmonary: There have been infrequent reports of serious (including fatal) interstitial lung disease (ILD) in patients receiving erlotinib for treatment of NSCLC or other advanced solid tumors. In Study BR.21, the incidence of ILD (0.8%) was the same in the placebo and erlotinib groups. The overall incidence in erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Included in this rate of ILD are reported diagnoses of pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, alveolitis, and lung infiltration, irrespective of investigator assessed causality. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections.

f) Renal: Rare cases of acute renal failure or renal insufficiency have been reported (including fatalities). Many of these cases have been associated with dehydration associated with nausea, vomiting, diarrhea, and/or anorexia. There have been rare reports of renal failure in patients receiving erlotinib in combination with platinum-

containing chemotherapy regimens.

g) Other side effects: Other side effects noted in studies with erlotinib (with or without chemotherapy) include:

h) Events occurring in >10% of subjects-Fatigue, anorexia, nausea, vomiting, dehydration, stomatitis, infections, pruritus, dry skin, abdominal pain, weight loss, edema, constipation, fever, myalgia, depression, anxiety, dyspepsia, dizziness, headache, insomnia, neuropathy, alopecia, elevations in AST, ALT and bilirubin decreases in phosphate and albumin.

i) Hepatic failure and hepatorenal syndrome, GI perforation, cerebrovascular accidents, myocardial infarction and microangiopathic hemolytic anemia have also been reported in patients taking erlotinib.

1.2.4 Erlotinib and Bevacizumab Combination

1.2.4.1 Erlotinib and Bevacizumab Combination: Background

EGFR and VEGF are both involved with downstream angiogenic pathways, both directly and indirectly affect tumor cells. VEGF is downregulated by EGFR inhibition, and VEGF has been shown to inhibit EGFR autocrine signaling.(36, 37) Preclinical data in xenograft models using combinations of various EGFR and VEGF inhibitors demonstrate much greater anti-tumor activity than inhibitors of either alone.(38-41)

1.2.4.2 Erlotinib and Bevacizumab Combination: Phase I Clinical Trials/ Dosing Rationale/ Pharmacokinetics

A phase I/II clinical trial with combination bevacizumab and erlotinib in NSCLC by Herbst et al.(35) in non-small cell lung cancer patients determined the phase II doses to be erlotinib 150mg/day orally plus bevacizumab 15mg/kg intravenously every 21 days. Doses considered the highest single-agent dose of both agents were able to be used, since no dose-limiting toxicities or serious adverse events were observed in the phase I cohort of 12 patients. No pharmacokinetic interaction was observed between bevacizumab and erlotinib. All PK parameters estimated for erlotinib were similar to those reported by Hidalgo et al., and erlotinib exposure in the presence of bevacizumab after a single dose was similar to single-agent erlotinib for both 100mg and 150mg.(35, 42)

In the phase I cohort, 7 of 12 patients developed grade 1 or 2 proteinuria, and 2 of 12 had grade 1 epistaxis. No treatment related grade 3 or 4 toxicities were reported, and no maximum tolerated dose was reached. In the phase II portion cohort of 34 patients, the most common adverse events, regardless of attribution to the drugs, were: rash (85%), diarrhea (65%), hematuria (32%), infection (29%), proteinuria (9%), and epistaxis (6%). There were several serious adverse events: two patients had grade 3 hypertension, managed with antihypertensives; one patient's grade 3 hypertension resolved when bevacizumab was discontinued (erlotinib was maintained); one grade 3 rash, which resolved to grade 1 with dose reduction of erlotinib (bevacizumab was maintained); one grade 3 pruritus, which resolved to grade 2 with 2 days of treatment; three cases of grade 3 or 4 pneumonia.(35)

An second phase I/II trial by Vokes et al.(43) in squamous cell head and neck cancer patients confirmed the tolerability of fixed doses of erlotinib at 150mg orally daily and bevacizumab

15mg/kg every 3 weeks intravenously, with no dose limiting toxicities seen in the phase I cohort. However, serious hemorrhage events occurred in 3 patients; 1 patient with grade 4 bleed at a tumor site during a later cycle of phase I cohort, 1 patient with grade 3 at a known tumor site in phase II, and 1 grade 5 fatal bleed at a laryngeal vessel (not known to have tumor involvement) during phase II. No other grade 4 or 5 toxicities were seen. Other grade 2-3 toxicities seen in the 48 patients enrolled in both phase I and II were: rash (42%), diarrhea (19%), fatigue (24%), bleeding (4%, including the grade 3 mentioned above but not the grade 4 and 5), infection (20%), grade 2 only stomatitis (4%), and grade 2 only nausea (4%).

1.2.4.3 Erlotinib and Bevacizumab Combination: Phase II Clinical Trials

Several phase II clinical trials have demonstrated encouraging data with good PR rates and stable disease rates in otherwise refractory patients. Herbst et al. (44) in a randomized three-arm Phase II trial in second line treatment of recurrent NSCLC patients using the combination bevacizumab plus erlotinib vs. bevacizumab plus chemotherapy vs. chemotherapy alone, found that CR/PR responses were 17.9%, 12.5%, and 12.2% respectively. However, although there was no significant difference in PFS and OS between bevacizumab-erlotinib and bevacizumab-chemotherapy, the median OS times were 13.7, 12.6, and 8.6 months respectively.(44)

1.2.4.3.1 Current Study

As of December, 2014, accrual for both cohorts had been completed; 20 patients had been enrolled on cohort 1 (patients with HLRCC associated RCC) and 21 patients had been enrolled in cohort 2 (non HLRCC/sporadic papillary RCC). The overall response rate at this time in cohort 1 was 65% (13/20 confirmed PRs) and that in cohort 2 was 29% (6/21 confirmed PRs). Additionally, there was one unconfirmed partial responder in cohort 2. The median PFS in cohort 1 was 24.2 months [95% CI 12.8 -], while that in cohort 2 was 7.4 months [95% CI 3.73 – 10.2].

Additional response and PFS data (interim) are summarized in the table below.

Summary of Results			
Best Response by *RECIST*	Cohort 1 [HLRCC] (%)	Cohort 2 [Non-HLRCC] (%)	Total (%)
Complete response (CR)	0	0	0
Confirmed Partial response (PR)	13 (65%)	6 (29%)	18 (44%)

Summary of Results			
Overall Response Rate	**65%**	**29%**	**44%**
Stable disease (SD)	7 (35%)	12 (57%)	20 (49%)
Progressive disease (PD)	0	3 (14%)	3 (7%)
Disease Control Rate (SD+PR)	**100%**	**86%**	**93%**
Median Progression Free Survival –Months [95%CI]	**24.2 [95% CI 12.8 -]**	**7.4 [95% CI 3.73 – 10.2]**	**12.8 [95% CI 7.47 – 26.3]**

The regimen was well tolerated with an adverse event profile largely consistent with that previously described with this combination. The most commonly seen grade 3-4 adverse events included hypertension (24%) and proteinuria (12%). One patient died from complications arising from an upper gastrointestinal hemorrhage deemed possibly related to bevacizumab.

1.2.4.4 Erlotinib and Bevacizumab Combination: Toxicities

The simultaneous blockade of the EGFR pathway with a RTK inhibitor and an anti-VEGF antibody with the combination of bevacizumab and erlotinib may provide a potentially synergistic therapeutic effect. However, this has not shown to result in increased toxicity. Several phase II clinical trials have now been reported using the combination at the highest single-agent doses with tolerable toxicity profiles, and toxicities correspond directly with those seen in either agent alone.

The most common adverse events have been rash, diarrhea, infection, hematuria, and proteinuria. Rash has been attributed as a class-effect toxicity seen in erlotinib, similar to other EGFR-targeted agents. Bevacizumab has been associated with tumor bleeding (which can be life-threatening, especially in squamous cell histology), hypertension, proteinuria, asthenia, headache and nausea.

Phase II clinical trials have consistently reported similar toxicity profiles to those seen in both agents alone. Hainsworth et al.(45) reported in a Phase II trial of bevacizumab and

erlotinib in carcinomas of unknown primary that the most common toxicities were acneiform rash, diarrhea, and fatigue. Treatment related toxicities in 50 patients were as follows: grade 3 fatigue (16%), grade 3 and 4 rash (10%), grade 3 diarrhea (8%), grade 3 nausea and vomiting (8%), grade 3 and 4 proteinuria (6%), grade 3 bleeding (2%), grade 3 thrombocytopenia (2%), grade 3 pruritus (2%), grade 3 and 4 stomatitis (4%), grade 1 and 2 edema (10%), grade 1 and 2 neutropenia (12%), grade 1 and 2 hypertension (6%), and grade 1 and 2 hypersensitivity reaction (2%). One patient had grade 5 exfoliative dermatitis and mucositis leading to septicemia and death.

By organ system, toxicities for both erlotinib and bevacizumab, either as single agents or in combination, include:

- Neurologic – Headache, asthenia, pain, reversible posterior leukoencephalopathy syndrome
- Cardiovascular – hypertension (including hypertensive crisis), hypotension, congestive heart failure, supraventricular arrhythmias, ventricular fibrillation, myocardial ischemia/infarction, left ventricular dysfunction
- Gastrointestinal – diarrhea, nausea, vomiting, constipation, gastrointestinal perforation, fistulae formation, mucositis and stomatitis, liver function test abnormalities, anorexia, colitis, dyspepsia, ileus, anastamosis leak, peptic ulcer
- Hematological – bleeding (including life-threatening and fatal hemorrhage, especially tumor-associated bleeding, including intracranial bleeding, pulmonary hemorrhage, and gastrointestinal bleeding), arterial thromboembolic events (including cerebrovascular accidents, transient ischemic attacks, myocardial infarctions, and visceral arterial ischemia), venous thrombotic events (including pulmonary emboli, deep venous thromboses, and thrombophlebitis), epistaxis, mucocutanous bleeding, leucopenia, neutropenia, thrombocytopenia, anemia
- Renal/GU – proteinuria (including nephritic syndrome), acute renal failure, fistula
- Dermatological –rash (most often acneiform), dermatitis (including exfoliative dermatitis/exfoliation), wound dehiscence and wound healing complications, ulceration, alopecia
- Pulmonary – dyspnea, interstitial lung disease, bronchospasm, cough, fistula, voice changes
- ENT- allergic rhinitis, paranasal sinus reactions (including septal perforation), dry mouth/xerostomia, dysgeusia
- Ocular – episcleritis and other ocular surface disease, dry eyes
- General – fatigue, hypersensitivity and infusion reaction, dehydration, edema, pruritus, infection, fever, chills, weight loss, pain
- Metabolic/Laboratory – elevations in alkaline phosphatase, tansaminases, bilirubin, creatinine, and proteinuria

1.2.5 Rationale for proposed clinical trial

The recognition that HIF upregulation may play an important role in the formation and propagation of renal cancer associated with HLRCC suggests that interventions directed against components of this pathway, such as VEGF and TGF-α/EGFR, may be of benefit in this patient population.

In pre-clinical studies, Isaacs, et al. noted that when the HLRCC gene (fumarate hydratase) is inactivated in cells, fumarate over-accumulates and competes with 2-oxyglutarate, the co-enzyme for the HIF prolyl hydroxylase.(5) This results in a VHL-independent mechanism for HIF accumulation. Furthermore, oxidative phosphorylation is severely compromised in these tumors due to the mutation of both copies of a critical Krebs' cycle enzyme. Therefore, for survival, these tumor cells are totally dependent on glycolysis for energy production and are exquisitely sensitive to ambient glucose concentration. We hypothesize that in addition to inhibiting angiogenesis, bevacizumab/anti-VEGF- based regimens might permit us to exploit the dependence of these tumors on glucose by impairing delivery of this critical metabolic substrate. We have also developed an HLRCC kidney cancer cell line (UOK262), derived from a primary renal tumor in an HLRCC patient. This cell line requires a high ambient glucose concentration for survival, a feature that is consistent with impairment of aerobic metabolism.

These preclinical data suggest that simultaneous targeting of vascular (VEGF, with bevacizumab) as well as autocrine growth (EGFR, erlotinib) pathways downstream from HIF provides an opportunity to affect tumor growth in kidney cancer associated with this rare hereditary cancer syndrome.

Additionally, the UOB/NCI follows several patients with metastatic RCC associated with HLRCC. These patients have generally proven to be refractory to a variety of interventions including cytokines and standard cytotoxic chemotherapy. On the other hand, we have observed evidence of antitumor activity with combined VEGF/EGFR blockade in these patients. We recently undertook a retrospective review of fifteen metastatic HLRCC patients followed on UOB diagnostic/natural history protocols (unpublished data). Five of these patients had received bevacizumab in combination with an EGFR antagonist (erlotinib in four patients and gefitinib in one). Of these, one patient had a complete response (CR) and continues to be disease free over 2 years following initiation of therapy; two patients had a partial response (including regression of large liver mets and adenopathy) lasting 18-24 months, while two other patients have had stable disease (15+ and 21+ months respectively), including one who had previously failed single agent erlotinib, several chemotherapeutic and an anti-VEGF TKI regimen. In contrast, no responses were seen in patients receiving a variety of 'conventional' agents including interferon, interleukin and cytotoxic chemotherapy.

The combination of bevacizumab and erlotinib has been studied in patients with clear cell RCC and appears to be associated with manageable toxicity at doses proposed in this LOI. In a single arm phase II study, Hainsworth et al. demonstrated a 25% objective response rate in patients with metastatic clear cell RCC receiving this combination, which is significantly higher than the response rate expected with either agent alone.(46) However, a subsequent randomized placebo-controlled Phase II clinical trial failed to demonstrate superiority of the combination over bevacizumab alone (no significant differences in PFS, RR or OS) in

metastatic clear cell RCC.(47) While this latter study has dampened enthusiasm for combined VEGF/EGFR blockade in clear cell RCC, its relevance to patients with non-clear cell histology as well as in molecularly well defined clear cell RCC subsets (i.e those with VHL inactivation vs those without) remains to be determined. Clear cell and papillary/HLRCC-associated RCC are clinically and histologically distinct entities and are driven by disparate genetic/molecular defects. Hence, although HIF upregulation occurs as a consequence of both VHL (clear cell RCC) and FH inactivation (HLRCC), there are doubtless other, as yet incompletely understood mechanisms/pathways that contribute to the differences observed in these two subtypes of RCC. The NCI clinical experience with dual VEGF/EGFR blockade in HLRCC (outlined above), combined with preclinical evidence suggesting upregulation of both VEGF and TGF- α /EGFR pathways provides a sufficiently compelling argument for the evaluation of bevacizumab/erlotinib in this patient population.

While we have considered comparing bevacizumab alone or in combination with erlotinib in consecutive single arm trials or in a randomized phase II trial as appealing alternatives, the relative rarity of this disease makes the proposed dual agent single arm study the most feasible study.

As part of this study, we also propose to evaluate the activity of this regimen in patients with sporadic papillary RCC, in whom there is no evidence of a heritable germline FH defect. There are currently no standard treatment options for patients with unresectable papillary RCC; single agent anti-VEGFR or anti-EGFR tyrosine kinase inhibitors appear to have modest single agent activity. Given the relatively recent recognition of this entity, we propose to explore the possibility that some variants of sporadic papillary RCC may share common clinical/molecular features with HLRCC-associated renal tumors that may render them amenable to treatment with this regimen. As part of this trial, an attempt will be made to further characterize these sporadic tumors, particularly with regard to the prevalence of somatic FH inactivation and VEGF/EGFR pathway activation.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

Patients must meet all the following criteria to be eligible for study enrolment:

- Diagnosis of advanced RCC associated with HLRCC (cohorts 1 & 3) or sporadic/non-HLRCC papillary RCC (cohort 2 & 4)
- Measurable disease, as outlined in RECIST 1.1
- No more than two prior regimens targeting the VEGF pathway; no prior bevacizumab therapy
- Age ≥ 18 years.
- Performance status ECOG 0-2
- Patients must have normal organ and marrow function as defined below: WBC count ≥ 3,000/uL, absolute neutrophil count ≥ 1,500/uL, platelet count ≥100,000/uL, serum creatinine ≤ 2x upper limit of reference range or creatinine clearance ≥ 30 ml/min, AST

and ALT <2.5 x upper limit of reference range, total bilirubin < 1.5x upper limit of reference range (<3 x upper limit of reference range in patients with Gilbert's disease), alkaline phosphatase ≤ 2.5 x upper limit of reference range (or ≤ 5 x upper limit of reference range if considered to be related to liver or bone metastases by the PI)

- Recovery from acute toxicity of prior treatment for RCC (to ≤ grade 1 the active version of CTCAE or to a level permitted under other sections of Inclusion/ Exclusion criteria).
- At least 4 weeks from completion of major surgery and a healed surgical incision
- Negative pregnancy test (within 7 days of enrolment) in women of childbearing potential
- No myocardial infarction, GI perforation/fistula, intraabdominal abscess, cerebrovascular accidents within six months prior to study entry
- No coagulopathy or bleeding diathesis
- Ability to understand and the willingness to sign a written informed consent document.
- Archival tissue block or unstained tumor tissue available for correlative studies

2.1.2 Exclusion Criteria

- Prior invasive malignancy of other histology, with the exception of adequately treated basal or squamous cell carcinoma of the skin, or any other malignancy for which the patient does not currently require treatment and/or has no evidence of disease for >= 2 years.
- Patients with known brain metastases unless treated with an appropriate modality with no evidence of progression/recurrence for >3months
- Hypertension not controlled by medical therapy (resting systolic blood pressure greater than 140 mmHg or diastolic blood pressure greater than 90 mmHg on at least two occasions over a 24 hour period despite optimal medical management).
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure (New York Heart Association grade III or greater, **Appendix B)**, unstable angina pectoris, or psychiatric illness/social situations that would limit compliance with study requirements.
- Serious, non-healing wound or ulcer; bone fracture within 3 months prior to study entry
- Patient known to be HIV-positive and requiring antiretroviral therapy (due to the risk of potential drug interactions)
- Concomitant therapy with potent inhibitors of CYP450 3A4 (e.g. ketoconazole, verapamil etc., see **Appendix C**) or with potent CYP450 1A2 inhibitors (fluoroquinolone antibiotics including ciprofloxacin, levofloxacin, and norfloxacin; ticlodipine, cimetidine, amiodarone, etc. see **Appendix C**)
- Pregnant women are excluded from this study because bevacizumab and erlotinib are anti-cancer agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to

treatment of the mother with these agents, breastfeeding should be discontinued if the mother is treated on this study

- All men and women of childbearing potential must be willing to use effective contraception as determined by the principal investigator (including but not limited to abstinence, hormonal contraceptives (birth control pills, injections, or implants), intrauterine device (IUD), tubal ligation, vasectomy) from the time of enrollment to at least six months following the last dose of drug
- Any known hypersensitivity to bevacizumab, erlotinib or other excipients of these drugs
- Documented baseline proteinuria >1000mg/day on 24 hour urine collection. Only patients with 1+ or greater proteinuria on UA and a spot urine protein:creatinine ratio of > 0.5 will undergo a 24 hour urine collection for quantitation of proteinuria.
- Left ventricular ejection fraction <40% as measured on transthoracic echocardiogram.

2.1.3 Inclusion of Women and Minorities

- Both men and women and members of all races and ethnic groups are eligible for this trial.

2.1.4 Recruitment Strategies

Participants in this study will be recruited through internal referral, our local physician referral base, through Cancer Hotline information, listing on cancer trial websites, and through a variety of other IRB-approved recruitment material sent to oncologists. This protocol may also be abstracted into a plain language announcement posted on NIH websites and on NIH social media forums.

2.2 Screening Evaluation

Screening evaluation testing/procedures are conducted under the separate screening protocol, 01C0129.

Subjects will be screened per **Study Calendar**.

2.3 Patient Registration and Status Update Procedures

Registration and status updates (e.g. when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Cohort 1	Patients with HLRCC

2	Cohort 2	Patients with sporadic papillary RCC
3	Cohort 3	Patients with HLRCC (opened after cohorts 1 & 2 closed)
4	Cohort 4	Patients with sporadic/non HLRCC papillary RCC (opened after cohorts 1 & 2 closed)

Arms

Number	Name	Description
1	Bevacizumab+ Erlotinib	All patients will be receiving fixed starting dose of bevacizumab (10 mg/kg IV every 2 weeks) and erlotinib (150 mg/day PO)

Subjects in cohorts 1, 2, 3 and 4 will be directly assigned to arm 1.

3 STUDY IMPLEMENTATION

3.1 Study Design

This is an open label, single arm phase II study utilizing a fixed starting dose of bevacizumab (10 mg/kg IV every 2 weeks) and erlotinib (150 mg/day PO).

Treatment cycles will consist of 28 days; erlotinib will be administered daily on days 1-28, and bevacizumab every 2 weeks IV. There will be no break between 2 consecutive cycles (i.e., erlotinib administration will be continuous).

The patient will return to the NIH Clinical Center to undergo clinical and laboratory evaluation prior to the start of each cycle.

Patients will be evaluated radiologically for evidence of response or progression approximately 8 weeks after initiation of therapy, every 8 weeks thereafter for the first 32 weeks, and then every 12 weeks while on treatment. Patients with evidence of disease response or stable disease will continue to receive therapy in the absence of serious toxicity.

In the event of a complete response, treatment will continue for 2 cycles beyond CR at which point consideration will be given to discontinuing both agents. Patients may be retreated at the discretion of the PI in the event of disease recurrence.

3.2 Drug Administration

3.2.1 Bevacizumab Administration

Patients will receive treatment with bevacizumab 10mg/kg, administered by intravenous infusion on days 1 and 15 of each 28 day cycle (+/- 3 days). The initial dose of bevacizumab will be infused over 90 minutes +/- 15 minutes. If well tolerated, the second infusion will be

over 60 +/- 10 minutes, and if tolerated, all subsequent infusions are to be administered over 30 +/- 10 minutes.

In the event of an infusion-related event, the infusion of bevacizumab should be stopped and held until resolution of acute symptoms. The PI or AI will be notified of the infusion-related event at the time of the occurrence. Upon resolution, the infusion may be restarted (as outlined in section **3.3.2**) at a rate that will increase the total infusion time by 30 minutes beyond the current time.

3.2.2 Erlotinib Administration

Erlotinib is to be administered orally at a daily dose of 150 mg initially. Patients are to take erlotinib at least 1 hour before or 2 hours after meals.

3.3 Treatment Modifications

3.3.1 General Plan to Manage Safety

a) Bevacizumab-Specific

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section **2.1.2**) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before enrolment on trial and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, daily blood pressure monitoring, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason other than progression will be evaluated approximately three months after the decision to discontinue treatment as outlined under Off Study Criteria. (see Section **3.10.3**).

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment as well as by patient self-monitoring. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Proteinuria will be monitored by urine protein:creatinine (UPC) ratio or dipstick at least every 2 weeks.

- If patients on treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin/restart bevacizumab until 4 weeks after that procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 wk and bevacizumab no earlier than 8 wk **after surgery).**
- Women of childbearing potential should have a negative pregnancy test prior to starting therapy with bevacizumab and should use adequate contraceptive methods during and for

at least 6 months after bevacizumab therapy. Women who become pregnant while on bevacizumab will discontinue the drug.

b) Erlotinib specific

Skin toxicities will be monitored by routine physical examination and managed symptomatically. The following agents may be used to treat rash: alcohol-free emollient cream, diphenhydramine, topical or oral corticosteroids, and topical (clindamycin) or oral antibiotics (tetracycline, minocycline, doxycycline). Topical drying agents are not recommended.

Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and Erlotinib dose reduction/interruption as described in Section **3.3.3**.

Although quite rare, ILD can be life threatening. Therefore, patients will be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, Erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often used empirically. Erlotinib should not be restarted in those patients suspected of having drug-related ILD. See Section **3.3.3** for management guidelines, including Erlotinib dose interruption.

Liver function abnormalities, including elevated serum ALT, AST, and/or bilirubin, have been observed infrequently with single-agent Erlotinib and occasionally with Erlotinib in combination with concomitant chemotherapy. Periodic monitoring of liver function is recommended. Erlotinib dosing should be interrupted if changes in liver function are severe (as outlined in section **3.3.3**).

Women of childbearing potential should have a negative pregnancy test prior to starting therapy with Erlotinib and should use adequate contraceptive methods during and for at least 3 months after Erlotinib therapy is discontinued. Women who become pregnant while on erlotinib will be taken off the drug.

It is not known whether Erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because the effects of Erlotinib on infants have not been studied, women should be advised against breast-feeding while receiving Erlotinib therapy.

3.3.2 Dose Modifications

Patients will be asked to record side effects/symptoms developing or worsening on therapy on a Side Effect Diary which will be reviewed by the research nurse/PI/associate investigator during clinic visits. Treatment modifications will be made in the event of toxicities (graded based on NCI Common Toxicity Criteria for Adverse Events, version 4.0) related to either bevacizumab or erlotinib according to the guidelines below. Dose modifications for laboratory abnormalities will be required only if these abnormalities are clinically significant (regardless of grade). There will be no dose modifications for electrolyte abnormalities (potassium, sodium, calcium, magnesium, phosphorus) that can be corrected (to ≤ grade 1 or baseline) within 48 hours. In the event one of the agents is discontinued permanently, the patient can continue to receive the second agent in the absence of an indication requiring permanent discontinuation of that agent. **Sections 3.3.3 and 3.3.4 outline toxicities**

mandating withholding of dose modification; however, bevacizumab and/or erlotinib may be placed on hold temporarily for less severe AEs or for other reasons if it is felt to be in the best interests of the patients.

3.3.3 Dose Modifications for Toxicities Related to Bevacizumab

There will be no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes. If bevacizumab needs to be held for >16 weeks due to dose-limiting toxicity as outlined below, the agent will be permanently discontinued. This limit does not apply to patients in whom bevacizumab has been temporarily discontinued to enable performance of major elective surgery; these patients can restart bevacizumab once the surgical scars have healed adequately regardless of the duration for which the agent has been discontinued. The following guidelines will be used to guide bevacizumab dosing in the event of toxicity related to the drug.

1. Hypertension: Hypertension is one of the most common toxicities experienced with bevacizumab. Subjects will be asked to monitor their blood pressure at home at least once a day and contact the UOB team for elevated readings. Elevated BP readings should be confirmed by a qualified health care professional when possible and decisions regarding grading of hypertension and initiation/intensification of antihypertensive therapy will generally be driven by BP measurements performed by a health care professional. Table 3.3.2.1 outlines the management plan for patients developing hypertension on therapy. Although the active version of CTCAE criteria will be used to grade hypertension, the scheme outlined in the table below will be used to guide dose modifications. Early treatment of grades 1-2 hypertension to prevent or minimize the risk of developing more persistent or clinically significant hypertension is allowed and is not considered a grade 3 event.

The choice of agents and dosage used may vary based on individual circumstances. Calcium channel blockers, beta blockers, diuretics, ACE inhibitors, and angiotensin receptor blockers are examples of classes of antihypertensicve agents that may be used.

Hypertension will be managed in accordance with the guidelines outlined in the table below:

	BP Measurements - Systolic/Diastolic	**Treatment/Dose Modification**
A	>140 mmHg (systolic) OR >90 mmHg (diastolic)	• Add new or additional antihypertensive medications or increase dose of existing medications. • Maintain dose of bevacizumab and erlotinib. • If unable to control BP to <140/90 in two weeks, hold bevacizumab and follow guidelines under row C
B	>160 mmHg (systolic) OR >100 mmHg (diastolic) OR Symptomatic	• Hold bevacizumab. • Add new or additional antihypertensive medications or increase dose of existing medications. • Resume treatment at same dose level when BP falls to <140/90 or baseline.
C	>140 mmHg (systolic) OR >90 mmHg (diastolic) Despite therapy for at least 2 weeks	• Hold bevacizumab. • Maintain or intensify antihypertensive therapy • Resume treatment at same dose level when BP falls to <140/90 or baseline
D	CTCAE Grade 4	• Discontinue bevacizumab • No further treatment with bevacizumab allowed except in patients benefiting from therapy in whom treatment may be restarted if BP is controlled to <140/90 within 3 weeks and there are no permanent sequelae. Patient will be removed from study if a second episode of grade 4 hypertension occurs

2. Hemorrhage/Bleeding: The following scheme will be used

Grade 1/2 non-pulmonary and non-CNS events	No dose modification
Grade 3 Non-pulmonary and non-CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab.
Grade 4 non-pulmonary or non-CNS hemorrhage	Discontinue bevacizumab.
Grade 1 pulmonary	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence.
Grade 2, 3, or 4 pulmonary or any grade CNS hemorrhage	Discontinue bevacizumab

3. Proteinuria:

   If random protein:creatinine ratio performed prior to bevacizumab administration demonstrates the spot urine protein:creatinine ratio is >3.5, bevacizumab should be held until a 24 hour urine protein can be obtained. Bevacizumab can continue as long as 24 hour urine protein remains less than 3.5g/24 hours. If proteinuria is greater than 3.5g/24 hours, bevacizumab is to be held and 24 hour urine remeasured in 1-2 weeks. Bevacizumab can be restarted when proteinuria decreases to less than 3.5 g/24 hours.

4. Surgical or periodontal procedures: If there is a need for an elective major surgical or periodontal procedure, bevacizumab should be held for 4-8 weeks prior to the procedure and must not be resumed until 4 weeks after the surgical procedure (in the case of high risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that bevacizumab be restarted no earlier than 8 wk after surgery). Longer delays may be

necessary if clinically indicated in order to ensure that adequate healing has taken place prior to bevacizumab resumption. Minor oral or periodontal procedures or surgical procedures may be done with no delay/discontinuation of bevacizumab at the discretion of the PI.

5. Thrombosis

   Arterial Thrombosis: Patients will be taken off study in the event of arterial thrombosis. Arterial thrombosis includes angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, any visceral or peripheral artery thrombosis.

   Venous Thrombosis: For venous thrombosis requiring systemic anticoagulation, the patient may continue with bevacizumab while on systemic anticoagulation per the following guidelines.

Venous Thrombosis	
Grade 1 or 2	No intervention/dose modification
Grade 3 OR Asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** all of the criteria below are met: − Subjects on heparin must have a stable dose of heparin prior to restarting bevacizumab. − The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) − The subject must not have had grade 2 or greater hemorrhagic events while on study ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
Symptomatic Grade 4	Discontinue bevacizumab

6. Allergic reactions and cytokine release syndrome (acute infusion reaction):

   Patients with grade 1/2 events can have their infusion interrupted until resolution of acute symptoms, and then restarted at 50% of the rate at which the reaction occurred. The infusion rate may be increased by 50% every 30 minutes if well tolerated. Infusions may be started at the original rate during the next dose of bevacizumab. Patients who develop grade 3/4 allergic/infusional reactions should have bevacizumab discontinued.

7. Reversible posterior leukoencephalopathy syndrome (RPLS): Bevacizumab should be held in patients with signs and symptoms suggestive of reversible posterior leukoencephalopathy syndrome (RPLS), pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.
8. Bowel perforation: Patients who develop a bowel perforation will discontinue bevacizumab permanently.
9. For other grade 3 toxicities related to bevacizumab, the agent will be held until resolution to ≤ grade 1 or baseline and then resumed at the same dose. For grade 4 toxicities, bevacizumab will be discontinued; resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the grade 4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with retreatment.
10. Fistula formation: For any grade tracheo-esophageal fistula, Bevacizumab will be permanently discontinued. For any fistula other than TE- that is grade 1 or 2, bevacizumab will be held until resolution. For grade 3-4 non tracheo-esophageal fistulae, bevacizumab will be permanently discontinued.

3.3.4 Dose Modifications for Toxicities Related to Erlotinib

Erlotinib Dose Reduction Scheme: The following scheme of dose reduction will be followed when erlotinib-related toxicities necessitate dose modification.

Starting Dose: 150 mg/d

First Dose Reduction: 100mg/d

Second Dose Reduction: 50mg/d

The following guidelines will be used to guide erlotinib dosing in the event of toxicity related to the drug.

1. Skin Rash:

Skin toxicities will be monitored by routine physical examination and managed symptomatically. If a patient develops a skin rash, the following actions will be taken for the management of this reaction:

- The rash should be graded/assessed by a physician as soon as possible according to the CTCAE cutaneous toxicity criteria and documented accordingly
- If a rash of CTCAE grade 2 or lower is detected, symptomatic treatment should be provided and erlotinib continued at the current dose. If grade 2 skin rash is considered intolerable by the patient, a dose reduction should be considered. When skin toxicity improves by at least one grade level, the dose may be re escalated as tolerated at PI discretion.
- A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams or oral corticosteroids, topical or systemic antibiotics, topical or systemic antihistamines, emollients and occasionally retinoid creams.

- If a rash of CTCAE grade 3 is detected, erlotinib should be withheld until recovery to grade 1 or below, at which point erlotinib may be restarted at one dose level lower
- Patients with CTCAE grade 4 rash will discontinue erlotinib permanently.
- If erlotinib must be withheld for >4 weeks due to cutaneous toxicity, the patient will be taken off the agent permanently

2. Management of gastrointestinal (GI) Toxicities

Nausea and/or vomiting

In subjects who have emesis and are unable to retain study treatment, every attempt should be made to obtain control of nausea and vomiting. The dose of erlotinib may be repeated if emesis occurs within 30 minutes of taking the tablets or all the tablets are seen in the emesis. Nausea, vomiting, or both may be controlled with antiemetic therapy. Patients developing grade 3 or 4 nausea/vomiting despite optimal antiemetic therapy should have erlotinib withheld until resolution to grade 1 or below, at which point erlotinib may be restarted at one dose level lower.

Diarrhea

Diarrhea should be treated with standard medications (such as loperamide) to avoid dose modification or interruption, if possible. Diarrhea related to erlotinib has been successfully managed with anti-diarrheal agents such as loperamide. Once diarrhea is determined to be related to erlotinib, an acceptable strategy for symptomatic management is initiation of loperamide 2mg orally administered following the first episode, which can be repeated as frequently as every 2 hours while awake (or administered at a dose of 4mg every 4 hours during sleeping hours) (not to exceed a total of 16mg/24 hours) until the patient is diarrhea-free for 4-6 hours.

No dose modifications will be necessary for CTCAE grade 1 or 2 diarrhea. If CTCAE grade 3 diarrhea develops despite adequate prophylaxis, erlotinib should be withheld until diarrhea resolves to ≤ grade 1. Once the diarrhea resolves to less than or equal to grade 1, treatment with erlotinib may recommence with a dose reduction of one level. Patients should be maintained at the reduced dose of erlotinib without attempt at dose re-escalation. Patients experiencing Grade 4 diarrhea should be discontinued from erlotinib treatment.

3. Interstitial Lung Disease:

Although relatively rare, ILD can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often used. Erlotinib should not be restarted in those patients suspected of having drug-related ILD.

4. Patients who develop other grade 3 or 4 toxicities related to erlotinib will have their treatment withheld until resolution to ≤ grade 1, at which point erlotinib may be restarted with a dose reduction of one level.

3.3.5 Management of Female Study Subjects

Women of childbearing potential should have a negative pregnancy test prior to starting therapy with erlotinib and bevacizumab and should use adequate contraceptive methods during and for at least 6 months after discontinuation of therapy. It is not known whether erlotinib or bevacizumab are excreted in human milk. Because many drugs are excreted in human milk and because the effects of erlotinib and bevacizumab on infants have not been studied, women should be advised against breast-feeding while receiving therapy.

3.4 Correlative Studies for Research

3.4.1 Planned Research Studies

3.4.1.1 Tumor Biopsy

Tumor biopsies (renal primary or metastases or cutaneous leiomyomas) may be obtained from patients who have easily accessible lesions. Core or excisional biopsy of an easily accessible sentinel lesion (such as cutaneous/subcutaneous lesions, percutaneously accessible hepatic lesions, lymph nodes etc.) may be performed at study entry and again at approximately at 8 weeks following initiation of therapy. Biopsies that are to be used solely for research purposes will be obtained only if they can be performed with minimal risk of complications from the procedure and only after the procedure has been explained to the patient and informed consent obtained. Kidney or liver biopsies will not be performed solely for research purposes in patients while on bevacizumab. Major surgical procedures such as laparotomy or laparoscopic procedures will not be performed solely to obtain biopsies for research purposes. The biopsies will be performed by members of the interventional radiology, dermatology or surgical staff. A portion of the biopsies will be frozen in liquid nitrogen immediately and transferred to the UOB laboratory (Contact for receiving and processing specimen: Robert Worell/ Cathy Vocke, Ph.D. - Tel: 301-496-6353). Prior to freezing and depending on tissue availability, a small portion of the biopsy specimen may be transferred under sterile conditions to the UOB laboratory to be used to establish a tumor cell line.

In addition, attempts will be made to obtain any available archived tumor tissue on all patients to help evaluate FH status and/or relevant components of the VEGF/EGFR pathways.

3.4.1.2 Sample Processing

Collection of blood samples for research analysis may be obtained at periodic intervals which meet the NIH Guidelines for Blood Draw Limit (MAS - M95-9). No more than 10.5 mL/kg or over 550mL will be obtained from adults over an eight week period of time.

Samples will be processed for the following planned studies. In the event of limited sample availability, we plan to prioritize studies in the order listed below:

3.4.1.2.1 Analysis of somatic FH mutation, CGH and c-MET mutation to attempt to correlate clinical effects of bevacizumab and erlotinib with molecular abnormalities (may be performed on archived tumor tissue when available). Sequencing of EGFR to identify mutations sensitive to EGFR TKIs may also be performed.

3.4.1.2.2 Immunohistochemistry-To evaluate the effect of bevacizumab and erlotinib on tumor microvessel density, proliferation and apoptosis

3.4.1.2.3 HIF expression, EGFR expression and VEGFR2 expression, and evaluation of components of the EGF and VEGF pathways may be performed to explore the correlation between these biomarkers and clinical response. Evaluation of the components of the FH and Keap1/Cul3/NRF2 pathway by IHC and other techniques may also be performed when possible.

3.4.1.2.4 Analysis by RT- PCR of transcriptional targets affected by EGFR and VEGF signaling pathways, including but not limited to p27 KIP1, E-cadherin, b-catenin etc.

3.4.1.2.5 cDNA arrays to compare gene expression profiles in tumor cells before and during treatment with bevacizumab and erlotinib. Blood samples for evaluation of basal plasma levels of angiogenesis biomarkers such as VEGF and to assess the effect of bevacizumab and erlotinib on these biomarkers, 10cc lavender top tube, will be obtained prior to first dose, at end of 8, 16, 24 and 32 weeks. And at the time of disease progression, 5-10 cc of venous blood will be collected into CPT tubes containing sodium citrate and thoroughly mixed.

3.4.1.2.6 1. **Circulating Tumor Cells:**

Peripheral blood will be collected to correlate changes in circulating tumor cells with clinical response. CTCs will be assessed using ferrofluidic enrichment and multi-parameter flow cytometric detection. CTCs are identified by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers.
Draw blood into one 10-cc lavender top tubes at (1) baseline, just prior to beginning therapy, (2) C2D1, prior to therapy and (3) C3D1, prior to therapy. Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel- trepel@helix.nih.gov; and Sunmin Lee- lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330. Keep blood at ambient temperature. A member of the Trepel Lab will pick up the sample.

2. **Circulating Endothelial Cells (CEP and CEC):**

Peripheral blood will be obtained pre-treatment and post-treatment with bevacizumab and erlotinib and coded samples will be used for analysis of angiogenesis markers such as circulating endothelial cells (CEC) and circulating endothelial progenitor cells (CEP). CEP and CEC will be assessed by multiparameter flow cytometry. Cells will be analyzed for forward and side

scatter, and cells expressing hematopoietic markers will be excluded. Endothelial cells will be identified using co-expression of markers, such as CD31, CD146 and CD133. The cell populations will also be analyzed for viability using scatter profiles and a vital stain, such as Hoechst 33258. Multiparameter flow analysis will be performed with a Miltenyi Quant equipped with FlowJo software. The outcome measures will be the number of CEC and CEP per 10^6 mononuclear cells or per microliter of peripheral blood, analyzed in samples taken before and after treatment. These numbers will then be examined for correlations with various parameters to assess their potential utility as surrogate biomarkers for drug activity, for establishing the optimal biologic dose, for patient stratification, and monitoring of therapy-related side effects.

Draw blood into two 8-cc CPT citrate (BD) tubes at (1) baseline, just prior to beginning therapy, (2) C2D1, prior to therapy and (3) C3D1, prior to therapy. Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel- trepel@helix.nih.gov; and Sunmin Lee- lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330. Keep blood at ambient temperature. A member of the Trepel Lab will pick up the sample.

3. **Immune Subsets:**

Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to Tregs, MDSC, effector and exhausted CD8+ T-cells, and CD14+ monocytes. Assessment will include functional markers, i.e. PD-1, Tim-3, CTLA-4 CD40, HLA-DR and/or PD-L1. Draw blood into one 8-cc CPT citrate (BD) tubes at (1) baseline, just prior to beginning therapy, (2) C2D1, prior to therapy and (3) C3D1, prior to therapy. Contact the Trepel Lab, Developmental Therapeutics Branch, NCI by email (Jane Trepel- trepel@helix.nih.gov; and Sunmin Lee- lees@pop.nci.nih.gov) when the patient is scheduled and by phone as soon as the blood is drawn at 240-760-6330. Keep blood at ambient temperature. A member of the Trepel Lab will pick up the sample.

3.4.1.2.7 Correlative laboratory studies will be performed by investigators in the Urologic Oncology Branch (under the direction of Drs Linehan, Srinivasan, Bottaro) and/or Jane Trepel's laboratory and may involve collaboration with other NIH intramural investigators. Studies listed will be performed wherever possible and as permitted or dictated by clinical outcome and/or sample and resource availability.

3.4.2 Collection, Storage, Use and Disposition of Human Specimens

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

3.4.2.1 Clinical Samples

Blood and urine samples for clinically relevant, non-research hematology, serum chemistry, urinalysis, and skin biopsy tissue will be prepared using standard procedures. Routine clinical analyses will be performed by the NIH clinical center central laboratories or NCI Pathology department. Samples will be processed and disposed according to standard laboratory procedure.

3.4.2.2 Storage and research use of research human specimens

Sample Collection and Planned Research Studies: Research samples will be collected with a view to performing a variety of correlative/biomarker studies (as indicated in section 3.4.1.1).

Sample Processing and Storage: Each patient research sample will be assigned a unique patient identifier and relevant sample characteristics (such as timing of sample collection, treatment cycle and day identifiers) will be recorded. The location of all samples will be carefully tracked in the secure UOB database. All stored samples will be coded and no identifying patient information will be on placed on sample containers. Stored samples will be kept in freezers / refrigerators or secure containers located in the Urologic Oncology Branch research laboratories or in the laboratories of collaborators.

Timeframe for research studies: Samples will be stored until requested by an authorized researcher(s). All researchers are required to use the samples for research purposes associated with this trial (as per the NCI IRB approved protocol). Subjects will be given the option of consenting to future use of their research samples per the informed consent process with their option declared in the consent document. Samples from those patients who consent to this will be stored permanently. However, these samples will be used only for research studies on active NCI IRB approved protocols covered by a valid informed consent document. Samples will be destroyed at the completion of the study from those subjects who decline future use of their samples. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples provided they have an IRB approved protocol and patient consent. Any unused samples must be returned to the UOB laboratories as appropriate. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section 7.2.

3.5 Study Evaluation

3.5.1 Baseline Evaluation

Studies required at baseline which were also performed at screening do not need to be repeated if collected in a baseline appropriate timeframe. The following baseline studies must be performed within 4 weeks prior to initiation of study therapy.

- A complete history and physical with documentation of measurable disease and performance status
- Imaging studies: CT of the chest abdomen and pelvis (or MRI scans when appropriate)
- MRI (or CT with contrast) of the brain
- PET scan

- Bone Scan
- 12 lead ECG
- ECHO
- Photographic evaluation of skin leiomyoma (only in patients with HLRCC associated cutaneous leiomyomas)
- TSH, and if elevated, T3; free T4; anti-TPO and TSI; and lipid panel.
- Anti-Mullerian Hormone, FSH, LH, estradiol, progesterone in pre-menopausal women
- Serum Lactic Acid

The following must be performed within 7 days prior to initiation of study therapy

- Targeted history and physical examination focusing on any salient changes from baseline
- CBC with differential, PT/PTT, urinalysis, spot urine protein:creatinine ratio (patients with 1+ or greater proteinuria on UA and a spot urine protein:creatinine ratio of > 0.5 will undergo a 24 hour urine collection for quantitation of proteinuria)
- Acute Care Panel (Na, K, Cl, CO2, Creatinine, Glucose, and Urea Nitrogen)
- Mineral Panel (Phosphorus, Magnesium, Albumin, and Calcium)
- Hepatic Panel (Alk Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)
- Total Protein, CK, Uric Acid, and LD
- Urine or serum pregnancy test in women of childbearing potential

3.5.2 Before every cycle

a. Limited History and physical focusing on relevant changes from initial H&P
b. CBC with differential, Urinalysis, spot urine protein:creatinine ratio
c. Acute Care Panel (Na, K, Cl, CO2, Creatinine, Glucose, and Urea Nitrogen)
d. Mineral Panel (Phosphorus, Magnesium, Albumin, and Calcium)
e. Hepatic Panel (Alk Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)
f. Total Protein, CK, Uric Acid, and LD
g. Pregnancy test in women of childbearing potential

Labs can be completed +/- 5 days of scheduled visit
Circumstances may arise beyond our control where subject may not be able to complete required lab work, required visit, and/or bevacizumab at the scheduled time. Although every effort will be made to avoid scheduling conflicts, it is possible that the clinic visits and/or lab evaluations may be missed at times.

3.5.3 Restaging cycles:

Every two cycles (every 8 weeks) during first 8 cycles (first 32 weeks), then every three cycles (every 12 weeks) thereafter.

a. Limited History and physical focusing on relevant changes from initial H&P
b. CBC with differential
c. Acute Care Panel (Na, K, Cl, CO2, Creatinine, Glucose, and Urea Nitrogen)
d. Mineral Panel (Phosphorus, Magnesium, Albumin, and Calcium)
e. Hepatic Panel (Alk Phosphatase, ALT, AST, Total Bilirubin, and Direct Bilirubin)
f. Total Protein, CK, Uric Acid, and LD
g. Imaging studies: CT/MRI evaluation of known/suspected disease sites, bone scan (if positive for metastatic bony disease at baseline)
h. PET scan (if required clinically)
i. Dermatology Consult with photographic evaluation of skin leiomyoma (only in patients with HLRCC associated cutaneous leiomyomas)
j. TSH
k. Anti-Mullerian Hormone, FSH, LH, estradiol, progesterone in pre-menopausal women
l. Serum Lactic Acid

Due to holidays, Clinical Center closures or other special circumstances might necessitate performance of restaging scans outside the protocol specified window, and in these circumstances, restaging studies may be performed the week before or after the start of the restaging cycle and the reason documented in the patient chart.

3.5.4 Every 2 weeks Monitoring

a. Urinalysis and spot urine protein:creatinine ratio prior to every dose of bevacizumab. If random protein:creatinine ratio performed prior to bevacizumab administration demonstrates the spot urine protein:creatinine ratio is >3.5, bevacizumab should be held until a 24 hour urine protein can be obtained.

Labs can be completed +/- 5 days of scheduled visit

Circumstances may arise beyond our control where subject may not be able to complete required lab work, required visit, and/or bevacizumab at the scheduled time. Although every effort will be made to avoid scheduling conflicts, it is possible that the clinic visits and/or lab evaluations may be missed at times.

3.5.5 Daily Monitoring

Blood Pressure- Patient will be asked to measure and record his/her blood pressure at least once a day and will be provided with a BP monitor. Patients will be instructed to record BP readings on a BP monitoring diary which will be provided and will be reviewed by the research nurse/PI/AI at each clinic visit. In addition, patients will call the UOB research team for readings above 140/90 mmHg and may be instructed to have elevated readings confirmed by a local health care provider.

Patient will be instructed take their own BP daily with recognition that there will be occasions where there are missed BP readings due to unforeseen circumstances or patient oversight.

3.5.6 Study Calendar

Cycle	**Screening**	**Baseline**	**1**		**2**		**3**	**Every 2 weeks**	**Every Cycle**	**Restaging cycles[l] (End of Cycle 2 onward)**	**Disease Progression / End of Therapy [m]**
Day (D) of Cycle (+/- 5 days)			**1**	**15**	**1**	**15**	**1**		**1**		
Informed consent		X									
Complete Medical history and physical exam	X[a]	X[b]									
Study Eligibility incl availability of tissue and confirmation of dx	X										
Targeted History & Focused Physical [o]			X[d]		X		X		X		X
Vital signs/weight [o]	X[a, j]		X	X	X	X	X	X	X		X
ECHO	X[a]	X[b]									
12-lead ECG	X[a]	X[b]									

Cycle	**Screening**	**Baseline**	**1**		**2**		**3**	**Every 2 weeks**	**Every Cycle**	**Restaging cycles[l] (End of Cycle 2 onward)**	**Disease Progression / End of Therapy [m]**
Day (D) of Cycle (+/- 5 days)			**1**	**15**	**1**	**15**	**1**		**1**		
Acute Care Panel, Mineral Panel. Hepatic Panel, Total Protein, CK, Uric Acid, LD, CBC with differential[p]	X[d]		X[d]		X		X		X		X
Urinalysis and spot protein/creat[p]	X[d]		X[d]	X	X	X	X	X	X		
Pregnancy test	X[d]		X[d]		X		X		X		
ECOG PS[m]	X[a]	X[b]			X		X		X		X
Scans for Radiological and Clinical Tumor Assessment (RECIST)[q]	X[a]	X[b]					X			X	
MRI/CT Brain	X[a]	X[b]									

Cycle	**Screening**	**Baseline**	**1**		**2**		**3**	**Every 2 weeks**	**Every Cycle**	**Restaging cycles[l] (End of Cycle 2 onward)**	**Disease Progression / End of Therapy [m]**
Day (D) of Cycle (+/- 5 days)			**1**	**15**	**1**	**15**	**1**		**1**		
PET Scan[q]	X[a]	X[b]								X[f]	
Bone Scan[q]	X[a]	X[b]								X[e]	
Sample for Biomarkers		X			X		X			X[g]	X
Tumor biopsy (optional)		X			X						
Review of Patient Side Effect Diary/Pill Count Form					X		X		X		X
Tolerability/ AE reporting[n]					X		X		X		X
Concurrent treatment	X[a]		X		X		X		X		X
Dermatology Consult	X[h]										

Cycle	**Screening**	**Baseline**	**1**		**2**		**3**	**Every 2 weeks**	**Every Cycle**	**Restaging cycles[l] (End of Cycle 2 onward)**	**Disease Progression / End of Therapy [m]**
Day (D) of Cycle (+/- 5 days)			**1**	**15**	**1**	**15**	**1**		**1**		
Photography of skin lesions	X[a, h]	X[b, h]								X[h]	
TSH	X[a,i]	X[b, i]			X		X			X	
Anti-Mullerian Hormone, FSH, LH, estradiol, progesterone[k]	X[a]	X[b]								X	
Serum Lactic Acid	X[a]	X[b]								X	
Free T4; anti-TPO and TSI; and lipid panel	X[a]	X[b]									

a. Should be performed within 4 weeks prior to enrollment on study

b. Should be performed within 4 weeks prior to initiation of study therapy. Does not need to be repeated if performed within this timeframe at screening.

c. May be performed within 7 days prior to the initiation of study therapy. Does not need to be repeated if performed previously within this timeframe.

d. Should be performed within 7 days prior to enrollment on study

e. To be repeated at restaging if abnormal initially

f. If required clinically

g. Following cycles 2, 4, 6, and 8 for VEGF; and prior to therapy, C2D1, and C3D1 for CEC/CEP

h. Only in patients with HLRCC associated cutaneous leiomyomas

i. if elevated, T3

j. Vital signs will be done when clinically indicated by prescriber

k. In premenopausal women

l. Restaging cycles occur every 8 weeks during the 1st 8 cycles (32 weeks), then every 3 cycles (12 weeks) thereafter

m. Approximately 30 days following the last dose of study therapy

n. May be completed by remote visit with a member of the study team (e.g., if the patient is not able to return to the NIH CC). Remote visits will be conducted in compliance with NIH guidelines and FDA regulations. A patient may be referred to their local provider or asked to come to the NIH CC for an in-person assessment, if clinically indicated, and at the discretion of the PI. In the case of any visits with participants' local providers, records will be obtained.

o. Full physical exams and vital signs may be omitted during follow up visits if a patient is unable to return at the NIH Clinical Center and if the clinical evaluation does not indicate a need for collection.

p. As results are comparable across laboratories, if the patient is not able to return to the NIH Clinical center, laboratory tests may be obtained locally.

q. In the event that the patient is unable to return to the NIH Clinical Center during a follow up visit, imaging may be delayed, but will be completed as soon as feasible. Collection of research blood or urine will be omitted or collected in a delayed fashion.

3.6 Concurrent, Restricted and Excluded Therapies

Co-administration of erlotinib and drugs with potent CYP3A4 inhibitor effects is not allowed nor is the use of ciprofloxacin. Agents with potent inducer effects on CYP3A4 should be avoided where possible. Other agents with some modulation of and/or metabolization through CYP3A4 can be used with caution at the discretion of the Principal Investigator (see **3.6.1**).

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study.

Use of concurrent investigational agents to treat RCC is not permitted.

Grapefruit juice is a CYP3A4 inhibitor, therefore, consumption of grapefruit or grapefruit juice should be avoided during erlotinib treatment.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the exposure of erlotinib (AUC) by 46% and the maximum concentration (Cmax) by 61%. There was no change to Tmax or half-life. Therefore, drugs that alter the pH of the GI tract may alter the solubility of erlotinib and hence its bioavailability and should be avoided when possible.

In a single-dose study in healthy volunteers, the AUC was reduced by 64% in smokers when compared with nonsmokers. In BR.21, current smokers achieved erlotinib trough plasma concentrations that were approximately 2-fold lower than never smokers. Smokers should be advised to stop smoking while taking erlotinib as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking.

3.6.1 Restrictions

- Warfarin is allowed in therapeutic and low-doses and these patients should be monitored regularly for changes in their International Normalized Ratio (INR).
- The following agents that affect metabolism by the CYP450 3A4 or CYP450 1A2 systems will be avoided when possible and used only when considered necessary, after discussion with the PI or a responsible associate investigator- metronidazole, aprepitant, albendazole, phenobarbitol, modafinil, phenytoin, quinine, omeprazole, rabeprazole, rifampin (**Appendix C**).

3.7 Surgical Guidelines

Major elective surgical procedures should not be scheduled during protocol treatment or within 4 weeks of the last dose of bevacizumab. Patients undergoing unexpected major surgical procedures should have bevacizumab and erlotinib withheld. Treatment may be resumed at a later date at the discretion of the PI (bevacizumab should not be resumed earlier than 4 weeks post-operatively, with adequately healed incisions).

3.8 Radiation Therapy Guidelines

Patients requiring radiation therapy for RCC will discontinue study treatment.

3.9 Cost and Compensation

3.9.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.9.2 Compensation

Participants will not be compensated on this study.

3.9.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.10 Criteria for Removal from Protocol Therapy and Off Study Criteria

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.10.1 Off Treatment Criteria

Treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s) (as outlined in Section **3.3**)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Positive pregnancy test
- Investigator discretion

3.10.2 Follow Up

Patients with unresolved toxicities will be followed per section **5.1**.

Patients who stop treatment for reasons other than progression will be followed when possible in order to determine time to progression and overall survival. Follow-up will be performed either through visits to/evaluations at the NIH CC or at their local physician's office with records forwarded to us. Scans will be obtained at approximately 3-month intervals following discontinuation of treatment. Survival status may be obtained through publicly available data sources as well as other NIH protocols in which participants are co-

enrolled.

3.10.3 Off Study Criteria

- Investigator discretion
- Death
- Participant requests to be removed from study
- Patients will be taken off study at progression or if the patient is unable to comply with follow-up visits/evaluations.

4 SUPPORTIVE CARE

Supportive care will be provided in accordance with good medical practice.

5 DATA COLLECTION AND EVALUATION

5.1 Data Collection

Data will be prospectively collected and entered in a designated database (C3D). All radiographic images will be stored in the Dept. of Radiology, Clinical Center, NIH and will be reviewed by NIH CC staff radiologists.

Patients treated both inside and outside of NIH will require source documentation regarding dosage and timing of drug administration. For patients treated outside NIH, results of lab, radiology and pathology tests should be faxed to the PI. Data from NIH will be located in the CRIS. Data managers can enter the data from both sources electronically into the NCI C3D database.

Note: No patients are treated outside of NIH starting with Amendment V.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Document AEs from the first study intervention, Study Day 1, through 30 days after the agent was last administered.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **8.2.1**.

5.2 Response Evaluation

For the purposes of this study, patients should be re-evaluated for response every *8* weeks during the first 32 weeks and every 12 weeks thereafter. In addition to a baseline scan,

confirmatory scans should also be obtained ≥*4* weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).(48) Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

In patients with HLRCC, renal tumors, uterine leiomyomas and skin leiomyomas will be assessed independently. Renal tumors and uterine leiomyomas will be evaluated using RECIST criteria. For skin leiomyomas up to three lesions will be measured in the longest dimension. The following criteria will be used to determine response/progression.

- Partial response – decreased of 30% or more in sum of longest dimension compared to baseline.
- Complete response – complete disappearance of all measured/target and non target lesions.
- Progressive disease – increase of 20% or more in sum of longest dimension compared to smallest recorded sum of target lesions or appearance of one or more new lesions.
- Stable disease – no change in lesions or change insufficient to meet criteria for response or progressive disease.

5.2.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with either bevacizumab or erlotinib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

5.2.1.1 Measurable disease

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as:

- By chest x-ray: ≥20 mm;
- By CT scan:
    - Scan slice thickness 5 mm or under: as ≥10 mm
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

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

5.2.1.2 Non-measurable disease

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

5.2.1.3 Target lesions

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 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, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which

circumstance 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 diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

5.2.1.4 Non-target lesions

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.

5.2.2 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.

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

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.

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.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: 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.

Endoscopy, Laparoscopy: 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.

Tumor markers: 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. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published. (49-51) I In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.(52)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., 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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

5.2.2.1 Response Criteria

5.2.2.2 Evaluation of Target Lesions

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

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

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 progressions).

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

5.2.2.3 Evaluation of Non-Target Lesions

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.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

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 at a later time by the review panel (or Principal Investigator).

5.2.2.4 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.

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	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as 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."* 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		

5.2.3 Confirmatory Measurement/Duration of Response

5.2.3.1 Confirmation

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

5.2.3.2 Duration of Overall Response

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

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.

5.2.3.3 Progression Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

5.2.3.4 Overall Survival

5.3 Overall survival (OS) is defined as the duration of time from the date of study enrolment until time of death. Patients without a death event will be censored at the date survival assessment was last evaluated (e.g., clinic visit, phone call).Toxicity Criteria

CTCAE term (AE description) and grade: 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).

6 STATISTICAL CONSIDERATIONS

This is a phase II study to establish whether treatment with bevacizumab and erlotinib in patients with metastatic HLRCC and papillary type 2 renal cancer results in an adequate overall response rate to warrant further development.

Patients will be enrolled in four cohorts:

Cohorts 1 and 3: Patients with metastatic HLRCC renal cancer, diagnosed by either germline mutation of the FH gene, or based upon evidence of the clinical syndrome of HLRCC (characteristic renal cancer histology, cutaneous leiomyomas, uterine fibroids, and a family history)

Cohorts 2 and 4: Patients with sporadic papillary renal cancer.

6.1.1 For Cohorts 1 and 2 (see section **6.2** for cohorts 3 and 4)

The study will be designed with a Simon two-stage minmax design in two cohorts (i.e., separate design for each cohort). In each cohort, 13 patients will be accrued in the first stage. If there are no responses (either CR or PR) in 13 patients, accrual to the cohort will be terminated, and the treatment will be considered ineffective for the cohort. If at least one

patient responds among the 13 patients, then 7 additional patients will be accrued to the cohort. If 3 or more patients of 20 respond, then the treatment will be considered worthy of future investigation for that cohort. In either cohort, if fewer than 3 patients respond, the treatment will not be considered worthy of additional investigation for that cohort.

For each cohort, the two-stage minmax design is based on assuming an ineffective response rate of 5% and a targeted effective response rate of 25%. We also assume that the probability of accepting an ineffective treatment and the probability of rejecting an effective treatment are each 10%. With this design, we have a 51% chance of stopping accrual to a cohort at the end of the first stage if the response rate in that cohort is 5%.

Secondary objectives are listed in Section **1.1.2**. The follow-up times for biomarker endpoints are given in Section **3.4**. Analyses will focus on comparing changes in these biomarkers on treatment from the pre-study measurement. Longitudinal changes in continuous biomarkers (e.g. plasma VEGF) or imaging outcomes will be analyzed using paired Wilcoxon-ranked sum tests (which compares measurements at a single post-treatment time point with measurements at the pre-treatment time point) as well as with linear mixed models (which incorporates all follow-up times when evaluating change). Evaluation of time to progression and progression free survival will be based on restaging studies performed as outlined and will be summarized using Kaplan-Meier curves. Overall survival will be determined using the Kaplan-Meier method and include any-cause death.

6.2 Accrual Ceiling

The accrual ceiling for this study was originally 20 evaluable patients for each cohort. With an expected accrual of 5-8 patients per year for the sporadic RCC cohort, we expect to complete accrual within 3-4 years, while we anticipate that it will take 4-5 years to complete accrual to the HLRCC cohort (4-5 patients per year). The accrual ceiling for Cohort 2 has been increased to 21; this is to enable replacement of one subject in this cohort, who is deemed inevaluable.

Expansion Cohorts (Cohorts 3 and 4): The study was originally designed with a Simon two-stage minimax design separately for each of two cohorts, assuming an ineffective response rate of 5% and a targeted effective response rate of 25%. In addition, it was assumed that the probability of accepting an ineffective treatment and the probability of rejecting an effective treatment were each 10%. With this design, in each cohort, 13 patients were to be accrued in the first stage. If at least one patient responded among the 13 patients, 7 additional patients were to be accrued to the cohort. If 3 or more patients of 20 respond, then the treatment will be considered effective and worthy of future investigation.

As of May 2014, accrual for both cohorts had been completed; 20 patients had been enrolled on cohort 1 (patients with HLRCC associated RCC) and 21 patients had been enrolled in cohort 2 (non HLRCC/sporadic papillary RCC). The overall response rate at this time in cohort 1 was 60% (12/20 PRs) and that in cohort 2 was 29% (6/21 PRs). Additionally, there was one unconfirmed partial responder in each cohort. Since the number of responses in both arms has far exceeded the minimal 3 responses for the treatment to be deemed effective, further investigation of the treatment is warranted.

We propose an expansion of the current study with two additional patient cohorts, one each

for patients with HLRCC associated kidney cancer (cohort 3, N=20) and sporadic/non HLRCC papillary kidney cancer (cohort 4, N=20). We feel that several important issues can be better addressed by expanding the current protocol to include these additional cohorts. Some of these issues include:

Estimating the true response rate in each cohort with higher precision.

Allowing further exploratory biomarker analysis- While the response rates are high, particularly in the HLRCC cohort, the extent and duration of response was not uniform. This heterogeneity is particularly apparent in the non HLRCC cohort, with some patients experiencing significant and durable responses while others demonstrated rapidly progressive disease or appeared to derive only modest benefits. After this study was initiated, we have gained further insights into the molecular/biochemical pathways operating in HLRCC tumors; additionally, emerging data suggest that HLRCC tumors and some sporadic papillary tumors might share aberrant activation of some certain pathways, notably oxidative stress responses mediated by activation of the NRF2 pathway (53, 54). While the archival tissue obtained on the trial so far will allow us to study components of this pathway as potential biomarkers, additional samples obtained on the expanded trial will allow a more comprehensive evaluation.

The sample size for the expanded study was established by determining the number of patients required to have a 95% confidence interval of specified width for a given response rate. We assume the true response rate is 50% and 30% for cohort 3 and cohort 4, respectively. In order to have the expected width of the Wilson's score confidence interval be 0.4 (e.g. to distinguish a response rate greater than 0.7 from a response rate less than 0.3), it requires approximately 20 patients in cohort 3. For cohort 4 with 20 patients the expected width of the Wilson's score confidence interval is 0.37 (e.g. to distinguish a response rate greater than 0.52 from a response rate less than 0.15).

We will also estimate the response rate of combined samples from the current and expanded study. However, the response rate based on the naïve sample proportion of responses is biased, because it does not account for the fact that there has been at least one response in the first stage to continue to the second stage and more than 3 responses to expand the study for further investigation. We will derive a maximum likelihood estimate to take into account these truncation effects. Nevertheless, since the number of observed responses far exceeds these thresholds, the impact of these truncated effects is likely small (55). As a result, the sample proportion of response from the combined samples would likely be nearly unbiased and more precise (i.e. shorter 95% confidence interval) than the estimate based on either the original study or new added cohort alone. For example, without adjusting for the truncation effect, with the combined total of 40 patients in cohort 1, the expected width of the Wilson's score confidence interval would be 0.3.

Results of cohorts 3 and 4 will be combined with the results of cohort 1 and 2, respectively. The combined response rate needs to account for the fact that there had been at least one response in the first stage to continue to the second stage and more than 3 responses to expand the study. This is accomplished by obtaining the maximum likelihood estimator for the combined response rate, where the likelihood function is the product of two truncated binomial probability function for the responses in the two stages of the first cohort times the binomial probability function for the expanded cohort. The product of the two truncated

binomial probabilities equals the product of two binomial probabilities conditional on at least one response was observed in the first stage of the first cohort and at least 3 responses were observed in the entire first cohort. The maximum likelihood estimator of the combined response rate for the combined cohort 2 and cohort 4 will be obtained similarly. The maximum likelihood estimator does not have a closed-form solution and the Newton-Raphson algorithm would be used to obtain a numerical estimate of the combined response rate.

A total of 40 additional evaluable patients will be accrued. To allow for inevaluable patients, the accrual ceiling will be set at 22 patients for each additional cohort (cohorts 3 and 4). The total accrual ceiling for the entire trial (cohorts 1-4) will therefore be 85 patients. We estimate that an additional 2 years will be needed to complete accrual to cohorts 3 and 4.

7 HUMAN SUBJECTS PROTECTION

7.1 Rationale for Subject Selection

7.1.1 Research subject selection

Patients of all races and ethnic origins will be eligible.

7.1.2 Participation of Children

This protocol will exclude children below 18 years of age since there are no safety data available in this group of patients.

7.2 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **7.5**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation to assess ongoing capacity of the subjects and to identify an LAR, as needed.

Please see section **7.6.1** for consent procedure.

7.3 Evaluation of Benefits and Risks/Discomforts

7.3.1 Potential benefits

The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or outcome.

7.3.2 Potential risks

7.3.2.1 Study Drugs

Potential risks of study drugs include the possible occurrence of any of a range of side effects

that are listed in the consent document.

The most common risks of bevacizumab include nose bleeds, hypertension, fatigue, skin rash, headache and soreness in mouth or throat.

The most common risks of erlotinib include skin rash, diarrhea, appetite loss and fatigue.

The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described in Section **3**.

7.3.2.2 Blood Draws

Side effects of blood draws include pain and bruising, lightheadedness, and rarely, fainting.

7.3.2.3 ECG/Echocardiogram

Some skin irritation can occur where the ECG/EKG electrodes are placed. The test is completely painless, and generally takes less than a minute to perform.

There is no physical risk involved with echocardiogram. Side effects of an echocardiogram are discomfort from the transducer being firmly placed against the chest.

7.3.2.4 Scans

The radiation risks of the CT/PET and bone scans are discussed in section **7.3.2.6**. In addition to radiation risks, scans that employ contrast may cause allergic reactions, injection site reactions abdominal discomfort and fainting. MRIs carry no radiation risks but are contraindicated in participants with metal in their bodies. In participants that receive gadolinium contrast with MRIs, allergic reactions, injection site reactions and kidney damage may occur.

7.3.2.5 Serial biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

Biopsies may be performed with CT guidance. If that is the case, then this research study involves exposure to radiation as outlined in section **7.3.2.6**.

7.3.2.6 Radiation

In this research study, participants may have up to 2 CT-guided biopsies, 8 CT scans, 6 bone scans and up to 6 PET scans performed per year for disease assessment. Subjects undergoing scans will be exposed up to 13.68 rem annually. This level of exposure is associated with an increased risk of cancer.

7.4 Alternative Treatments

Patients will be apprised of other therapeutic options, both experimental and those of standard care.

7.5 Risk/Benefit Analysis

There are currently no standard therapeutic options for patients with metastatic renal cell carcinoma associated with HLRCC or for patients with advanced sporadic papillary RCC, who have a poor prognosis with most dying from metastatic disease and its sequelae. Patients participating in this trial may derive a benefit from the treatment administered. Although the individual agents used in this trial are not experimental, use of the combination of bevacizumab and erlotinib has not yet been FDA approved. However, the combination has been administered safely in prior phase I and II trials, and the majority of the side effects have been mild to moderate. The mechanism of action of the drugs suggests that the drugs could potentially render benefit in patients with some types of papillary renal cancer.

7.6 Consent Process and Documentation

The informed consent document will be provided as a physical or electronic document to the participant or consent designee(s) as applicable for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with policy, including HRPP Policy 303) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

Note: When required, witness signature will be obtained similarly as described for the investigator and participant as described below.

Consent will be documented with required signatures on the physical document (which includes the printout of an electronic document sent to participant). When required, witness signature will be obtained similarly as described for the investigator and participant.

For the optional biopsy for research, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

7.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **7.3**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **7.6**.

7.7 Patient Records and Quality Assurance

Complete records must be maintained on each patient treated on the protocol. These records will include primary documentation to confirm that:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol.
- Toxicity was assessed according to protocol.
- Response was assessed according to protocol.

8 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

8.1 Definitions

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

8.2 OHSRP Office and of Compliance and Training/IRB Reporting

8.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

8.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

8.3 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention **s**hould be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

9 MANUFACTURER SAFETY REPORTING

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death, and any study specific issue of concern.

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

9.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of study treatment and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

9.2 Definitions

9.2.1 Adverse Event

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with HLRCC or Sporadic Papillary Renal Cell Cancer that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations).

9.2.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization (see elaboration in **9.4.2**)
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and

may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.3 Adverse Events of Special Interest (AESIs)

AESIs are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the manufacturer is required. Such an event might require further investigation in order to characterize and understand it.

Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Data related to a suspected transmission of an infectious agent by the study drug (STIAMP), as defined below:

Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

9.2.3.1 Bevacizumab Events of Special Interest

- Hypertension ≥ grade 3
- Proteinuria ≥ grade 3
- GI perforation, abscesses and fistulae (any grade)
- Wound healing complications ≥ grade 3
- Hemorrhage ≥ grade 3 (any grade CNS bleeding; ≥ grade 2 hemoptysis)
- Arterial thromboembolic events (any grade)
- Venous thromboembolic events ≥ grade 3
- PRES (any grade)
- CHF ≥ grade 3
- Non-GI fistula or abscess ≥ grade 2

9.2.3.2 Erlotinib Event of Special Interest

Interstitial Lung Disease (ILD)

9.2.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

9.2.5 Relationship to Study Product

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

9.3 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to either bevacizumab or erlotinib (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of bevacizumab or erlotinib, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to bevacizumab or erlotinib; and/or the AE abates or resolves upon discontinuation of bevacizumab or erlotinib or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than bevacizumab or erlotinib (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to bevacizumab or erlotinib administration (e.g., cancer diagnosed 2 days after first dose of study drug).

9.4 Procedures for Eliciting, Recording, and Reporting Adverse Events

9.4.1 Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

9.4.2 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see section **9**), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female subject becomes pregnant while receiving investigational therapy or within 6 months after the last dose of study drug, or if the female partner of a male study subject becomes pregnant while the study subject is receiving the study drug or within 6 months after

the last dose of study drug, a report should be completed and expeditiously submitted to the Genentech, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to bevacizumab and erlotinib should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior bevacizumab or erlotinib exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE adequately to Genentech Drug Safety during follow up period.

g. Reconciliation (Case Transmission Verification of Single Case Reports)

The Investigator agrees to conduct reconciliation for the product. The Investigator will ensure that all single case reports have been received by Genentech.

The Investigator agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the Investigator emailing Genentech a Quarterly line-listing documenting single case reports sent by the investigator to Genentech in the preceding time period. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the Investigator and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The Investigator shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech shall be forwarded by Investigator to Genentech within five (5) calendar days from request by Genentech.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech by Investigator.

9.5 Adverse Event Reporting to Genentech

9.5.1 Non-serious Adverse Events

- All non-serious adverse events will be reported to Genentech both quarterly and at the conclusion of the study in a concatenated format using the Case Transmission Verification (CTV) form (see **APPENDIX D**). Please email the completed CTV form to CTVIST_Drugsafety@gene.com.
- All non-serious adverse events for Genentech quarterly and at conclusion of study include the following:
- All non-serious Grade 2 unexpected events that are possibly, probably or definitely related to the research and

- All non-serious Grade 3 that are possibly, probably or definitely related to the research.
- Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to 30 days following the last dose of the trial drug.

9.5.2 Exchange of Single Case Reports

The investigator will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs), AEs of Special Interest (AESIs), Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the Study for the Product.

Investigators must report all the above-mentioned single case reports adequately to Genentech within the timelines described below. The completed MedWatch or CIOMS I form or Genentech approved reporting forms should be faxed/emailed immediately upon completion to Genentech at the following contacts:

All protocol-defined AEs, SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints *with* an AE should be sent to:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

All Product Complaints *without* an AE should be sent to:

Email: kaiseraugst.global_impcomplaint_management@roche.com

It is understood and agreed that the Sponsor will be responsible for the evaluation of AEs/SAEs, AESIs, Special Situation Reports (including pregnancy reports) and Product Complaints (with or without an AE) originating from the study.

These single case reports will be exchanged between the parties as outlined below so that regulatory obligations are met.

Serious adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation Reports and Product Complaints (with or without an AE), where the patient has been exposed to the Genentech Product, will be sent on a MedWatch form or CIOMS I form or on Genentech approved reporting forms to Genentech Drug Safety. Transmission of these reports (initial and follow-up) will be either electronically or by fax and within the timelines specified below:

SADRs

Serious AE reports that are related to the Product shall be transmitted to Genentech within fifteen (15) calendar days of the awareness date.

Other SAEs

Serious AE reports that are unrelated to the Product shall be transmitted to Genentech

within thirty (30) calendar days of the awareness date.

AESIs

AESIs shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

9.6 Additional Reporting Requirements to Genentech

9.6.1.1 Special Situation Reports

Pregnancy reports

While such reports are not serious AEs or Adverse Drug Reactions (ADRs) per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the bevacizumab or erlotinib, shall be transmitted to Genentech within thirty (30) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of bevacizumab and erlotinib. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to Genentech within thirty (30) calendar days of the awareness date.

Other Special Situation Reports

In addition to all SAEs, pregnancy reports and AESIs, the following other Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech within thirty (30) calendar days:

- Data related to the Product usage during breastfeeding
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors)
- In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

9.6.1.2 Product Complaints

All Product Complaints (with or without an AE) shall be forwarded to Genentech within fifteen (15) calendar days of the awareness date.

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

- Note: Investigators should also report events to their IRB as noted in section **8.2**.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Sections C&D), the report should include the following information within the Event Description (section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

9.7 Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at:
https://www.fda.gov/media/69876/download

9.8 Study Close-Out

Any study report submitted to the FDA by the Investigator should be copied to Genentech. This includes the final study report. Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be sent to the assigned Clinical Operations contact for the study at Avastin-gsur@gene.com and to Genentech Drug Safety CTV oversight mailbox at: ctvist_drugsafety@gene.com.

9.9 Queries

Queries related to the study will be answered by the investigator. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the investigator and Genentech.

The investigator agrees that Genentech shall have the final say and control over safety queries relating to the Bevacizumab and Erlotinib (while supplied by Genentech). The investigator agrees not to answer such queries from regulatory authorities and other sources relating to the Bevacizumab independently but shall redirect such queries to Genentech.

The PI and Genentech will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The PI and Genentech will clearly indicate on the request the reason for urgency and the date by which a response is required.

9.10 Safety Crisis Management

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the study, may lead to labeling changes or regulatory actions that limit or restrict the way in which Bevacizumab and Erlotinib (while supplied by Genentech) is used, or where there is media involvement, the party where the crisis originates will contact the other party as soon as possible.

The investigator agrees that Genentech shall have the final say and control over safety crisis management issues relating to the Bevacizumab and Erlotinib (while supplied by Genentech). The investigator agrees not to answer such queries from regulatory authorities and other sources relating to the Bevacizumab independently but shall redirect such queries to Genentech.

9.11 Reporting to Regulatory Authorities and Investigators

Genentech as the Marketing Authorization Holder will be responsible for the reporting of individual case safety reports from the study to the regulatory authority in compliance with applicable regulations.

The PI will be responsible for the expedited reporting of safety reports originating from the study to the Institutional Review Boards (IRB) as noted in Section **8.2.1**.

The PI will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

9.10 Other Reports

The investigator will forward a copy of the Final Study Report to Genentech upon completion of the Study.

10 COLLABORATIVE AGREEMENTS

10.1 Cooperative Research and Development Agreement (CRADA)

The agents supplied by Genentech used in this protocol is provided to the NCI CCR under a Cooperative Research and Development Agreement (CRADA) between Genentech [hereinafter referred to as Collaborator], CRADA #02407. Therefore, the following obligations/guidelines, in addition to the provisions in the Intellectual Property Option to Collaborator contained within the terms of award, apply to the use of Agents in this study:

Agents may not be used for any purpose outside the scope of this protocol, nor can Agents be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agents are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient participating on

the study or patient's family member, the individual should sign a confidentiality agreement.

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

NCI must 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.

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

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.

Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations

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.

Any data provided to Collaborator(s) for phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial

Any manuscripts reporting the results of this clinical trial must be provided to Genentech for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to Genentech prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to Genentech. No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or

termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and Genentech and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

11.2 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.3 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National

Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11.4 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

12 PHARMACEUTICAL INFORMATION

12.1 Bevacizumab

12.1.1 Source

Source: Bevacizumab is commercially available. Bevacizumab will be supplied by Genentech.

How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in two vial sizes:

- Each 100 mg (25 mg/mL – 4 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.
- Each 400 mg (25mg/ml – 40 mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

12.1.2 Physiochemical Properties

Classification: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody composed of human IgG1 framework regions and antigenbinding complementarity-determining regions from a murine monoclonal antibody (muMAb VEGF A.4.6.1). Approximately 93% of the amino acid sequence, including most of the antibody framework, is derived from the human IgG1, and approximately7% of the sequence is derived from the murine antibody

Other Names: Recombinant humanized monoclonal anti-VEGF antibody (rhuMAB VEGF, Avastin®)

Code Number: rhuMAb VEGF, RO4876646

12.1.3 Molecular characterization

Chemical Structure: human IgG1 framework regions and antigenbinding complementarity-determining regions from a murine monoclonal antibody

Molecular Weight: ~149,000 daltons

Description: Clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution of IV infusion

Mechanism of Action: Inhibition of vascular endothelial growth factor (VEGF) resulting in inhibition of angiogenesis.

12.1.4 Toxicity

Please refer to package insert

12.1.5 Formulation and Preparation

Preparation: Vials contain no preservatives and are intended for single use only. Place the calculated dose in 100 mL of 0.9% sodium chloride for injection.

12.1.6 Stability and Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

12.1.7 Administration Procedures

Route of Administration: Intravenous

12.1.8 Incompatibilities

Please refer to package insert for further information.

12.2 Erlotinib

12.2.1 Source

Source: Erlotinib is commercially available. Erlotinib will be initially supplied by Genentech. Once Genentech is no longer able to supply erlotinib for this study, erlotinib will be purchased from commercial sources by the NIH Pharmacy.

How Supplied: Erlotinib is supplied as white film-coated tablets for daily oral administration, available in tablets of 25 mg, 100mg, and 150 mg each.

12.2.2 Physiochemical Properties

Classification: Erlotinib is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Facot Receptor (Her1/EGFR) tyrosine kinase inhibitor.

Other Names: OSI-774; Tarceva

12.2.3 Molecular characterization:

Chemical Structure: Erlotinib is a quinazolinamine with the chemical name N-(3ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4$-HCl

Molecular Weight: 429.90

Description: Off-white to pale yellow powder.

Mechanism of Action: Highly selective EGFR tyrosine kinase inhibitor.

12.2.4 Toxicity

Please refer to package insert

12.2.5 Formulation and Preparation

Formulation: Erlotinib tablets are available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg, and 163.9 mg) equivalent to 25 mg, 100 mg, and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose,

hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.

12.2.6 Solubility and Storage

Storage: Tablets should be stored at 25º C (77º F); excursions permitted to 15-30º C (59-86º C)

Solubility: Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol, and practically insoluble in acetonitrile, acetone, ethyl acetate, and hexane. Aqueous solubility of erlotinib hydrochloride is dependent on pH, with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4mg/mL occurs at a pH of approximately 2.

12.2.7 Administration Procedures

Route of Administration: Oral

12.2.8 Incompatibilities

Erlotinib is metabolized predominantly by CYP3A4, and potent inhibitors of CYP3A4 increase exposure while potent CYP3A4 inducers increase clearance of erlotinib. Please refer to package insert for further information and a partial list of interacting agents.

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13 APPENDIX A: ECOG PERFORMANCE STATUS

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

14 APPENDIX B: NEW YORK HEART ASSOCIATION (NYHA) CARDIAC CLASSIFICATION

The NYHA classification system relates symptoms to everyday activities and the patient's quality of life.

Class	**Symptoms**
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

15 APPENDIX C: LIST OF INTERACTING DRUGS

The following lists are not exhaustive and are only intended as a guide.

Potent inhibitors of CYP450 3A4- Prohibited at study entry and concomitantly while on erlotinib

Amprenavir
Atovaquone
Clarithromycin
Clotrimazole
Cyclosporine
Diltiazem
Erythromycin
Fluconazole
Gemfibrozil
Grapefruit, Grapefruit juice
Indinavir
Isoniazid
Itraconazole,
Ketoconazole
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telithromycin
Troleandomycin
Verapamil
St.John' Wort

Inhibitors of CYP450 3A4-To be avoided when possible; use only when considered necessary after discussion with PI/medically responsible investigator

Aprepitant

Metronidazole

Potent inhibitors of CYP450 1A2 (with or without additional inhibioton of CYP450 3A4-Prohibited at study entry and concomitantly while on erlotinib

Fluoroquinolone antibiotics such as ciprofloxacin, levofloxacin, and norfloxacin

Amiodarone

Cimetidine

Fluvoxamine

Mibefradil

Ticlopidine

Potential inducers of CYP450 1A2-To be avoided when possible; use only when considered necessary after discussion with PI/medically responsible investigator

Albendazole

Modafinil

Omeprazole

Phenobarbital

Phenytoin

Quinine

Rabeprazole

Rifampin

16 APPENDIX D: CASE TRANSMISSION VERIFICATION FORM

See below.

Supported Study Case Transmission Verification Form

Principle Investigator Name		
Genentech Study Number:		
Sponsor Study Number:		
Country of Occurrence:		
Reporting Period:	**From:**	**To:**
Periodic or Final Case Transmission Verification (CTV):	**Periodic CTV** ☐	**Final CTV** ☐

Details of Person Completing the Form:

Name:	
Date:	
Telephone Number:	**Email address:**

☐ **No Adverse Events (AEs), Adverse Events of Special Interest (AESIs) or Special Situation Events per study were submitted to the company's drug safety department in the reporting period listed above**

The following is a list of AEs, AESIs and other Special Situation Events per study submitted to the company's drug safety department in the reporting period listed above:

Case Number *(Company Use Only)*	Date of Awareness of AE *(Day-Mon-Year)*	Date AE sent to US Drug Safety	Patient's Study ID	Patient's Initials	Suspect Drug(s)	Event Term	Serious or Non Serious	Outcome	Causality

For any additional events continue on an additional form.
Please email the completed CTV form to CTVIST_Drugsafety@gene.com

For any additional events continue on an additional form.
If any AEs, AESIs or other Special Situation Events per study have been identified that were not reported to the company, report them immediately and contact the company's drug safety department.

Supported Study Case Transmission Verification Form

For Company Use Only:	
Date CTV form was reviewed:	
Name of reviewer:	
Signature of reviewer:	
Case Transmission Verification	
Section A	
All Adverse Events, Adverse Events of Special Interest and other Special Situation Events per study have been received by the drug safety department? ☐ Yes ☐ No (If no, complete **Section B**) No Adverse Event(s), Adverse Event(s) of Special Interest or other Special Situation Events per study reported: ☐	
Section B	
Provide a list of Adverse Event(s), Adverse Event(s) of Special Interest or other Special Situation Events per study not received by the drug safety department:	
Date CTV form sender was contacted:	
Date Adverse Event(s), Adverse Event(s) of Special Interest or other Special Situation Events per study were received by the drug safety department:	