A Phase II Study of Regorafenib in Patients with Progressive, Recurrent/Metastatic Adenoid Cystic Carcinoma

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-arm phase II study evaluating the clinical efficacy of regorafenib in the treatment of patients with progressive, recurrent/metastatic adenoid cystic carcinoma (ACC). Any number of prior therapies for recurrent/metastatic ACC is allowed. There are two primary endpoints for the study: 1) proportion of patients alive at 6 months without disease progression by RECIST v1.1 criteria (6-month PFS), and 2) best overall response rate (BOR = CR+PR) documented by RECIST v1.1 criteria. The secondary endpoints are the safety and tolerability of regorafenib. An exploratory endpoint is analyzing tumor tissues for biomarkers that correlate to regorafenib clinical efficacy. Patients enrolled in the study will be treated with regorafenib 160 mg orally daily for 3 weeks in a 4 week cycle. Dose reductions and delays can be implemented according to criteria outlined in Section 11. RECIST v1.1 tumor assessments will be made at baseline (CT or MRI) and then approximately every 2 cycles (or every 8 weeks (+/- 1 week)). After 10 months, imaging will be done approximately every 3 cycles (or every 12 weeks (+/- 1 week)). Patients may remain on study until progression of disease or unacceptable toxicity. Other reasons patients could potentially come off study include patient non-compliance, patient withdrawal of consent, or physician's clinical judgment that removal of the patient from the study is in his/her best interest.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives

1) To determine the proportion of patients alive at 6 months without disease progression by RECIST v1.1 criteria of patients with progressive, recurrent/metastatic ACC treated with regorafenib.

2) To determine the best overall response rate documented by RECIST v1.1 criteria of patients with progressive, recurrent/metastatic ACC treated with regorafenib.

Secondary Objective

To determine the safety/tolerability of regorafenib.

Exploratory Objective

To perform tumor tissues analyses for putative biomarkers and explore their association with regorafenib clinical efficacy.

3.0 BACKGROUND AND RATIONALE

Recurrent/metastatic (R/M) ACC

Adenoid cystic carcinomas (ACCs) are malignant neoplasms composed of epithelial and myoepithelial cells that commonly arise from both minor and major salivary glands. Rarely, ACC may also originate at other sites, such as the trachea, lung, and breast. While localized disease is potentially curable, nearly 40% of patients develop distant metastasis despite aggressive surgery and radiation with disease-free intervals ranging from 1 month to 19 years[1,2]. Metastatic disease is incurable and can be either indolent (10% of patients with distant metastases survive more than 10 years) or alternatively more aggressive (54% of patients with distant metastases survive less than 3 years)[2]. There are no effective therapies and the development of new treatments is urgently needed.

Systemic therapies tested in R/M ACC to date possess limited effectiveness

We conducted an exhaustive review of all chemotherapy studies conducted between 1966 and 2009 for R/M ACC which included 34 clinical trials that involved less than 500 patients[3]. Most were small, single institution studies of variable methodological quality. In this literature, only 18 objective major responses out of 141 patients (13%) treated with single agent cytotoxic chemotherapy were reported. Mitoxantrone as a single agent was studied in the most number of patients in clinical trials of variable quality; the pooled response rate (an imperfect estimate of true activity) from these studies was around 10%[4,5]. Ultimately, the true response rate of cytotoxic chemotherapy can only be concluded to be modest; the actual rate of response is difficult to ascertain across several different trials of variable quality. Insufficient data exists to suggest that combination chemotherapy improves response rates or clinical benefit over single agent treatment.

Given the limited efficacy of cytotoxic drugs, several targeted therapies have also been tested. With up to 90% of ACC tumors possessing high c-kit expression and case reports of responses to imatinib, six studies have been reported for imatinib in ACC with disappointingly only 2 objective responses in 71 evaluable patients[6-11]. Studies with gefitinib, cetuximab, lapatinib, and bortezomib all have failed to yield any objective responses[3].

The oncogenic transcription factor c-myb is overexpressed in ACC

In 2009, Persson et. al. confirmed the existence of a t(6;9)(q22-23;p23-24) translocation in ACC tumors of the breast and head/neck[12] (Figure 1A). This cytogenetic alteration creates a gene fusion of the c-myb and NFIB transcription factors. The translocation was identified in all 11 tumors analyzed. The *MYB-NFIB* fusion characterized in that publication predominantly involved a breakpoint between intron 14 of *MYB* and intron 8 of *NFIB*. Minimally, this resulted in the loss of the last 38 amino acids on the c-myb protein and the addition of the last 5 amino acids of the NFIB protein to the C-terminal end of the truncated c-myb gene (Figure 1). This results in the loss of several microRNA binding sites in the 3' UTR ("untranslated region") of the *MYB* gene, leading to upregulated levels of c-myb expression in ACC tumors relative to non-ACC tumors at both the mRNA transcript and protein level[12,13]. c-myb overexpression presumably enhances transcriptional activity of c-myb, leading to the overexpression of 14 *MYB* target genes, including *vascular endothelial factor A (VEGFA), KIT*, *fibroblast growth factor -2 (FGF2),* and *BCL2*[12], all of which have been previously proposed to be potentially critical genes for therapeutic targeting in ACC.

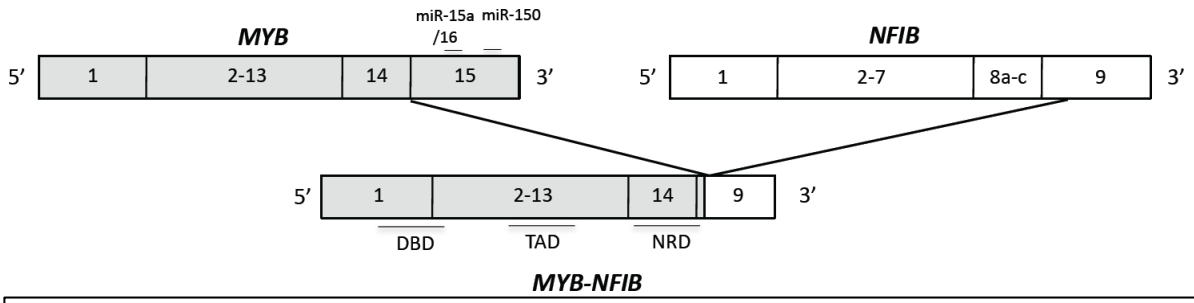

Figure 1. Schematic of the t(6;9) translocation. *DBD*, DNA Binding Domain; *TAD*, Transactivation Domain; *NRD*, Negative Regulatory Domain; *miR*, microRNA. Adapted from Persson et. al. "Recurrent fusion of MYB and NFIB transcription factor genes in carcinomas of the breast and head and neck". PNAS, 2008.

Mitani et. al. recently published a comparative analysis of 123 salivary gland cancers (72 primary ACC tumors, 17 ACCs metastatic to the lung and lymph nodes, and 34 salivary tumors of other non-ACC histologies) and 5 normal salivary gland tissue samples[13]. These authors observed that the *MYB-NFIB* fusion gene was present in 27.7% of primary ACCs, 35.2% of metastatic ACCs, and none of the non-ACC salivary cancer histologies or normal salivary tissues. As expected, elevated *MYB* expression was detected in 85% of fusion positive tumors at about 100-fold higher levels than non-ACC tumors. Interestingly, 70% of fusion negative tumors also demonstrated elevated c-myb expression at an approximately 40-fold higher level over non-ACC tumors and just 2-fold lower than fusion-positive ACCs, suggesting alternate mechanisms of c-myb overexpression and supporting the hypothesis that c-myb plays a central role in the pathogenesis of this disease.

c-myb is a bona fide oncogene. It was first discovered as the transforming gene co-opted by the Avian myeloblastosis virus (AMV) and later the *MYB* gene locus was identified as a common integration site for several avian and murine retroviruses leading to the development of leukemia[14]. It was recently reported that the *MYB* gene locus is involved with chromosomal translocations and genomic duplications associated with a new subtype of human T-cell acute leukemia[14,15]. *MYB* overexpression has also been described in solid tumors. In colon cancer, *MYB* overexpression has been reported in >80% of cases[14] and when found expressed with Bcl-xl correlates with poor prognosis[16]. *MYB* overexpression has also been implicated in the pathogenesis of breast, melanoma, pancreatic, and esophageal cancers[14].

Results from two whole exome and genome sequencing projects in ACC have recently been reported[17,18]. These analyses revealed a relatively "quiet" genome with a low somatic mutation rate (0.31 non-silent events per megabase[17]) and wide mutational diversity. These studies verified the importance of MYB in ACC biology with one study confirming 57% of tumors possessed the *MYB-NFIB* translocation and an additional 8% had alterations resulting in MYB pathway dysregulation[17]. Mutations in chromatin-remodeling genes were also a prominent feature in the genetic landscape of ACCs (35%[17] and 50%[18] rates of mutation in the two studies). Alterations in several other biologic pathways were found to occur at lower frequencies.

Targeting c-myb activity in ACC

Devising strategies to directly block the function of a non-kinase transcription factor is a challenge. One approach is to inhibit the activity of critical c-myb target genes responsible for promoting oncogenesis. An analysis of 7 fusion positive ACC tumors confirmed that *MYB* overexpression indeed correlates to upregulation of 14 *MYB* transcriptional target genes, including the regorafenib-relevant targets *VEGFA (*ligand that induces angiogenesis by engaging VEGF receptors (VEGFRs)), FGF2 (ligand that activates a subset of FGF receptors (FGFRs)), and the receptor tyrosine kinase (RTK) *KIT* (c-kit)[12].

Regorafenib-relevant pathways and targets in ACC

Beyond c-myb mediated activation, several lines of evidence suggest that VEGFR, c-kit, and FGFR pathways are potentially critical to ACC biology.

VEGF pathway: High levels of VEGF ligand have been detected in salivary malignancies in general, and ACC specifically, correlating to more advanced clinicopathologic features (including stage, recurrence, and metastases) in several studies[19-21]. Multivariate analyses have also shown that high VEGF expression in ACC tumors is an independent prognostic factor for survival[21]. These data suggest that the VEGF pathway may be critical for ACC pathogenesis and/or progression for tumors that overexpress VEGF ligand.

c-kit: c-kit is highly expressed in >90% of ACCs[22-26]. A 2004 case report described impressive clinical responses in two patients with c-kit positive ACC treated with 600 mg daily of imatinib mesylate, a small molecule inhibitor of c-kit and platelet derived growth factor receptor (PDGFR)[27]. While subsequent imatinib studies failed to show significant clinical activity [6-11], one requiring “strong” c-kit expression and progressive disease at study entry reported two responses out of 15 evaluable patients[11]. A recent phase II study of dasatinib also failed to produce RECIST responses in ACC patients, though 52% of the patients with progressive disease at study entry did have stable disease on drug[28]. These data indicate that c-kit targeting only has modest efficacy at best, and leaves open the possibility that combining c-kit inhibition with other ACC-relevant kinase targets may produce greater efficacy.

FGF pathway: There is now emerging evidence that the FGF pathway is activated in adenoid cystic carcinomas. Immunohistochemistry revealed that FGF1, FGF2, and FGFR1 are expressed in ACCs, while normal salivary tissues are completely negative or only weakly positive for these proteins[29]. The recent characterization of the genetic landscape of ACCs revealed mutations in FGF16 ligand, FGFR2, and FGFR4[17,18] as well as a tandem duplication within FGFR2 discovered in one tumor[17]. Interestingly, transgenic mice overexpressing *FGF8b* develop salivary cancers, and injection of FGF ligand in a 9,10-dimethyl-1,2-benzanthracene (DMBA) carcinogenesis mouse model for salivary malignancies increased the incidence of salivary cancer formation. Such data suggests that the FGF pathway is activated in ACC and may contribute to salivary cancer oncogenesis.

Preliminary clinical efficacy data for multi-kinase inhibitors in ACC

Evidence for both MYB-dependent and -independent mechanisms of VEGFR/c-kit/FGFR activation in ACC biology has raised interest in evaluating multikinase inhibitors against

these targets in ACC patients. Preliminarily, studies have suggested clinical activity with these agents. The first study conducted was a phase II trial of sunitinib (VEGFR, PDGFR, KIT inhibitor) in patients with progressive, recurrent/metastatic ACC[30]. While no responses were observed, 8 out of the enrolled 14 patients had stable disease for 6 months or more, potentially meaningful given that progressive disease was required for enrollment[30]. Results from a sorafenib[31] (VEGFR, PDGFR inhibitor) and a dovitinib[32] (VEGFR, PDGFR, FGFR1-3, KIT inhibitor) phase II ACC trial were reported in abstract form at the 2013 ASCO Annual meeting. Both agents elicited an approximately 11% response rate. An axitinib (VEGFR, PDGFR, c-kit inhibitor) phase II study also recently completed enrollment at MSKCC. The data has not yet been presented, but the study was a 2-stage design that met the clinical efficacy rule required for progressing to the second stage. These preliminary data suggest that combined VEGFR, PDGFR, c-kit inhibition plus or minus FGFR targeting translates to some clinical efficacy in ACC.

Regorafenib

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI)[33].

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Ab1 at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models.

Preclinical data with regorafenib

In vivo, regorafenib exhibited anti-angiogenic and anti-proliferative effects in human colon and breast xenografts as demonstrated by a reduction in microvessel area, reduced Ki-67 staining, and reduced pERK1/2 staining in tissue sections from tumor xenografts, and dose-dependent inhibition of growth in multiple xenograft models (breast, colon, renal, NSCLC, melanoma, pancreatic, thyroid, ovarian)[33]. Immunohistochemical ex-vivo studies with a phospho–specific monoclonal anti-ERK 1 / 2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB 231 and BxPC-3), but not in NSCLC (H460).

In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody[33]. These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

Clinical experience with regorafenib

Two phase III global randomized studies have evaluated the efficacy of regorafenib. The CORRECT (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy) trial is an international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 760 patients with mCRC whose disease has progressed after approved standard therapies[34]. Metastatic colorectal cancer patients were randomized to regorafenib plus best supportive care (BSC) or placebo plus BSC. Treatment cycles consisted of 160 mg of regorafenib (or matching placebo) once daily for three weeks on / one week off plus BSC. The primary endpoint of this trial was overall survival. Secondary endpoints included progression-free survival, objective tumor response rate and disease control rate. The safety and tolerability of the two treatment groups were also compared.

At a preplanned second interim analysis, there was a statistically significant survival benefit for regorafenib. The estimated hazard ratio for overall survival was 0.773 (95% confidence interval [CI], 0.635 to 0.941; 1-sided p = .0051). Patients treated with regorafenib had a median overall survival of 6.4 months, compared with 5.0 months for placebo — a 29% increase in survival. In addition to improved overall survival, progression-free survival was superior; median progression-free survival was 1.9 months (95% CI, 1.88 to 2.17) for regorafenib and 1.7 months (95% CI, 1.68 to 1.74) for placebo. The estimated hazard ratio for progression-free survival was 0.493 (95% CI, 0.418 to 0.581; 1-sided p< .000001). There was a substantial difference in disease control rate in the regorafenib and placebo groups (44% vs. 15%; p<.000001). Regorafenib demonstrated comparable efficacy benefits across patient subgroups analyzed including age, number of mets, number of lines of prior therapy, and kras status.

The most frequent grade 3+ adverse events in the regorafenib group were hand–foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). The efficacy and safety from the CORRECT study supported FDA approval in September 2012.

The efficacy and safety of regorafenib were examined in the Phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options[35]. The study involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib. Patients were randomized 2:1 to regorafenib (160 mg orally once daily on a 3 weeks on/1 week off cycle) or placebo, plus best supportive care.

The results showed that treatment with regorafenib led to a statistically significant 3.9-month improvement in progression-free survival (PFS), compared with placebo (4.8 months vs. 0.9 months; hazard ratio [HR] = 0.27; p <.0001). Overall survival was statistically similar between groups as expected due to a trial design that allowed crossover to regorafenib for disease progression (85% for placebo and 31% regorafenib randomized patients). The median survival period without tumor growth among patients on regorafenib was 4.8 months while for the control group on placebo it was less than a month. The overall disease control rate combining partial responses with durable stable disease for at least 12 weeks was 53% with regorafenib compared with 9% in the control

group. The most common grade ≥3 adverse events associated with regorafenib were hand-foot skin reaction (56.1%), hypertension (48.5%), and diarrhea (40.9%). The efficacy and safety of the GRID study data supported FDA approval February 2013.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a single-arm phase II study of patients with progressive, recurrent/metastatic adenoid cystic carcinoma (R/M ACC) treated with regorafenib. There are two primary objectives for the study: 1) to determine the proportion of patients alive at 6 months without disease progression by RECIST v1.1 criteria (6-month PFS), and 2) to determine the best overall response rate (BOR = CR+PR) documented by RECIST v1.1 criteria. Thirty-eight patients will be enrolled in the study. If at least 21 patients are alive and free of progression at 6-month, or if at least 5 patients have a response at any time while being enrolled in the study, the regimen will be considered worthy of further investigation. Regorafenib safety and tolerability will be assessed utilizing Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) as a secondary endpoint. An exploratory objective is to analyze tumor tissue in order to identify potential biomarkers that correlate to regorafenib clinical efficacy.

4.2 Intervention

All eligible patients will receive a starting regorafenib dose of 120 mg daily taken orally for 3 weeks in a 4-week cycle. Patients for whom regorafenib dose reduction was not performed or required may have their treatment dose increased to the FDA-approved dose of 160 mg daily orally for 3 weeks in a 4-week cycle in cycle #2 or beyond (this is not mandatory). RECIST v1.1 tumor assessments will be made at baseline (CT or MRI) and then approximately every 2 cycles (or every 8 weeks (+/- 1 week)). After 10 months, imaging will be done every 3 cycles (or every 12 weeks (+/- 1 week)). Patients may remain on study until progression of disease or unacceptable toxicity

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Regorafenib (Bayer) or its major human active metabolites M-2 and M-5 inhibits the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Ab1 at concentrations of regorafenib that have been achieved clinically.

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 tablets and a 3-gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F). The study drug must be exclusively used for the investigation specified in this protocol and it will only be accessible to authorized staff.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patients must have pathologically or cytologically confirmed adenoid cystic carcinoma. Cancers arising from non-salivary gland primary sites are allowed.
- Patients must have recurrent and/or metastatic disease not amenable to potentially curative surgery or radiotherapy.
- At least 2 weeks must have elapsed since the end of prior systemic treatment (4 weeks for bevacizumab- containing regimens) or radiotherapy with resolution of all treatment-related toxicity to NCI CTCAE Version 4.0 grade ≤1 (or tolerable grade 2) or back to baseline (except for alopecia, lymphopenia, or hypothyroidism). Any number of prior therapies for recurrent/metastatic ACC are allowed.
- Patients must have RECIST v1.1 measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan.
- Patients must have documentation of a new or progressive lesion on a radiologic imaging study performed within 6 months prior to study enrollment (progression of disease over any interval is allowed) **and/or** new/worsening disease related symptoms within 6 months prior to study enrollment. Note: This assessment will be performed by the treating investigator. Evidence of progression by RECIST criteria is not required.
- Patients must have archival tissue from the primary tumor or metastases available for correlative studies. Either a paraffin block or twenty unstained slides are acceptable. If twenty slides are not available, a lesser amount may be acceptable after discussion with the Principal Investigator, Dr. Alan L. Ho.
- Patients must agree to undergo biopsy of a malignant lesion. Biopsies do not need to be done if either the investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient. Patients may also be exempt if frozen tumor tissue has been collected within 12 months of study enrollment that the Principal Investigator deems is appropriate/sufficient for analysis on this protocol.
- Age ≥ 18 years.
- ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
- Life expectancy of at least 12 weeks (3 months) as determined by the investigator.
- Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements:

- Total bilirubin ≤ 1.5 x the upper limits of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Alkaline phosphatase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
- Lipase ≤ 1.5 x the ULN
- Amylase ≤ 1.5 x the ULN
- Serum creatinine ≤ 1.5 x the ULN or calculated creatinine clearance ≥60 ml/min
- Platelet count ≥ 100,000 /mm3, hemoglobin (Hb) ≥ 9 g/dL, absolute neutrophil count (ANC) ≥1500/mm3. Blood transfusion to meet the inclusion criteria will not be allowed.

- Women of childbearing potential must have a negative serum pregnancy test performed within 2 weeks prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the consent form until at least 3 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Subject must be able to swallow and retain oral medication.

6.2 Subject Exclusion Criteria

- Concurrent anti-cancer therapy (chemotherapy, definitive radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment. Concurrent therapy with bisphosphonates or denosumab for bone metastases is allowed. Palliative radiation to non-target lesions is also allowed.
- Prior use of regorafenib.
- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form).
- Concurrent use of strong CYP3A4 inhibitors (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole). or strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort).
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Active or clinically significant cardiac disease including:
    - Congestive heart failure – New York Heart Association (NYHA) > Class II.
    - Active coronary artery disease that is not medically treated.
    - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
    - Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) is not allowed if the medication dose and/or INR/PTT are not considered stable by the treating physician. If the dose and/or INR/PTT are stable, therapeutic anticoagulation with Vitamin-K antagonists is allowed with close monitoring. Anticoagulation with heparin or heparinoids is allowed.
- Evidence or history of bleeding diathesis or coagulopathy.
- Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.
- Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of study treatment.
- Subjects with a past or current diagnosis of another malignancy that will interfere with conduct of the trial. Patients with past or current cancer diagnoses other than ACC are allowed to enroll if the investigator believes it will not interfere with trial conduct.
- Patients with phaeochromocytoma.
- Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
- Active infection that would impair the ability of the patient to receive study treatment.
- Symptomatic metastatic brain or leptomeningeal tumors (asymptomatic or treated metastatic brain and leptomeningeal tumors are allowed).
- Presence of a non-healing wound or non-healing ulcer that is not tumor related.
- Renal failure requiring hemo-or peritoneal dialysis.
- Patients with seizure disorder requiring medication.

- Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
- History of organ allograft (including corneal transplant).
- Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
- Any malabsorption condition.
- Women who are pregnant or breast-feeding.
- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. Patient recruitment most likely will occur in the medical oncology clinics of the Head and Neck Disease management team. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Investigators will discuss the study and review/sign the informed consent documents with the patient.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review.

8.0 PRETREATMENT EVALUATION

Within 30 days of starting treatment, the following tests need to be done:

- History and Physical Examination
- Vital signs, including weight
- Performance Status (ECOG or Karnofsky Performance Status)
- Electrocardiogram (ECG)
- Radiology studies (CT or MRI) for disease assessment.

- Record of concomitant medications
- Signed Informed Consent Form
- Request for archival tumor tissue (if tissue is not already available at MSKCC; receipt of tissue is not required for study enrollment or initiation.)
- Research tumor biopsy (this can be performed any time prior to start of study drug): Patients may be exempt from biopsy if either the investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient. Patients may also be exempt if frozen tumor tissue has been collected within 12 months of study enrollment that the Principal Investigator deems is appropriate/sufficient for analysis on this protocol. For those undergoing research biopsy on protocol, radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered reasonably safe for the patient. Tissue will be flash frozen in liquid nitrogen as directed by the Principal Investigator (the biopsy sample(s) will be placed into a cryovial, which will be submerged in a liquid nitrogen bath until the tissue is frozen.) Some tissue may be prepared by fixation according to institutional guidelines as directed by the Principal Investigator.
- Research blood draw (this can be performed any time prior to start of study drug): approximately 10 mL of blood, preferably in a lavender top tube (with EDTA).

Within 14 days of starting treatment, the following tests need to be done:

- Complete Blood Count (including platelets)
- Comprehensive Panel, including liver function tests (Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium), LDH, phosphorus
- Coagulation studies consist of the prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). These are only required for patients on anti-coagulation medications (heparin, low-molecular weight heparin, or coumadin). These do not need to be checked for patients not on these anti-coagulation medications.
- Lipase
- Serum pregnancy test in women of child-bearing potential.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Administration

Regorafenib 120 mg daily taken orally will be administered for 3 weeks on /1 week off. One cycle is 28 days. Three 40-mg regorafenib tables should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast. Some examples of low fat breakfasts are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).

- One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

Patients for whom regorafenib dose reduction was not performed or required may have their treatment dose increased to the FDA-approved dose of 160 mg daily orally for 3 weeks in a 4-week cycle in cycle #2 or beyond (this is not mandatory).

If doses are missed or vomited, this must be indicated in the patient's pill diary. Missed doses not directed by the investigator(s) that constitute ≤ 20% of the mandated doses for a given cycle will not be considered (a) protocol violation(s). Missed or skipped doses will not be made up (i.e., the week/day count on therapy will continue regardless of whether doses have been missed or skipped). Study treatment will be administered in cycles of 4 weeks in duration. Patients will bring their pill diaries for review at their clinic visits but it will not be considered a protocol violation if the patient forgets the diary.

Patients will receive a sufficient supply of study drug to last until their next scheduled appointment.

9.2 Concomitant Medications and Therapies

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation. Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided on protocol, if possible.

Co-administration of a strong CYP3A4 inducer (rifampin) with a single 160 mg dose of Stivarga decreased the mean exposure of regorafenib, increased the mean exposure of the active metabolite M-5, and resulted in no change in the mean exposure of the active metabolite M-2. Avoid concomitant use of Stivarga with strong CYP3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort)

Co administration of a strong CYP3A4 inhibitor (ketoconazole) with a single 160mg dose of Stivarga increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of Stivarga with strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazodone, posaconazole, telithromycin, and voriconazole). Please refer to http://medicine.iupui.edu/flockhart/ for additional information regarding drug interactions with cytochrome P450 isoenzymes.

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates or denosumab.
- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are considered stable by the treating physician.

9.3 Schedule of Events (for ALL patients initiating treatment)

9.3.1 Patients will initiate treatment with regorafenib on Week 1, Day 1. The required laboratory tests (detailed in **Section 10**) can be performed up to 7 days prior to initiation of treatment. It is unnecessary to repeat these laboratory tests if the screening assessments of the same tests were performed within 7 days prior to first dose of therapy. All other Week 1 evaluations (detailed in **Section 10**) may be performed up to 3 days prior to initiation of study treatment.

9.3.2 The onset of regorafenib-induced hypertension often occurs during the first cycle of treatment for most patients who develop hypertension. During the first 6 weeks of treatment, it is strongly recommended that patients have their blood pressures checked even in weeks that they are not evaluated at MSKCC. There are no restrictions on how the blood pressure is to be obtained during those weeks, and can include monitoring on home blood pressure equipment, at other physician offices, at MSKCC, or at commercial outlets. Blood pressure values may be recorded in the pill diaries that will be reviewed at each MSKCC clinic visit or verbally reported to the study team. If the systolic blood pressure is >150 mm Hg and/or the diastolic blood pressure is > 90 mm Hg and/or symptoms develop that are perceived to be related to elevated blood pressure (for example headaches or visual disturbance), patients will be instructed by study staff to contact their study physician immediately for guidance. A re-check of the blood pressure can be requested at the study physician's discretion to determine the accurate value of the patient's blood pressure before protocol-dictated action(s) is/are taken in response to a reported blood pressure value (this applies both to recommended and protocol-mandated blood pressures taken at MSKCC or outside of MSKCC). The study

physician may at his/her discretion determine which external values likely reflect the true blood pressure to guide clinical decision-making.

9.3.3 Patients for whom regorafenib dose reduction was not performed or required may have their treatment dose increased to the FDA-approved dose of 160 mg daily orally for 3 weeks in a 4-week cycle in cycle #2 or beyond (this is not mandatory).

9.3.4 Patients will be required to complete a pill diary concerning their use of regorafenib every 28 days. If a patient misses a dose of regorafenib for personal reasons (i.e. forgetting to take medication, nausea, etc.), the missed dose should be documented on the patient's pill diary (Appendix B). Missed doses not directed by the investigator(s) that constitute ≤ 20% of the mandated doses for a given cycle will not be considered (a) protocol violation(s). Doses held at the discretion of the physician are never protocol violations. Missed or skipped doses will not be made up (i.e., the week/day count on therapy will continue regardless of whether doses have been missed or skipped).

9.3.5 Evaluations during treatment will be performed according to the schedule detailed in **Section 10**. Guidelines for dose reductions are provided in **Section 11**.

9.3.6 Tumor measurements with CT and/or MRI will be performed as outlined in **Section 10.**

9.3.7 Treatment may be discontinued at any time for progression of disease, unacceptable toxicity, patient withdrawal of consent, patient non-compliance, or investigator judgment.

9.4 Correlative Studies

Exploratory Objective: To perform tumor tissues analyses for biomarkers that correlate to regorafenib clinical efficacy.

9.4.1 *Background Studies/Preliminary Data:* We hypothesize that ACC responses to regorafenib will be linked to baseline activation of the vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor receptor (FGF), and/or c-kit (CD117) pathways via overexpression of the oncogenic transcription factor c-myb and/or other mechanisms outlined in Section 3.0. In order to evaluate this hypothesis, the studies described below will be performed upon both archival and research biopsy tissues, depending on the availability of funding. Included amongst these studies are exploratory approaches that may also suggest myb-independent mechanisms that may mediate drug susceptibility or resistance.

9.4.2 *Study Plan for fixed tissue:* Studies evaluating c-myb protein expression, t(6;9) translocation status, the VEGF/PDGF/FGF/KIT pathways, and other potentially relevant genes/proteins will be conducted in fixed tissues.

Expression of VEGF/PDGF/FGF/KIT pathway proteins will be evaluated by immunohistochemistry (IHC). c-myb expression will also be evaluated by IHC. The presence or absence of the t(6;9) translocation will be assessed by fluorescent in-situ hybridization (FISH). These studies will be performed upon collected archival

samples and/or the fixed portions of the research biopsies obtained on this study, depending on the availability of tissue. Evaluation of the t(6;9) fusion breakpoint may also be pursued with RT-PCR cDNA amplification and sequencing if feasible, though the need for high yield and quality RNA to perform this analysis may necessitate using frozen tissues obtained from the research biopsies.

We anticipate that all 38 patients will have archival tissue available for these analyses. We will explore correlations between the tumor IHC status of the target proteins listed above, as well as presence of the t(6;9) translocation, with clinical benefit from regorafenib. Please see Section14.0 for biostatistical considerations for these studies.

9.4.3 *Study Plan for research biopsy tissues:* (to be performed in MSKCC Core facilities and Dr. Timothy Chan's laboratory (MSKCC HOPP) The research biopsy samples will be divided for fixation and flash freezing at the discretion of the Principal Investigator. A member of the research team will be present at the biopsy procedure and transport the tissues to the MSKCC Tumor Procurement Service for accessioning. The tissues will then be transported by the research team to Dr. Chan's Human Oncology and Pathogenesis Program (HOPP) laboratory in the Zuckerman Research Center for analysis and storage. These samples will be used to evaluate the genomic and transcriptomic landscape of the tumors with the exploratory goal of evaluating myb-dependent and/or -independent markers of regorafenib susceptibility and resistance.

DNA and RNA will be extracted from frozen samples and/or paraffin tissue. The research peripheral blood sample collected on the study will be used as a control, matched normal sample (microdissection of normal tissue in the tumor samples may also be used for this purpose).

DNA will be submitted for whole exome or whole genome sequencing (in collaboration with Dr. Timothy Chan's group). It is possible that at the time these studies are to be conducted a customized-panel of ACC specific alterations that can be analyzed in a highly sensitive array based approach from fixed tissues will be available. In that scenario, fixed tissue from the collected archival tissue or the research biopsies will be used for this genomic analysis, preserving the frozen tissue for other assays. Hence, the specific assay that will be employed to analyze for genomic alterations will be dependent upon the technology available at the time of analysis. Comparisons of DNA between tumor and normal tissue (from the research blood draw) will be performed as appropriate, thus generating germline sequence data. There is no intention to analyze the germline data beyond utilizing it as a normal control for the tumor tissue analysis, and generally germline data will not be communicated to the patient.

The following procedure will be followed by MSKCC investigators for the unique situation in which a potentially actionable incidental finding has been discovered in the course of research conducted on samples collected under this protocol:

In the event an investigator's research identifies a finding that he or she believes should be communicated to the subject (and/or family designee), the investigator shall communicate this to the OCR-IRB. The finding will be reviewed by a group convened by the IRB to determine whether the incidental finding should be discussed with the subject. In the event that group convened by the IRB determines that the finding should be discussed with the subject, and the subject has consented to be re-contacted, then the treating/consenting physician shall be contacted by the OCR-IRB representative and asked to refer the subject to the Clinical Genetics Service for further discussion of the research finding. After appropriate counseling and consent, the Clinical Genetics Service will request permission to confirm the result in a New York DOH-approved laboratory prior to communication of the specific result. If the patient is not available (e.g. deceased), then the surrogate designated on the consent will be contacted and the above will occur.

We hypothesize that the transcription factor c-myb is a central driver of ACC oncogenesis, presumably through activation of an oncogenic transcriptional program. Several c-myb target genes have been previously identified, but a c-myb transcriptional signature in ACC has yet to be defined. Extracted RNA will be analyzed with gene expression arrays on the Affymetrix GeneChip system, or some other equivalent technology that may be available at the time of analysis.

Frozen tissues from the research biopsy may be evaluated for relevant protein targets by Western blot or other proteomic assays that may be available at time of analysis.

Assuming that only approximately 10% of patients do not qualify for the research biopsy, we anticipate obtaining biopsies on 34 patients. Please Section 14.0 for the biostatistical considerations for these studies.

9.4.4 *Study Plan for research biopsy tissues:* (to be performed in MSKCC Core facilities or Champions Oncology Inc.) Emerging evidence suggests that mouse patient derived xenografts (PDXs) models can be faithful representations of *in situ* human cancer biology, and be used to predict clinical drug efficacy in patients. ACC PDX models have been created by other groups, and represent the only experimental model system in which new therapeutic approaches and ACC biology can be explored pre-clinically. Patients who will undergo a research biopsy on this protocol and have sufficient tissue to create PDX models may be selected to have a portion of their biopsy submitted for this purpose. These patients will be approached to sign consent for IRB protocol #06-107, “Storage and Research Use of Human Biospecimens” and the models will be created as outlined in IRB protocol #14-091(PI: Dr. Elise DeStanchina) , “Establishment and Characterization of Unique Mouse Models Using Patient-Derived Xenografts”. These models will be established by the MSKCC Antitumor Assessment Core Facility, our institutional core facility responsible for establishing and testing xenograft mouse models. Alternatively, through a collaboration established with Champions Oncology, Inc., patient’s tumors may be collected and sent to Champions for model creation and conduct of experiments. Those models will be provided back to Memorial Sloan Kettering Cancer Center for research purposes.

Portions of the research biopsy may also be used to establish cell line or spheroid *in vitro* models in Memorial Sloan Kettering Cancer Center. Such efforts will help develop new laboratory systems to help interrogate ACC biology and develop novel therapeutic approaches that build upon findings from this clinical/correlative study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Study Calendar

Regorafenib taken orally will be administered for 3 weeks on /1 week off. One cycle is 28 days. The evaluations/tests scheduled for Cycles 1 through 3+ may be performed up to 3 days prior to the start of the week designated in the table below if not otherwise specified. After Cycle 12 and beyond, MD visits and labs are required every odd cycles, and labs only during even cycles.

	Pre-Study[a]	C1 Wk 1	C1 Wk 2	C1 Wk 3	C1 Wk 4	C2 Wk 1	C2 Wk 2	C2 Wk 3	C2 Wk 4	C3+ Wk1	C12+ Even Wk 1	C13+ Odd Wk 1	Off Study[g]
Regorafenib[b]		X	X	X		X[b]	X	X		X	X	X	
Informed consent	X												
Medical history	X												
Concurrent meds	X	X- -X											X
Physical exam	X	X[d]	X	X		X		X		X[f]		X[f]	X
Vital signs	X	X[d]	X	X		X		X		X[f]		X[f]	X
Blood pressure monitoring (on non-clinic weeks)[j]					X		X						
Weight	X	X[d]	X	X		X		X		X[f]		X[f]	X
Performance status	X	X[d]	X	X		X		X		X[f]		X[f]	X
CBC w/diff, plts	X	X[e]		X		X		X		X[f]	X[f]	X[f]	X
Comprehensive panel[c]	X	X[e]		X		X		X		X[f]	X[f]	X[f]	X
Lipase, Amlyase blood test	X												
Coagulation studies[l]	X	X		X		X		X		X[f]	X[f]	X[f]	
ECG	X												
Beta-HCG (serum)	X[k]												
Request for archival tumor tissue	X												
Research tumor biopsy[h]	X												
Research blood draw	X												
Adverse event evaluation		X- -X[m]											X
Tumor measurements[i]	X	CT and/or MRI will be performed every 8 weeks (+/- 1 week) (<u>or</u> approximately every 2 cycles). After 10 months, scans will be performed every 12 weeks (+/- 1 week)(<u>or</u> approximately every 3 cycles). Documentation (radiologic) must be provided for patients removed from study for progressive disease. Objective responses should be confirmed with a second assessment performed at least 4 weeks later. **Every effort should be made to have tumor measurements performed 6 months (+/- 1 week) after the start of treatment, if possible, for assessment of the primary endpoint.**											
	a: See Section 8.0 for the timing of these tests/evaluations prior to the start of therapy. b: Patients will start the study taking regorafenib 120 mg orally daily for 3 weeks in a 4 week cycle**.** Patients for whom regorafenib dose reduction was not performed or required may have their treatment dose increased to the FDA-approved dose of 160 mg daily orally for 3 weeks in a 4-week cycle in cycle #2 or beyond (this is <u>not</u> mandatory). If a patient misses a dose of regorafenib for personal reasons (i.e. forgetting to take medication, nausea, etc.), the missed dose should be documented on the patient's pill diary (Appendix B). Missed doses not directed by the investigator(s) that constitute ≤ 20% of the mandated doses for a given cycle will not be considered (a) protocol violation(s). Doses held at the discretion of the physician are never protocol violations. Missed or skipped doses will not be made up (i.e., the week/day count on therapy will continue regardless of whether doses												

	have been missed or skipped). c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. d: These Week 1 evaluations may be performed up to 3 days prior to the start of treatment. e: These Week 1 laboratory tests may be done up to 7 days prior to starting treatment. It is unnecessary to repeat these laboratory tests if the screening assessments of the same tests were performed within 7 days prior to the first dose of therapy. f: After the completion of Cycle 2, the CBC, serum chemistry blood tests, coagulation studies (if required), physical examinations, vitals signs, performance status, and weight will be done once every cycle, preferably on week 1 of every cycle. If the patient cannot be seen on week 1, these evaluations may be completed up to 1 week prior or during another week within the cycle at the discretion of the treating physician. g: Off-study evaluation will be performed within 30 days of the patient's last dose of regorafenib. h: Patients may be exempt from biopsy if either the investigator or person performing the biopsy judges that no tumor is accessible for biopsy or that biopsy poses too great of a risk to the patient. Patients may also be exempt if frozen tumor tissue has been collected within 12 months of study enrollment that the Principal Investigator deems is appropriate/sufficient for analysis on this protocol. For those undergoing research biopsy on protocol, radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered reasonably safe for the patient. Tissue will be flash frozen in liquid nitrogen as directed by the Principal Investigator (the biopsy sample(s) will be placed into a cryovial, which will be submerged in a liquid nitrogen bath until the tissue is frozen.) Some tissue may be prepared by fixation according to institutional guidelines if directed by the Principal Investigator. i: The treating physician may reschedule radiology scans due to treatment delays at his or her discretion. If the patient has CT and/or MRI scans completed early for any reason (i.e. suspicion of disease progression), the next set of scans may be ordered in 8 weeks (+/- 1 week) from that assessment (or in 12 weeks (+/- 1 week) for patients who are on treatment for more than 10 months). **Every effort should be made to have tumor measurements performed 6 months (+/- 1 week) after the start of treatment, if possible, for assessment of the primary endpoint.** j: The onset of regorafenib-induced hypertension often occurs during the first cycle of treatment for most patients who develop hypertension. During the first 6 weeks of treatment, it is strongly recommended that patients have their blood pressures checked even in weeks that they are not evaluated at MSKCC. There are no restrictions on how the blood pressure is to be obtained during those weeks, and can include monitoring on home blood pressure equipment, at other physician offices, at MSKCC, or at commercial outlets. Blood pressure values may be recorded in the pill diaries that will be reviewed at each MSKCC clinic visit or or verbally reported to the study team. If the systolic blood pressure is >150 mm Hg and/or the diastolic blood pressure is >90 mm Hg and/or symptoms develop that are perceived to be related to elevated blood pressure (for example headaches or visual disturbance), patients will be instructed by study staff to contact their study physician immediately for guidance. A re-check of the blood pressure can be requested at the study physician's discretion to determine the accurate value of the patient's blood pressure before protocol-dictated action(s) is/are taken in response to a reported blood pressure value (this applies both to recommended and protocol-mandated blood pressures taken at MSKCC or outside of MSKCC). The study physician may at his/her discretion determine which external values likely reflect the true blood pressure to guide clinical decision-making. k. Serum pregnancy test is required within 14 days of drug treatment for all women of child-bearing potential. l. Coagulation studies consist of the prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). These are only required as indicated on the calendar for patients on anti-coagulation medications (heparin, low-molecular weight heparin, or coumadin). These do not need to be checked for patients not on these anti-coagulation medications. m. During even cycles after cycle 12, adverse event will be conducted by phone assessment.

11.0 TOXICITIES/SIDE EFFECTS

The starting dose of regorafenib is 120 mg once daily. Study medication will be administered on a 3 weeks on/1 week off schedule (3 weeks out of every 4). Patients for whom regorafenib dose reduction was not performed or required may have their treatment dose increased to the FDA-approved dose of 160 mg daily orally for 3 weeks in a 4-week cycle in cycle #2 or beyond (this is not mandatory).

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines described in sections below. Dose modifications will follow predefined dose levels. Dose adjustments for hematologic toxicity are based on the blood counts obtained in preparation for the day of treatment.\

For patients who must undergo a procedure or surgery while on study that requires wound healing or involves risk for significant bleeding, regorafenib should be held 2 weeks prior to the scheduled surgery/procedure. The decision to resume reografenib after the surgery/procedure should be based on clinical judgement of adequate wound healing

11.1 General Considerations for Managing Regorafenib-related Adverse Events

This section contains general recommendations for the management of adverse events. Patients developing a regorafenib-related CTCAE Grade 1 or 2 adverse events may have their dose continued at the same dose level.

Notes: The recommendations for the management of adverse events in this section are to serve as general guidelines; dose reductions or delays for any event of any CTCAE grade may always be considered for safety reasons at the discretion of the treating investigator. If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade. In the case of two or more toxicities of the same grade, the investigator may dose reduce according to that deemed most causally related to study treatment.

The modifications of regorafenib will follow the following predefined dose levels:		
Dose level +1 (standard starting dose)	160 mg po qd	Four 40-mg tablets of regorafenib
Dose level 0	120 mg po qd	Three 40-mg tablets of regorafenib
Dose level - 1	80 mg po qd	Two 40-mg tablets of regorafenib

Recommended dose modification for toxicities <u>except</u> hand-foot-skin reaction, hypertension, and ALT/AST/bilirubin for adverse events related to regorafenib			
NCI-CTCAE v4.0[a]	**Dose Interruption[b]**	**Dose Modification[b]**	**Dose for Subsequent Cycles**
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[c]	Reduce by 1 dose level	If dose was reduced and toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 4.0

b. Dose modification or interruption is not required for alopecia, non-refractory hypersensitivity and asymptomatic laboratory abnormalities. Dose modification or interruption is not required for nausea, vomiting and diarrhea if optimal supportive management has not been instituted.

c. If no recovery after a 4 week delay, treatment should be permanently discontinued unless subject is deriving clinical benefit.

11.2 Hand-foot skin reaction related to regorafenib

Grading for Hand-Foot-Skin-Reaction			
	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndrome[a]	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
Further description/ examples of skin changes	Numbness, dysesthesia / paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden
a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.			

At first occurrence of HFSR, independent of grade, prompt institution of supportive measures such as topical emollients, low potency steroids, or urea-containing creams should be considered.

Recommended (not mandated) prevention/management strategies for skin toxicities consistent with HFSR are summarized below:

Control of calluses

Before initiating treatment with regorafenib:

- Check condition of hands and feet.
- Suggest a manicure/pedicure, when indicated.
- Recommend pumice stone use for callus or 'rough spot' removal.

During regorafenib treatment:

- Avoid pressure points.
- Avoid items that rub, pinch or create friction.

Use of creams

- Non-urea based creams may be applied liberally.
- Keratolytic creams (e.g. urea-based creams, salicylic acid 6%) may be used sparingly and only to affected (hyperkeratotic) areas.
- Alpha hydroxyl acids (AHA) based creams may be applied liberally 2 times a day. Approximately 5% to 8% provides gentle chemical exfoliation.
- Topical analgesics (e.g. lidocaine 2%) are to be considered for pain control.
- Topical corticosteroids like clobetasol 0.05% can be considered for subjects with Grade 2 or 3 HFSR. Use of any grade of HFSR is allowed.

Tender areas should be protected as follows:

- Use socks/gloves to cover moisturizing creams
- Wear well-padded footwear
- Use insole cushions or inserts (e.g. silicon, gel)
- Foot soaks with tepid water and Epson salts

Recommended dose modification for hand-foot-skin reaction related to regorafenib		
Grade of event (NCI-CTCAE v4.0)	**Occurrence**	**Suggested Dose Modification**
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief.
Grade 2 (intolerable)	1st occurrence	Therapy may be interrupted and restarted at the same dose once toxicity resolves to Grade 0-1. Alternatively, regorafenib may be decreased by one dose level. Supportive measures should be instituted immediately. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1.[b, c]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, treat at reduced dose level.[b]
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level.[b, d]
	4th occurrence	Discontinue therapy.
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one dose level.[b, d]
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1.[c] When resuming treatment, decrease dose by one additional dose level.[b, d]
	3rd occurrence	Discontinue treatment permanently.

a. More conservative management is allowed if judged medically appropriate by the investigator.
b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.
e. The maximum daily dose is 160 mg.

11.3 Hypertension related to regorafenib

Hypertension is a known AE associated with regorafenib treatment. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification.

Management of Treatment-Emergent Hypertension related to regorafenib		
Grade (CTCAE v4.0)	**Antihypertensive Therapy**	**Regorafenib Dosing**
1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	• Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: • If BP previously within normal limits, start anti-hypertensive monotherapy • If patient already on anti-hypertensive medication, titrate up the dose.	• Continue regorafenib • If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	• Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Patients requiring a delay of >4 weeks should go off protocol therapy b. If BP remains controlled for at least one cycle, dose re-escalation permitted per investigator's discretion. c. Patients requiring >2 dose reductions should go off protocol therapy.		

11.4 Liver function abnormalities related to regorafenib

For patients with observed worsening of serum liver tests considered related to regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 6-5 should be followed.

Regorafenib is a UGT1A1 inhibitor. Mild, indirect (unconjugated) hyperbilirubinemia may occur in patients with Gilbert's syndrome.

Dose modifications/interruption for ALT and/or AST and/or bilirubin increases related to regorafenib			
Observed elevations[a]	**1st Occurrence**	**Restart**	**Re-occurrence**
Baseline G0 to G1 or baseline G1 to G2	Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks[c].		Continue with therapy with monitoring at the investigator's discretion.
Baseline G0 to G2	Delay until < G1 and check AST, ALT, bilirubin 2x/week.	Reduce 1 dose level and check AST, ALT, bilirubin weekly for at least 4 weeks.[a, c]	Discontinue
Baseline any grade to G3	Delay until < G1 if baseline was G0 OR until G1 if baseline was G1 OR until G2 if baseline was G2. Check AST, ALT, bilirubin 2x/week. If ALT or AST > 8 x ULN with a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values, consider permanent discontinuation at the first occurrence.	Reduce 1 dose level and check AST, ALT, bilirubin weekly assessments for at least 4 weeks.[a, c]	Discontinue
a: Severity Grade per NCI-CTCAE v 4.0. b: If ALT, AST, and bilirubin remain stable for two full cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation, check ALT, AST, and bilirubin 2x/week for 2 weeks, then 1x/week for 4 weeks. "G", abbreviation for "CTCAE v4.0 Grade". c: This schedule of AST, ALT, and bilirubin monitoring need not be repeated for a given			

dose level if already completed once.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Please refer to Section 10 regarding the timing of tumor measurement assessments.

Documentation (radiologic) must be provided for patients removed from study for progressive disease (not necessary if removed based on criteria for clinical progression). Objective responses should be confirmed with a second assessment performed at least 4 weeks later.

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) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (uni dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with regorafenib.

Evaluable for objective response. Only those patients who have measurable disease present at baseline and have received at least one dose of therapy 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.

12.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT

scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable 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.

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.

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.

12.3 Methods 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.

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 [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. 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 [*JNCI* 92:1534-1535, 2000].

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.

12.4 Response Criteria

12.4.1 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.

12.4.2 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).

12.4.3 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

12.4.4 Duration of 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.

12.4.5 6-month Progression-Free Survival

Proportion of patients alive and free of progression at 6 months.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Disease progression on treatment with regorafenib
- Patients may be removed from the study for protocol non-compliance.
- If at any time the patient develops unacceptable toxicity he/she will be removed from study.
- Participants can be removed from the study at any time if the study doctor feels that it is in their best interest to do so.
- Patients may withdraw consent from the study at any time.

14.0 BIOSTATISTICS

Two co-primary objectives will be evaluated: best overall response rate (BOR; CR+PR by RECIST v1.1 observed at any time between start of treatment and patient's removal from the study) and 6-month PFS (proportion of patients alive and progression-free at 6 months). If either one of these objectives is met, the treatment would be considered worthy of further investigation.

Our recent literature review of all systemic chemotherapy studies reported for R/M ACC patients from 1966 to 2009 revealed that these were generally small studies of variable, poor methodological quality from which definitive conclusions regarding the efficacy of chemotherapy are difficult to establish[3]. Objective responses with cytotoxic chemotherapy were infrequent, and in 10 studies evaluating different targeted agents (imatinib, gefitinib, cetuximab, lapatinib, bortezomib) involving 157 ACC patients, only 2 objective responses were reported (in response to high dose imatinib). Notably, there is no data addressing potential efficacy of systemic therapy beyond the first line setting in R/M ACC[3]. Therefore, we will adopt a null hypothesis of BOR of 5% and an expected BOR of 20% as the alternative hypothesis. In order to demonstrate that the BOR in the studied population is >5% with a one-sided type I error of 5% and power of 90%, at least 5 responses need to be observed among 38 patients enrolled.

Among all published phase II single-agent trials performed in recurrent/metastatic ACC, we identified six studies involving 106 patients that reported a 6-month progression-free survival (PFS) with single-agent therapy (imatinib[7], cetuximab[36], gemcitabine[37], paclitaxel[38], lapatinib[39], and sunitinib[30]). The mean 6-month PFS from these studies was 40.1%. Three of these studies did not require evidence of radiographic or clinical disease progression for study entry[7,36,38] ; of the remaining three studies, two required evidence of RECIST progression or clinical deterioration within 6 months[30,39] and the other study required symptomatic and/or progressive disease by undefined criteria[37]. Based on these studies, we will adopt a null hypothesis for 6-month PFS of 40% and an expected 6-month PFS of 65% as the alternative hypothesis. In order demonstrate that 6-month PFS in the

studied population is > 40% with a one-sided type I error of 5% and power of 90%, at least 21 of the 38 patients enrolled need to be alive and free of progression at the 6-month time point (exact binomial design).

Assuming that 6-month PFS and BOR are independent, the overall type 1 error is <0.1. The type 1 error decreases very slightly if PFS and BOR are positively correlated.

Patients who receive at least one dose of medication will be included in the evaluation of the primary objectives. Patients who do not have a recorded CR or PR and are removed from the study without a final radiologic evaluation will be classified as non-responders for BOR evaluation. If patients discontinue the study before the 6-mo PFS evaluation without evidence of progression, every effort will be made to bring them in for a 6-mo radiologic evaluation. If this is not possible, the patients will be classified as progressors for the purpose of the 6-month PFS evaluation.

The secondary endpoint is the evaluation of safety/tolerability of regorafenib.

Safety will be assessed in terms of AEs, laboratory data and vital sign data, which will be collected for all patients. Appropriate summaries of these data will be presented. AE will be listed individually per patient according to CTCAE version 4.0, and the number of patients experiencing each AE will be summarized. The safety population will comprise all patients who receive at least one dose of study treatment.

Due to the limited sample size, the analyses investigating the association between correlative markers and response to therapy will be exploratory. Levels of c-kit, VEGF, VEGFR, PDGF, PDGFR, in archival tumor tissue will be quantified by immunohistochemistry (IHC) and their association with objective response to regorafenib will be investigated using the non-parametric Wilcoxon rank-sum test. Similarly, association between c-myb (strong staining, 2+ vs other) or t(6;9) translocation and response will be tested using Fisher's exact test.

We will investigate, in an exploratory fashion, whether gene alterations that we detect are associated with response. Further, we will use linear models for microarray data (LIMMA), which performs moderated t-tests by discounting changes in low expressing genes with low variance, to identify genes who are differentially expressed between responders and non-responders. Multiplicity correction will be undertaken by controlling the false discovery rate.

We anticipate an accrual rate of approximately 2-3 patients/month; therefore we expect accrual to be completed within 15 months.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Not applicable

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into the secure Clinical Research Database (CRDB). Source documentation will be available to support the computerized patient record.

Whole exome or genome sequencing data will be deidentified; samples will be labelled with patient study IDs to preserve links to clinical data. The deidentified genomic data will be stored to a protected server that is specifically set aside for clinical trial data.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*.. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol is assessed for the level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority is already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Risks, Benefits, Toxicities/side effects

Potential risks to human subjects include drug related toxicity, placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan, PET scan). All efforts will be made to avoid any complication by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood tests.
If an adverse medical event occurs, the patient will first contact the primary oncologist or the Principal Investigator. At nights and on weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information also recorded.

Alternatives/options

Participation in this trial is voluntary. Depending on the specific details of the situation, patient options without being in a study might include:

- Other palliative chemotherapy off study.
- Participation in a different clinical trial
- Best supportive care

Financial Costs/Burdens

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, and doctor's fees. Patients will not be charged the cost of analysis for the research correlates. The patient also will not be charged for the subsequent research analysis of these specimens. Regorafenib is provided by Bayer and therefore is not billable to research participants.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

It is also stated in the consent and Research Authorization that research data (e.g. genomic sequence) may be placed into databases monitored by the National Institutes of Health, and

may be made accessible to investigators approved by the U.S. government. It is difficult to identify genotype/phenotype specifics since multiple diseases are studied under the auspices of this protocol and therefore, the requirements for submission of genotype/phenotype data into the NIH GWAS Repository (or any other public database) will be followed as per the MSKCC IRB GWAS SOP-503.

17.2 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

17.2.1 SAE reporting for the Drug Supplier

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death.

b. Is life-threatening.

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours.

   - The admission is pre-planned. (i.e. elective or scheduled surgery arranged prior to the start of the study)

   - The admission is not associated with an AE. (e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity. Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another medically important serious event as judged by the investigator.

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.

When required, and according to local law and regulations, serious adverse events must be reported to the Ethics Committee and Regulatory Authorities.

All serious adverse events should be reported to Bayer within 24 hours. In the event of such an event, the investigator should refer to the Pharmacovigilance section of the contract for reporting procedures.

The Investigator may report serious adverse drug reactions (SADRs) using:

A MedWatch form available at http://www.fda.gov/medwatch/

All reports shall be sent electronically to:

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address:	Global Pharmacovigilance - USA
Mail only:	Bayer HealthCare Pharmaceuticals Inc.
	P.O. Box 1000
	Montville, NJ 07045-1000
Address:	340 Changebridge Road
FDX or UPS only	Pine Brook, NJ 07058

Reports for all Bayer products can also be phoned in via our Clinical Communications Dept:

Phone: 1-888-842-2937

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent

form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: Pill Diary