Phase II Study of Regorafenib in Good Performance Status Patients with Newly Diagnosed Metastatic Colorectal Adenocarcinoma

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.

Participating Institutions	Site PI's Name*	Site's Role
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Table of Contents

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Protocol title**:** Phase II study of regorafenib in good performance status patients with newly diagnosed metastatic colorectal adenocarcinoma

Study population**:** Patients with newly diagnosed unresectable stage IV colorectal adenocarcinoma. Patients must have asymptomatic to minimally symptomatic disease. They must be untreated for colorectal cancer, or progression on any first line 5FU (such as FOLFOX or FOLFIRI). They must have excellent performance status, ECOG 0 or 1.

Study design**:** Multi-center, open-label, non-randomized, single-arm phase II

Number of patients**:** 37

Study drugs**:** Regorafenib, administered orally

Dose and regimen**:** Regorafenib administered daily 3 weeks on, 1 week off for all cycles. Starting dose will be 80 mg daily administered for week 1 of cycle 1 and dose escalated to 120mg weeks 2 and 3 of cycle 1 and all remaining cycles if no excess toxicity is experienced by the patient at the discretion of the treating physician. Patients will continue on treatment until progression of disease. Each cycle consists of 28 days.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary**:** To determine the 16 week progression free survival, in patients with previously untreated, asymptomatic or minimally symptomatic metastatic colorectal cancer.

Secondary: The secondary objectives are overall survival, disease control rate, duration of stable disease and toxicity

Tertiary: a.) To evaluate pretreatment tumor samples to attempt to identify molecular markers of responsiveness or resistance to regorafenib.
b.) To obtain and evaluate tumor tissue at the time of progression to evaluate genetic alterations in subclones and for markers of resistance to regorafenib
c.) To obtain and evaluate circulating DNA pre and throughout treatment to assess for genetic alterations prior to clinical or radiographic progression.

3.0 BACKGROUND AND RATIONALE

At the present time, standard practice in the care of patients with unresectable metastatic colorectal cancer (mCRC) is to administer palliative cytotoxic chemotherapy, most commonly with either the FOLFOX or FOLFIRI regimen, with or without concurrent bevacizumab. These regimens have considerable toxicity, however, and a substantial number of patients who present with metastatic disease have it discovered on CT or MRI only, and have few or no tumor-related symptoms. Such patients are potentially over treated by subjecting them to standard cytotoxic therapy. Some of these patients are observed with progressive disease until such time as symptoms develop, however

many are uncomfortable without therapy and as such receive systemic chemotherapy. The option of treatment with an oral tyrosine kinase inhibitor with demonstrated efficacy would be an attractive option for many of these patients. Such patients, being untreated and largely asymptomatic, are likely to be most able to benefit from treatment with regorafenib.

The select group of patients that would be considered eligible for this study, would have low volume asymptomatic disease, defined as nodal, peritoneal, liver or lung disease measuring up to 3cm OR no more than two sites of disease >4.5 cm, which would not be considered resectable for cure. In this population a targeted agent which achieved disease stabilization with minimal side effects would be preferable to cytotoxic
chemotherapy. As such a delay in the initiation of cytotoxic therapy would significantly improve quality of life, and the survival benefits demonstrated by regorafenib in the most refractory patients may be even more prominent in this healthier patient population.

3.1 Regorafenib Background

Regorafenib is a novel diphenylurea oral multikinase inhibitor of angiogenic (VEGFR1-3, TIE2), stromal (PDGFR-β, FGFR1), and oncogenic kinases (KIT, RET, RAF) with potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI) (1).

Regorafenib potently inhibits angiogenic kinases VEGFR 1-3, TIE2, PDGFR-β, and fibroblast growth factor receptor 1(FGFR1) in biochemical (IC50 between 4 and 311 nanomolar [nM]) and cellular (IC50 between 3 and ~200 nM) kinase phosphorylation assays. The VEGF, TIE2 and PDGF receptors are relevant to tumor angiogenesis (2, 3). PDGF receptors may also play a role in patients with chronic myeloproliferative cancers (4).

Furthermore, it potently inhibits mutant oncogenic kinases KIT (cellular IC50 c-KITK642E = 22 nM) and RET (cellular IC50 RETC634W ~10 nM), which play a role in human gastrointestinal stromal and thyroid cancers, respectively, and B-RAF, a member of the *RAS/RAF/MEK/ERK* signaling pathway (biochemical IC50 of wt B-RAF = 28nM and of B-RAFV600E = 19nM). In addition, it biochemically inhibits Raf-1 (IC50 = 2.5 nM) and the p38 MAPK (IC50 = 24 nM) (1).

3.1.1 Preclinical

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). (1) Immunohistochemical ex-vivo studies with a phospho –specific monoclonocal 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. (1) These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

3.1.2 Clinical Experience

Regorafenib as a single agent has been evaluated in two phase I dose escalation trials (Study

11650 with a 21 days on/7 days off dosing schedule and Study 11651 with a continuous dosing schedule), one phase II trial (Study 11726 with 21 days on/7 days off dosing schedule) in subjects with renal cell carcinoma, and other development studies. As of June 2010, about 250 subjects with advanced solid tumors have been treated with regorafenib at dose levels ranging between 10 and 220 mg once daily.

Study 11650 is an open label, single-agent Phase I study to determine the safety, tolerability, maximum tolerated dose, pharmacokinetics, and biomarker status of regorafenib in 76 subjects with advanced solid-organ malignancies (5, 6). The most common tumor types were colorectal carcinoma (51%), soft tissue sarcoma (9%), ovary carcinoma (7%), and malignant melanoma (7%). In this study, subjects were administered increasing doses of regorafenib beginning at 10 mg up to 220 mg once daily, given on 21 consecutive days, followed by 7 days off study drug administration, for each 28 day cycle. Regorafenib plasma exposure increased in a dose-dependent fashion up to 160 mg once daily and appeared to reach a plateau at this dose. Given in a 3-weeks-on 1-week-off schedule, the dose of 160 mg daily has been chosen as the recommended dose for future studies with single agent regorafenib. (5, 6) The overall median drug administration duration was 65.5 days (range 3 to 906 days). (5, 6)

The most common study drug emergent adverse events (all grades) were fatigue (50%), voice changes (47%), hand-foot - skin reaction (46%), diarrhea (42%), and infection (any event, 41%). (6) The most common drug-related treatment-emergent adverse events (all grades) occurring in > 30% of the subjects were hand-foot skin reaction (46%), voice changes (45%), and fatigue (34%).(6)

The most common study drug emergent adverse events (grades 3-4) were hand-foot skin reaction (21%), infection (any event, 14%), and hypertension (14%). (6) The most common drug-related treatment-emergent adverse events (grade 3-4) occurring in > 5% of the subjects were hand-foot skin reaction (21%), hypertension (9%), and diarrhea (7%). (6)

Drug-related treatment-emergent adverse events leading to dose reduction, interruption, or discontinuation in ≥ 2 subjects (≥ 3%) were dermatological toxicities (24%), fatigue (9%), diarrhea (5%), thrombocytopenia (5%), infection with an unidentified pathogen (3%), hypertension (3%), vomiting/nausea (3%), and worsening of the general health status (3%). Most of the subjects with dermatological toxicities leading to a dose reduction, interruption, or discontinuation had a hand-foot skin reaction (n=14 [18%]). (6)

Of the 58 subjects evaluable for response, 3 (5%) had partial response and 40 (69%) had stable disease according to RECIST 1.0. (6)

Study 11726 is a multi-center, uncontrolled, open-label, non-randomized phase II trial conducted to evaluate the anti-tumor activity and safety of regorafenib (160 mg once daily on a 21-day on/7-day off schedule) in 49 subjects with previously untreated, histologically or cytologically confirmed, unresectable and/or metastatic, measurable predominantly clear cell renal cell cancer (RCC), with an ECOG performance status of 0 or 1 and “low” or “intermediate” risk as per Motzer score. The primary efficacy endpoint for this study was determination of the objective tumor response rate (as assessed by RECIST 1.0). No subject achieved a complete response. Of the 48 subjects evaluable for response, 15 (31.3%) subjects had a confirmed partial response and 24 (50.0%) subjects had stable disease as their best response. The median PFS and TTP were 251 days and 251 days respectively. (7)

All 49 treated subjects experienced at least one treatment-emergent adverse event (TEAE) during the study and 48 (98.0%) subjects had AEs related to the study drug. The most commonly reported

drug-related TEAEs across all grades included hand-foot skin reaction in 32 (65.3%) subjects; fatigue in 26 (53.1%) subjects; hypertension in 23 (46.9%); and diarrhea, oral cavity mucositis (functional/symptomatic), and alopecia, each in 21 (42.9%) subjects.

These events were primarily mild to moderate in intensity and were manageable. Eight (16.3%) subjects discontinued study medication due to AEs. Twenty (40.8%) subjects reported SAEs and 14 (28.6%) subjects had drug-related SAEs. The majority of these events were resolved or improved with dose reductions, treatment delays, or remedial therapies. Renal failure was the most commonly reported treatment-related SAE and study drug was discontinued for 4 of the 5 subjects who had renal failure. There were 4 subjects who died within 30 days of receiving their last dose of study medication. Most hematological and biochemical toxicities were grade 1 or grade 2. Grade 4 hematological and biochemical toxicities were rare. (7)

A phase III study, the CORRECT (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy) was a randomized, double-blind, placebo-controlled study that enrolled 760 patients with mCRC whose disease has progressed after approved standard therapies. 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.(8)

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 of regorafenib were also examined in the phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options. 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.

3.2 Correlative Studies:

We will evaluate the genomic profiles of the tumors in an effort to identify markers of sensitivity or resistance to regorafenib. We will test the tumor tissue for all patients for expression of mutations in the KRAS/BRAF and PIK3CA/AKT pathway using a next-generation sequencing platform. Specimens will be reviewed in the MSKCC Department of Pathology to ensure greater than 50% tumor content and for histologic verification. Genomic DNA will be extracted by standard techniques and analyzed using an assay developed by Dr. Michael Berger (PhD, MSKCC Department of Pathology). This assay uses targeted, massively parallel sequencing to analyze all exons of 341 genes selected for their known roles in cancer initiation or progression (examples include *APC, EGFR, KRAS, BRAF, TP53, NF1,* etc.). Massively parallel sequencing libraries (Illumina, San Diego, CA) will be generated according to the manufacturer's directions. Approximately 7,000 biotinylated RNA baits (Agilent, Santa Clara, CA) will be designed and synthesized corresponding to the coding sequence of the selected 341 genes. Genomic DNA will be subjected to solution-phase hybrid capture using the RNA baits, followed by massively parallel sequencing. To exclude germline single nucleotide polymorphisms, concurrent analysis of normal tissue DNA will be performed. Somatic alterations, including mutations, insertions and deletions, and copy number changes, detected by this assay will be correlated with clinical parameters.

We will also analyze the plasma for mutations in circulating DNA via the BEAMing technique. Quantitative analysis of mutations in plasma will be performed via BEAMing analysis as previously described. (10). We will collect plasma samples (lavender top tubes) from MSK patients pre treatment,
and every 4 weeks until disease progression. The analyses will be performed at MSKCC in Dr. Solit's laboratory

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an open-label, phase II study of regorafenib for patients with metastatic colorectal carcinoma. The treatment will be repeated every week for three weeks on and one week off. Patients will be evaluated for response after every 2 cycles (8 weeks).

Clinical endpoints to be evaluated will include overall response (ORR), progression-free survival (PFS), overall survival (OS), complete response (CR) and partial response (PR) and adverse events (AE). Archived tissue biopsies (either primary or metastatic site) will be utilized for correlative analyses. Correlative studies will include analysis of archived tumors for mutations in signal transduction pathways such as the RAS/RAF/MEK and PIK3CA, via the Berger assay (IMPACT) This assay uses targeted, massively parallel sequencing to analyze all exons of 341 genes selected for their known roles in cancer initiation or progression (examples include *APC, EGFR, KRAS, BRAF, TP53, NF1,* etc.). Massively parallel sequencing libraries (Illumina, San Diego, CA) will be generated

according to the manufacturer's directions. Biopsies will be performed at the time of progression for the patients enrolled at Memorial Sloan Kettering.

Safety will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. The assessments will be based on recorded adverse events, physical examinations, and clinical laboratory assessments.

The study will enroll patients with metastatic colorectal cancer who meet the inclusion/exclusion criteria as outlined in sections 6.1 and 6.2. Patients tolerating regorafenib will be permitted to continue treatment until disease progression. Up to 12 patients will be enrolled and receive regorafenib orally.

4.2 Intervention

All patients that meet the eligibility criteria who have signed the informed consent and have enrolled on the trial will receive single agent regorafenib daily, 3 weeks on 1 week off for all cycles. Dose will be escalated to 120 mg in week 2 of cycle 1 and all remaining cycles if no excess toxicity is experienced by the patient at the discretion of the treating physician.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Regorafenib

Other names: BAY 73-45060

Classification: Kinase Inhibitor

Regorafenib 40-mg tablets contains regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, polyvinyl alcohol-part hydrolyzed, talk, titanium dioxide E171 (color index 77891), Macrogol/PEG 33350, lecithin (soy), iron oxide yellow – E172 (color index 77491), iron oxide red – E172.

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.

Regorafenib will be provided by Bayer as 40-mg tablets, which are coated, not divisible, gray-orange-red, oval (length 16 mm, width 7 mm, thickness 4.9-5.6 mm), and 472 mg each in total weight. Tablets are in an immediate-release dosage form with rapid dissolution characteristics under the *in vitro* test conditions. Regorafenib will be administered for 3 weeks on /1 week off . One cycle is 28 days. If the patient does not experience excess toxicity in week 1 of cycle 1, the dose will be escalated to 120 mg at the discretion of the treating physician for weeks 2 and 3 of cycle 1 and all remaining cycles.

Two 40-mg regorafenib tablets 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), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

5.1 Drug Logistics and Accountability

All study drugs will be stored at the investigational sites in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel.

5.1.1 Accountability

The investigator at each site, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the “Policy and Guidelines for Accountability and Storage of Investigational Agents” or to obtain a copy of the drug accountability form.)

5.1.2 Destruction and Return

At the end of the study, unused supplies of regorafenib (Bay 73-4506) should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to Bayer.

A completed “Unused Study Drug Disposition Form Destruction or Return Confirmation” should be sent to Bayer at the following address:

E-mail: Karen.marini@bayer.com

OR

Fax: 973-709-2193

OR

Mail: (VP of Medical Affairs named in contract) at

Bayer HealthCare Pharmaceuticals

6 West Belt

Wayne, NJ 07470

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Age ≥ 18 years.
2. Life expectancy of at least 12 weeks (3 months).
3. Untreated for metastatic colorectal cancer or progression on any first line 5-FU containing regimen(such as FOLFOX or FOLFIRI)
4. Histologically proven colorectal adenocarcinoma
5. Metastatic disease, unresectable disease involving one or more sites including liver, lung, lymph nodes and peritoneum, with each nodule measuring ≤3cm OR no more than two sites of disease (two nodules) >4.5 cm.
6. ECOG 0 or 1
7. Adequate bone marrow, liver and liver 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-transferease (AST) ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
    - Alkaline phosphastase limit ≤ 2.5 x ULN (≤ 5 x ULN for subjects with liver involvement of their cancer)
    - Lipase ≤ 1.5 x the ULN
    - creatinine ≤ 1.5 x the ULN
    - Platelet count ≥ 100000 /mm3, hemoglobin (Hb) ≥ 9 g/dL, absolute neutrophil count (ANC) ≥ 1500/mm3. Blood transfusion to meet the inclusion criteria will not be allowed.
8. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days 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.
9. Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF 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 site principal investigator or a designated associate.
10. Subject must be able to swallow and retain oral medication.
11. If the patient is enrolled at MSK he/she must consent to a pre and post treatment biopsy (or have archived tissue available for the pretreatment analysis). Pretreatment archival tissue for patients enrolled outside of MSK should be submitted to MSK. If there is no archival tissue available, a repeat biopsy is not required for non-MSK patients.

6.2 Subject Exclusion Criteria

1. Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management.
2. Active or clinically significant cardiac disease including:
   - o Congestive heart failure – New York Heart Association (NYHA) > Class II.
   - o Active coronary artery disease.
   - o Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
   - o Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
3. Evidence or history of bleeding diathesis or coagulopathy.
4. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication.
5. Subjects with any previously untreated or concurrent cancer that is distinct in primary site or
6. Recent history of prior cancer except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before enrollment are allowed.
7. Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
8. Ongoing infection > Grade 2 NCI-CTCAE v4.0.
9. Symptomatic metastatic brain or meningeal tumors.
10. Presence of a non-healing wound, non-healing ulcer, or bone fracture.
11. Patients with seizure disorder requiring medication.
12. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
13. Pleural effusion or ascites that causes respiratory compromise (≥ NCI-CTCAE version 4.0 Grade 2 dyspnea).
14. History of organ allograft (including corneal transplant).
15. Any malabsorption condition.
16. Women who are pregnant or breast-feeding.
17. Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
18. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.

7.0 RECRUITMENT PLAN

All patients meeting the eligibility requirements will be considered for enrollment regardless of sex, race, or religion. Eligibility criteria may not be waived by the investigator. Discussions regarding protocol enrollment and patient eligibility will begin with any of the investigators named on the protocol. Patients will be made aware of the protocol, its specific aims and objectives, and

the potential risks and benefits the patient may incur. Patients will be required to read, agree to, and sign an IRB-approved informed consent form prior to registration on this trial. There will be no financial compensation for patients enrolling on this protocol.

MSK patients will be consented by consenting professionals listed on the protocol title page. Screening will be performed as noted in section 8.0. Patients will be identified and referred from their physicians either within MSKCC or from an outside institution.

Patients will also be enrolled at SUNY Downstate and Queens Cancer Center. 12 patients total will take part in this study. About 8 patients are expected to be treated at MSKCC; the remainder are expected to be accrued at the participating sites.

8.0 PRETREATMENT EVALUATION

A window of +/- 2 days can be applied to scheduled visits.

8.1 Screening Visit

The Screening visit is to be conducted within 2 weeks of Day 1 (Day -14 to Day 1). I

- Review of study eligibility criteria
- Completion of consent form
- Medical History
- Record concomitant medications taken up to 30 days prior to Day 1
- Physical Examination, including height and weight
- Vitals (temperature, HR, BP and RR) • ECOG Performance Status evaluation
- Laboratory Assessments
    - Hematology: CBC with differential, platelets
    - Chemistry: Na, K, Cl, Mg, CO_2, BUN, Cr, CPK, glucose (random), Ca, Phosphorus, AST, ALT, Alk Phos, total bilirubin, LDH, total protein, albumin, uric acid, lipase, amylase
    - Serum β-HCG for women of childbearing potential
    - Urinalysis
- 12 lead ECG
- CT chest abdomen and pelvis (or MRI if CT cannot be done) (this can be done within 4 weeks of starting treatment)
- Biomarkers: Tumor tissue sampling: a tumor block of archived diagnostic biopsy or 10-15 precut slides if possible, if tissue is available The patients treated on study at MSK will have pre treatment tumor biopsies.

9.0 TREATMENT/INTERVENTION PLAN

Amended: 13-Oct-2015

IRB PB

All patients that meet the eligibility criteria who have signed informed consent and have enrolled on the trial will be treated with regorafenib daily 3 weeks on, 1 week off as per the tables below:

Cycle 1:

Week	Dose (flat)
1	80mg*
2	120mg**
3	120mg
4	Off

*Starting dose level

** Dose will be escalated if no excess toxicity is experienced by the patient at the discretion of the treating physician

Cycle 2 and beyond:

Week	Dose (flat)
1	120mg
2	120mg
3	120mg
4	Off

The following assessments should be performed on the first day of each cycle (every 4 weeks) prior to receiving study treatment (+/- 7 days)

9.1 All cycles, Day 1

- Record concomitant medications
- Vitals (temperature, HR, BP and RR) physical examination (including height and weight) and performance status assessment
- Laboratory Assessments
    - Hematology
    - Chemistry: Na, K, Cl, Mg, CO_2, BUN, Cr, CPK, glucose (random), Ca, Phosphorus, AST, ALT, Alk Phos, total bilirubin, total protein, albumin, LDH, uric acid, lipase, amylase
    - CEA
- 12-lead ECG
- Record Adverse Events (CTCEA v4.0)
- Biomarker blood sample: Day 1 of cycles 1, 2, 3 and 4.

9.2 Cycles 1 & 2, Day 8 and Day 15

- Record concomitant medications
- Vitals (temperature, HR, BP and RR) physical examination (including height and weight) and performance status assessment

- Laboratory Assessments
    - Hematology
    - Chemistry: Na, K, Cl, Mg, CO_2, BUN, Cr, CPK, glucose (random), Ca, Phosphorus, AST, ALT, Alk Phos, total bilirubin, total protein, albumin, LDH, uric acid, lipase, amylase
- Record Adverse Events (CTCAE v. 4)

Please note: Cycles 1 and 2 will have assessments on Days 1, 8, and 15. After 2 cycles patients can be seen once every 4 weeks. Therefore, on all subsequent cycles (3+), assessments should be done only on Day 1 of each cycle.

- Radiological imaging studies to evaluate tumor status will be repeated every 2 Cycles while on study. However, if a tumor response status of complete response (CR) or partial response (PR) is assigned from these studies, then a repeat scan(s) must be done no sooner than 4 weeks after the scan documenting CR or PR to confirm these findings.

9.3 End of Treatment Visit

When a patient is taken off treatment, the following assessments should be performed 14 days (+/- 7 day) after study treatment has stopped:

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- Laboratory Assessments
    - Hematology
    - Chemistry: Na, K, Cl, Mg, CO_2, BUN, Cr, CPK, glucose (random), Ca, Phosphorus, AST, ALT, Alk Phos, total bilirubin, total protein, albumin, LDH, uric acid, lipase, amylaseo CEA
- Record Adverse Events (CTCAE v. 4)
- 12-lead ECG
- Biomarker: plasma prepared from fresh blood collected at the patient's final visit.
- Tumor biopsy

10.0 EVALUATION DURING TREATMENT/INTERVENTION

	Screening	Pre-Dose	Treatment Visits						Final Visit
			Cycle 1 and 2			Cycle 3 and beyond			
			Day 1	Days 8 and 15	Days 21-28	Day 1	Days 8-15		
Regorafenib[3]			x	x		x	x		
Medical history	x								
Physical Exam	x	x	x	x		x			x
Vital Signs	x	x	x	x		x			x
Blood tests	x	x	x	x		x			x
CEA		x	x			x			x
Urine tests	x								
Imaging Test (CT scan)[2]	x								
ECG	x		x			x			x
Record other Medications	x	x	x	x		x			x
Pregnancy if applicable		x							
Research Blood Tests[4]			x			x			
Tumor tissue Biopsy sample	x[1]								x[1]
Record side effects			x	x		x			**x**
Pill Diary			x	x		x			**x**

1. Biopsy for the patients enrolled at MSK only
2. Required every 2 cycles, can be an MRI if CT cannot be done
3. Regorafenib is taken daily for 3 weeks, followed by a one week break
4. Research blood test will be taken on Day 1 of cycles 1-4 and Final Visit

11.0 TOXICITIES/SIDE EFFECTS

Study medication will be administered on a 3 weeks on/1week off schedule [3 weeks out of every 4]. The starting dose of regorafenib is 80 mg once daily for week 1 of cycle 1. If no excess toxicity is experienced by the patient in cycle 1 week 1, the dose will be escalated to 120 mg at the discretion of the treating physician.

The most common toxicities seen with regorafenib were hand–foot skin reaction, fatigue, diarrhea, hyperbilirubinemia, and hypertension.

11.1 Dose Modifications

Doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are related to protocol therapy according to the guidelines shown in the Dose Delays/Dose Modifications table that follows. 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.

The modifications of regorafenib will follow the following predefined dose levels:				
Dose Level	**Dose**	**Tablets**	**If no SDRT**	**If with SDRT****
0*	80 mg po qd	Two 40-mg tablets of regorafenib	Proceed to next dose level	---
1	120 mg po qd	Three 40-mg tablets of regorafenib	Continue at current dose level	Decrease to 80mg

*starting dose level
** SDRT = Significant Drug related toxicities
***Dose escalation will be at the discretion of the treating physician

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 after consulting with the MSK principal investigator.

If more than 1 dose reductions are required, treatment with regorafenib will be discontinued. If a dose reduction has been performed, intra-subject dose re-escalation can be considered (up to the maximal 120 mg daily dose) at the discretion of the treating physician provided that the toxicity(ies) has resolved to baseline.

Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/ST/bilirubin

NCI-CTCAE v4.0[a]	**Dose Interruption**	**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 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. Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.
c. If no recovery after a 4 week delay*, treatment should be permanently discontinued unless subject is deriving clinical benefit.
* Modify according to study specific cycle length The table above outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except HFSR and hypertension.

In addition to these recommended dose modifications, subjects who develop diarrhea, mucositis, anorexia or other events predisposing to fluid loss or inadequate fluid intake should be carefully monitored and rehydrated as clinically necessary. This is in order to minimize the risk of postural hypotension and renal failure.

Grading for Hand-Foot-Skin-Reaction

	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndromea	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.

Recommended dose modification for hand-foot-skin reaction[a]

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	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. 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.

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 administered.

Recommended 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% should be considered for subjects with Grade 2 or 3 HFSR. Avoid systemic steroids.

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

Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured on days 1, 8, and 15 during the first two cycles of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is > 140 mm Hg systolic or > 90 mm Hg diastolic (NCI CTCAE v4.0), then the subject must contact study personnel. 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. If necessary, the table below outlines suggested dose reductions.

Management of Treatment-Emergent Hypertension

	Antihypertensive Therapy	Regorafenib Dosing
Grade (CTCAE v4.0)	None	• Continue regorafenib
1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)		• 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 OR More than one drug or more intensive therapy than previously used indicated	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

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 >1 dose reductions should go off protocol therapy.

Liver Function Abnormalities

For patients with observed worsening of 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 study drug

Observed elevations	1st Occurrence	Restart	Re-occurrence
AST and/or ALT ≤ 5 X ULN (< G3)	Continue dosing, with weekly monitoring of liver function until transaminases return to <3 X ULN (≤ G1) or baseline.		
ALT and/or AST >5 X ULN (≥ G3)	Interrupt dosing, with weekly monitoring until transaminases return to < 3 X ULN or baseline.	If the potential benefit for reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: Reduce one dose level and measure liver tests weekly for at least 4 weeks.	Discontinue
ALT and/or AST > 20 X ULN (≥ G4)	Discontinue		

ALT and/or AST > 3 X ULN (≥ G2) with concurrent bilirubin > 2 X ULN	Discontinue treatment and measure liver tests weekly until resolution. Exception: patients with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for

ALT/AST elevations.

During the first 2 cycles of treatment, ALT, AST and bilirubin must be checked on days 1, 8 and 15.

Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. The same dose-modification algorithm used for skin toxicities can be used to address these toxicities. However, the preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status).

Anti-diarrhea medications may be introduced if symptoms occur. Previous trials have shown that the diarrhea could be managed with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours.

11.2 Treatment compliance

An adequate record of receipt, distribution, and return of all study drugs must be kept in the form of a Drug Accountability Form.

Subject compliance with the treatment and protocol includes willingness to comply with all aspects of the protocol, and to have blood collected for all safety evaluations. At the discretion of the MSK principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

11.3 Prior and concomitant therapy

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 and in the CRF (including start/stop dates, dose frequency, route of administration, and indication). 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, if possible.

There is no clinical information on the effect of CYP3A4 inhibitors on the PK of regorafenib. Substances that are inhibitors of CYP3A4 activity such as ketoconzzole are expected to decrease metabolism of regorafenib and thus increase regorafenib plasma concentrations. There are no clinical data evaluating the effect of chronically coadministererd CYP3A4 inhibitor on regorafenib's efficacy. Since there is a possibility of increased regorafenib toxicity upon chronic coadministration of CYP3A4 inhibitors with regorafenib, chronic coadministration of CYP3A4 inhibitors with regorafenib should be avoided, if possible. See Appendices 2 and 3 for a list of inducers and inhibitors of P-Glycoproteins and CYP enzymes.

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
- 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 stable. Close monitoring (day5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

The following are not permitted:

- Other investigational treatment during or within 30 days before starting study treatment
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cycloosporin, and digoxin). Warfarin is metabolized by the cytocrome enzyme CYP2C9 and it's levels may be especially affected by regorafenib
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])

11.4 Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as AE (however, the condition for which the surgery is required may be an AE if worsens compared to baseline).

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

11.5 Definition of serious adverse event (SAE)

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.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Clinical Efficacy Assessments

Patients with measurable disease will be assessed by standard RECIST 1.1 criteria. [New Response Evaluation Criteria RECIST 1.1, EA. Eisenhower et al, European Journal of Cancer 45 (2009) 228-247]

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IRB PB

12.2 Definitions

Response and progression will be evaluated in this study using the international criteria proposed by the RECIST 1.1 Committee. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term “evaluable” in reference to measurability provides neither additional meaning nor accuracy and will not be used.

Measurable Disease

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20mm by chest X-ray.

Nonmeasurable Disease

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). 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. Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis

<10mm are considered non-pathological and should not be recorded or followed. 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 as noted above, 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 pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

12.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

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 should always be done rather than 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 and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When 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).

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, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

12.4 Response Criteria

Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour response for 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 diameters of target lesions, taking as reference the baseline sum diameters.

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

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.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions.

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

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): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.4.1 Confirmatory Measurement and Duration of Response

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error.

This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study). The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease. Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages,

treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Removal of Patients from Therapy or Assessment

A subject may discontinue or be discontinued from study medication for any of the following reasons:

Subjects **must be withdrawn from the trial** (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject has radiographic progression of disease.
- Subject is lost to follow-up.
- Death.

Subjects **may be** withdrawn from the study for the following reasons:

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Severe allergic reaction to regorafenib (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records.

The reason for withdrawal shall be recorded by the investigator. All patients who withdraw from the study prematurely will undergo all end-of-study assessments, if possible.

14.0 BIOSTATISTICS

This is a pilot study in which the primary endpoint is 16 week progression free survival (PFS) in patients with untreated newly diagnosed metastatic colorectal cancer. With 12 patients we can estimate the 16 week PFS to within +/-28%. Patients that come off study before 16 weeks before documented progression will be treated as events for the 16 week PFS endpoint. We anticipate that we will accrue 1-2 patients per month.

Secondary endpoints include overall survival, disease control rate, duration of stable disease and toxicity. Progression free survival is defined as the time from treatment start to progression or death whichever occurs first. Overall survival is defined as the time from treatment start to death or last follow up. Survival will be estimated using the Kaplan-Meier method. Disease control rate (defined with RECIST 1.1 criteria at 16 weeks (2nd scan) as CR, PR or SD), will be estimated using proportions and exact binomial 95% confidence intervals provided. Duration of stable disease will be defined as the time from stable disease to the time of documented progression. Toxicity will be summarized using descriptive statistics.

Correlative analyses are exploratory in nature due to the limited sample size. Associations between molecular markers and PFS and OS will be assessed using the log-rank test. Genetic alterations will be summarized using descriptive statistics. Associations between genetic alterations and PFS and OS will be assessed using the log-rank test. Genetic alterations in circulating DNA will be characterized using descriptive statistics. Genetic alterations that appear both in circulating DNA and in the post-treatment biopsy tissue will also be characterized descriptively. Genetic alterations that appear in circulating DNA will be characterized using descriptive statistics at the different time points of collection. Genetic alterations that appear both in circulating DNA and in the post-treatment biopsy tissue will also be characterized descriptively over time.

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.

15.1.1 Registration for Participating Sites

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center.

The following documents must be sent for each enrollment within 24 hours of the informed consent form being signed:

- The completed or partially completed MSK eligibility checklist

- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (e.g. laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and ECG report).

The site research staff will conduct a review of all documents. If the eligibility checklist is not complete or source documentation is missing, the participant will be registered PENDING and the site will be responsible for sending the completed registration documents within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site is in good standing, the site research staff will send the completed registration documents to the MSK PPR Office for participant enrollment as stated in section 15.1.

Once the participant is registered, the participant will be assigned a number in the MSK Clinical Research Database (CRDB). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

16.0 DATA MANAGEMENT ISSUES

A MSKCC 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 coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database (Clinical Research Database, CRDB) at Memorial Sloan-Kettering Cancer Center. Source documentation will be available to support the computerized patient record.

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating site(s) will enter data remotely into electronic Case Report Forms (eCRFs) using the internet based system, Clinical Research Database. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A schedule of required forms is shown in section 16.0.3.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be filed on site throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation
- Demographics, Medical History and Concomitant Medications
- Physical Exams and Vital Signs
- Laboratory reports
- Pill Diaries

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject identifiable information it may encounter.

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into the MSK Clinical Research Database and study-specific paper CRFs. Source documentation should be kept on file by the site.

Data should be entered into the MSK Clinical Research Database according to chart 16.1.

Chart 16.1: Data and Source Submission Requirements and Timelines

	Baseline	Pre-Dose	Cycle 1 and 2, Day 1	Cycle 1 and 2, Days 8 and 15	Cycle 3 and beyond, Day 1	SAE	Off Study
Submission Schedule							
Source Documentation	Within 24 hours (see section 15.1.1)	Source documentation to be properly filed on site					
eCRFs	Within 7 days of visit	Within 14 days of visit				Within 3 days of event (see section 17.2); updates to be submitted as available	Within 14 days of visit
Required Forms							
Demographics	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X		X
Physical Exam	X	X	X	X	X		X
Vital Signs	X	X	X	X	X		X
Treatment		X	X	X	X		X
Laboratory	X	X	X	X	X		X
Lesion/EOD					X		X
Adverse Event		X	X	X	X		X
Serious Adverse Event						X	
Off Study							X
Pill Diary			X	X	X		X
ECG	X						X
Imaging	X						

16.1 Quality Assurance

Data collection will principally look at:

- Adherence to eligibility criteria. The study RSA will ensure that all eligibility criteria are met and that the checklist is complete and signed by the consenting professional prior to initiation of treatment. All supporting source documentation must be maintained in the patient's electronic medical record.
- 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.
- Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Each site accruing participants to this protocol will be audited by the staff of the DRP for protocol and regulatory compliance, data verification and source documentation.

Audits will be conducted annually during the study (or more frequently if indicated) and at the end or closeout of the trial. Ideally the first audit will occur shortly after the first patients are enrolled. The number of participants audited will be determined by available time and the complexity of the protocol. Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participants' responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at MSKCC 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://cancertrials.nci.nih.gov/researchers/dsm/index.html. 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://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.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 will be assessed for its 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.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB).

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the participating site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at each participating site.
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSK and first approved by the MSK IRB/PB. Upon receipt of MSK IRB/PB approval, MSK will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSK for each amendment within the stated timelines:

- Participating Site IRB approval

- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSK or a participating site, approval from the MSK IRB/PB is required prior to the action. Participating sites should contact the MSK PI who will in turn seek approval from the MSK IRB/PB.

A protocol violation is any change or departure from the research protocol that occurred without prior approval from the MSK IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSK as soon as possible. The MSK PI will in turn report the violation to the MSK IRB/PB.

Participating sites should report deviations and violations to their institution's IRB as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSK as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSK.

16.3.3 Document maintenance

The MSK PI and participating site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondences are maintained in an on site regulatory binder and sent to MSK as outlined within the protocol. A regulatory binder for each site will also be maintained at MSK; this binder may be paper or electronic.

After study closure, the participating sites will maintain all source documents, study related documents and CRFs for 3 years.

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

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).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- 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
- 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.

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

17.3 SAE Reporting for Participating Sites

Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgement must be sent to MSK upon receipt.
- Participating sites are responsible for reporting all SAEs to the MSK PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSK PI of any grade 5 event immediately

- Participating sites should use the SAE Report Form found in MSK's internet-based Clinical Research Database, CRDBi-Multicenter, to report SAEs to MSK

SAE contact information:
Email: CercekA@mskcc.org to the attention of 13-211 Research Staff

Responsibilities of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB as specified in 17.2.
- The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSK IRB/PB.
- The MSK PI is responsible for informing all participating sites about any SAE report pertaining to a grade 5 event as soon as possible.

17.4 Safety Reports

MSK must submit outside safety reports to the MSK IRB/PB according to institutional guidelines. Outside safety reports will be distributed to the participating sites immediately upon receipt if not directly received from Bayer. Participating sites are responsible for submitting safety reports to their local IRB per their local IRB guidelines.

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.

18.1 Informed Consent Procedures for Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSK. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

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20.0 APPENDICES

Appendix 1: Pill Diary

Appendix 2: **Inducers and Inhibitors of P-Glycoproteins**

Table 2. Inducers and Inhibitors of P-Glycoprotein.[3,4,6,7,10,12,13,14,17,18]	
Inducers	Inhibitors
Rifampin (eg, **Rifadin**)	**Amiodarone** (eg, **Cordarone**)
Ritonavir (eg, **Norvir**)	**Atorvastatin** (**Lipitor**)
St. John's wort	**Chlorpromazine** (eg, **Thorazine**)
Yohimbine	**Clarithromycin** (**Biaxin**)
	Cyclosporine (eg, **Neoral**)
	Diltiazem (eg, **Cardizem**)
	Erythromycin (eg, **E-Mycin**)
	Felodipine (**Plendil**)
	Fluphenazine (eg, **Prolixin**)
	Hydrocortisone (eg, **Cortef**)
	Indinavir (**Crixivan**)
	Itraconazole (**Sporanox**)
	Ketoconazole (eg, **Nizoral**)
	Lidocaine (eg, **Xylocaine**)
	Mifepristone (**Mifeprex**)
	Nelfinavir (**Viracept**)
	Nicardipine (eg, **Cardene**)
	Nifedipine (eg, **Procardia**)
	Progesterone (eg, **Prometrium**)
	Propranolol (eg, **Inderal**)
	Quinidine
	Reserpine
	Ritonavir (eg, **Norvir**)
	Saquinavir (eg, **Fortovase**)
	Tacrolimus (**Prograf**)
	Tamoxifen (eg, **Nolvadex**)
	Testosterone (**Delatestryl**)
	Trifluoperazine
	Verapamil (eg, **Calan**)

Appendix 3: **Inducers and Inhibitors of CYP enzymes**

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline, caffeine	fluvoxamine	smokers versus non-smokers [2]
2B6	efavirenz		rifampin
2C8	repaglinide, rosiglitazone	gemfibrozil	rifampin
2C9	warfarin, tolbutamide	fluconazole, amiodarone (use of PM versus EM subjects) [3]	rifampin
2C19	omeprazole, esoprazole, lansoprazole, pantoprazole	omeprazole, fluvoxamine, moclobemide (use of PM versus EM subjects) [3]	rifampin
2D6	desipramine, dextromethorphan, atomoxetine	paroxetine, quinidine, fluoxetine (use of PM versus EM subjects) [3]	none identified
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, triazolam	atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin	rifampin, carbamazepine