Phase II study of FOLFOX plus regorafenib in patients with unresectable or metastatic esophagogastric cancer

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a single-arm, Phase II study of regorafenib in combination with 5-Fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) as first line therapy in patients with metastatic esophagogastric adenocarcinoma.

Primary Objective: To determine the six months progression free survival (PFS) in the first-line treatment of patients with metastatic or unresectable esophagogastric adenocarcinoma. With a total of 36 esophagogastric adenocarcinoma patients, we have 80% power to detect an improvement in the 6-month progression free survival (PFS) from a historical control of 40% to 61% with type I error rate of 5%.

Secondary Objective: To determine overall survival (OS), response rate, toxicity rates in the first-line treatment of patients with metastatic or unresectable esophagogastric adenocarcinoma.

Study population: Patients with newly diagnosed metastatic or unresectable esophagogastric adenocarcinoma. Patients must be untreated for metastatic esophagogastric adenocarcinoma, except for perioperative therapy > 6 months prior to recurrence.

Study design: Single institution, open-label, non-randomized, single-arm phase II

Number of patients: 36

Study drugs: Regorafenib, administered orally

Dose and regimen: Regorafenib 160 mg daily on days 4 to 10 and days 18 to 24 as four 40 mg coprecipitate tablets + mFOLFOX on Day 1 and Day 15 of each cycle. Each cycle consists of 28 days. Treatment will be administered on an outpatient basis. All patients will receive systemic chemotherapy with the mFOLFOX regimen and regorafenib. There are several variations of the basic FOLFOX regimen. The specific version of the FOLFOX regimen used at MSKCC is mFOLFOX6. mFOLFOX6 will be given on Day 1 of each cycle. Patients will receive Oxaliplatin 85 mg/m2 IV (over 120 minutes), leucovorin 400 mg/m2 IV (over 120 minutes), 5-FU 400 mg/m2 IVP, and 5-FU 1200 mg/m2/day CIVI x 2 days, every two weeks. Treatment will be performed on the scheduled day ± 7 days. In case of discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off. The 3 weeks on/1 week off schedule is supported by the single agent regorafenib data in colon cancer and GIST.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:
To determine if the addition if regorafenib to FOLFOX chemotherapy improves 6 month progression free survival (PFS) in the first-line treatment of patients with metastatic or unresectable esophagogastric adenocarcinoma.

Secondary Objectives:
Determine of the addition of regorafenib to FOLFOX chemotherapy affects:

1) Overall survival
2) Response rate
3) Toxicity rates

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Exploratory objective:
To archive available unstained slides/tumor block and patient blood sample (normal DNA comparison) stored in tissue procurement service (TPS) for future correlative analysis. The patients will be asked to provide at least 15 unstained slides. Tissue submission is encouraged, but not mandated for enrollment in the study.

3.0 BACKGROUND AND RATIONALE

3.1 Esophagogastric cancer

In the United States, approximately 21,600 and 17,990 new cases of gastric and esophageal cancer respectively are diagnosed annually with ~26,200 deaths attributable to the disease.[1] For locally advanced disease, outcome hinges on the ability to achieve complete resection and multidisciplinary treatment approaches include perioperative systemic chemotherapy and/or radiotherapy. Most esophagogastric cancers are locally advanced at the time of diagnosis, with the overall 5-year survival rate for distant or metastatic disease of ~ 3%.[1]

Chemotherapy remains the mainstay of treatment for metastatic disease, improving survival when compared to best supportive care. Currently, there is no single standard of care chemotherapy regimen for advanced gastric carcinoma. Of the available treatments, combination chemotherapy provides increased response rates and overall survival at the cost of increased toxicity. Nonetheless, even with the most aggressive regimen, median survival is only 9.2 months.[2]

3.2 5-Fluorouracil, Leucovorin and Oxaliplatin (FOLFOX) in esophagogastric cancer

In advanced esophagogastric cancer, 5-fluoruracil has been the cornerstone of chemotherapy regimens and as a single agent results in response rates of 20-30%.[3] Studies have shown that when 5-fluorouracil is combined with other cytotoxics, there is a significant improvement in response rate and time to progression at the expense of increased toxicity.[4] The addition of docetaxel to cisplatin and 5-flurouracil has demonstrated an improved overall survival in advanced esophagogastric cancer patients (9.2 vs 8.6 months).[2] However, there is significantly more grade 3 and 4 neutropenia, complicated neutropenia, diarrhea and neurosensory toxicity, making this combination regimen suitable for only a carefully selected patient population treated by physicians familiar with its administration.

Studies using combined 5-fluorouracil and oxaliplatin have demonstrated similar outcomes when compared to other reference regimens in advanced esophagogastric cancer. [5-9] The substitution of oxaliplatin for cisplatin has been shown to be non-inferior in terms of overall survival, with significantly less grade 3 and 4 neutropenia, nephrotoxicity, nausea, renal toxicity, thromboembolism and alopecia. [5,10,11] Aproximately 40% of the FOLFOX-treated patients were progression free at 6 months with a trend toward improved median PFS and overall survival with 5FU/Oxaliplatin versus 5FU/Cisplatin (5.8 v 3.9 months, respectively; P= .077) and (10.7 v 8.8 months, respectively). [5]

FOLFOX is well tolerated, has proven activity in advanced esophagogastric cancer[12] and is safe in combination with other biologic agents. The tolerability and safety of mFOLFOX in esophagogastric cancer is well established and compares favorably to 5-Fu/Cisplatin regimen.[5,13,14] This regimen is increasingly used as a chemotherapy backbone in studies exploring novel biologic agents (e.g. NCI 8376 randomized Phase II study in gastric and gastroesophageal junction cancer of FOLFOX +/- hedgehog inhibitor GDC 0449).

Because there are preliminary safety data combining regorafenib with FOLFOX in colon cancer, a phase I study is not required (Bayer data on file). FOLFOX is a well tolerated, effective regimen

in advanced gastric cancer and is safe in combination with regorafenib. Adding a third cytotoxic agent (i.e. epirubicin or docetaxel) would necessitate phase I testing and most certainly add additional toxicities.

3.3 Rationale of the study

Regorafenib is of particular interest in esophagogastric cancer given the Phase III data demonstrating the increase in overall survival vs placebo in patients with metastatic colorectal cancer progressing after standard therapies.[15] Furthermore regorafenib provides a significant improvement in progression-free survival compared with placebo in patients with metastatic gastrointestinal stromal tumors (GIST) after progression on standard treatments with imatinib and sunitinib.[16] The efficacy and safety data supported FDA approval for colon and GIST (data described in Section 3.3.1.2).

Regorafenib, the first small-molecule multi-kinase inhibitor with proof of efficacy in colorectal cancer[15], is being studied in 1st line setting in colorectal cancer combination with FOLFOX and has a potential for new standard of care in patients with advanced esophagogastric cancer. MSKCC investigators have a track record over several decades in performing such trials, including two multicenter studies evaluating bevacizumab in metastatic disease.[17,18] There is a clear rationale to study more than one VEGF targeted agent in esophageal cancer, as has been indicated by MSKCC experience in developing bevacizumab and the MSKCC initiated phase II study of single agent sorafenib in 2nd/3rd line setting in patients with metastatic esophagogastric cancer. The phase II study of single agent sorafenib in patients with metastatic esophagogastric cancer finished accrual at MSKCC (IRB# 09-016, Janjigian et al manuscript in preparation). Patients receive sorafenib 400mg daily BID x 28 day cycles in 2nd or 3rd line setting until disease progression or unacceptable toxicity or serious intercurrent illness. The primary endpoint of the trial is to assess progression free survival (PFS). Secondary endpoints include response and therapy tolerance. Thirty-five patients have been accrued, with 34 evaluable; median number of prior therapies 2. One (3%) ongoing complete response (40+ months) was observed in a patient with Stage IV esophageal adenocarcinoma biopsy proven metastatic neck lymphadenopathy, recurrence after prior chemoradiotherapy and surgery. A second patient with GE junction adenocarcinoma had protracted stable disease in bulky celiac node disease (26+ months). 23 patients (68%) had stable disease. Median PFS is 3.6 months (95% CI 1.8 to 3.9 months), with median overall survival 8.8 months (95% CI 5.9 to 11.1 months). Overall, sorafenib is well tolerated in this patient population. Significant grade 3 toxicities included hand foot reaction (3 patients), rash (1 patient), dehydration (3 patients) and fatigue (2 patients). Twenty-seven of 33 tumors (82%) tested positive for phospho-ERK by immunohistochemistry.

Encouraging response and survival were observed in a phase II trial combining sorafenib with chemotherapy in patients with metastatic gastroesophageal junction cancer.[19] Forty-four chemotherapy-naïve patients with Eastern Cooperative Oncology Group performance status 0 or 1, of whom 80% had metastatic disease and two thirds had poorly differentiated gastric or GEJ adenocarcinoma were enrolled. The treatment regimen was sorafenib 400 mg orally twice a day for 21 days, docetaxel 75 mg/m2 intravenously on day 1, and cisplatin 75 mg/m2 intravenously on day 1, repeated every 21 days. The primary end point was response rate to the combination. Toxicity, overall survival, and progression-free survival were assessed as secondary end points. Eighteen of the 44 eligible and treated patients showed partial responses (41%; 90% CI, 28% to 54%). The median progression-free survival was 5.8 months (90% CI, 5.4 to 7.4 months). The median overall survival was 13.6 months (90% CI, 8.6 to 16.1 month). The major toxicity of this regimen was neutropenia, which reached grade 3 to 4 in 64% of patients. One patient experienced hemorrhage at the tumor site.

Our underlying research paradigm is that simultaneous targeting of multiple relevant pathways may lead to a more efficacious oncologic therapy. Regorafenib is the next generation inhibitor that targets pathway beyond VEGF that drive esophagogastric cancer. FGFR2 and PDGFR alterations have been described in esophagogastric cancer, and are associated with high metastatic potential and aggressive tumor biology.[20] Platelet-derived growth factor receptor (PDGFR) has a role in promoting angiogenesis, tumor growth and metastasis. Along with the fibroblast growth factor receptor (FGFR), PDGFR regulates the migration and adherence of pericytes and smooth muscle cells to endothelial cells, providing support and stability to vessel walls. Chemotherapy potentiates the effects of targeted agents, as suggested by promising overall survival in a recent Phase II study of sorafenib in combination with chemotherapy. Therefore the proposed study combines FOFLOX and regorafenib.

3.3.1 Regorafenib

Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment. *In vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Ab1 at concentrations of regorafenib that have been achieved clinically. In *vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.[21]

The rationale for the dose of regorafenib in this study is based upon the phase I data from Study 11650 (in which escalating doses from 10 mg to 220 mg per day of regorafenib was administered on a discontinuous schedule [3 weeks out of every 4]). Signs of antitumor activity were observed in subjects receiving doses from 60 mg to 220 mg per day on a discontinuous schedule (3 weeks out of every 4). However, of the 220 mg/day cohort, 8 of 12 subjects required a dose reduction for toxicity, whereas only 1 subject of 12 on the 160 mg/day cohort required such a dose reduction. Thus, based upon the efficacy and toxicity data, 160 mg was chosen as the dose for this study.
Preliminary data from an ongoing phase I study, evaluating the safety, efficacy, and PK of regorafenib in combination with chemotherapy (mFOLFOX6 or FOLFIRI) in patients with metastatic CRC, support the feasibility of the combination therapy. From a clinical and PK perspective, the proposed combination of regorafenib with mFOLFOX6 (with 85 mg/m2 oxaliplatin) is expected to be tolerable. A PK interaction is not expected.

3.3.1.1 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). [21] Immunohistochemical ex-vivo studies with a phospho –specific monoclonal anti-ERK 1 / 2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB 231 and BxPC-3), but not in NSCLC (H460).

In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody. [21] These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

3.3.1.2 Clinical experience

Two phase III global randomized studies have evaluated the efficacy of regorafenib. [15,16] The CORRECT (Patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy) trial is an international, multicenter, randomized, double-blind, placebo-controlled study that enrolled 760 patients with mCRC whose disease has progressed after approved standard therapies.[15] 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 clinical benefit. The safety and tolerability of the two treatment groups were also compared.

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

The most frequent grade 3+ adverse events in the regorafenib group were hand–foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). The efficacy and safety from the CORRECT study supported FDA approval in September 2012. The efficacy and safety of regorafenib were examined in the Phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options.[16] 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. The median survival period without tumor growth among patients on regorafenib was 4.8 months while for the control group on placebo it was less than a month. The overall disease control rate combining partial responses with durable stable disease for at least 12 weeks was 53% with regorafenib compared with 9% in the control group. The most common grade ≥3 adverse events associated with regorafenib were hand-foot skin reaction (56.1%), hypertension (48.5%), and diarrhea (40.9%). The efficacy and safety of the GRID study data supported FDA approval February 2013.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This will be a single institution, single arm study of regorafenib 160 mg daily on days 4 to 10 and days 18 to 24 as four 40 mg coprecipitate tablets + FOLFOX on Day 1 and Day 15 of each cycle.

Each cycle consists of 28 days. Treatment will be administered on an outpatient basis. All patients will receive systemic chemotherapy with the FOLFOX regimen and regorafenib. There are several variations of the basic FOLFOX regimen. The specific version of the FOLFOX regimen used at MSKCC is mFOLFOX6. mFOLFOX6 will be given on Day 1 of each cycle. Patients will receive Oxaliplatin 85 mg/m2 IV (over 120 minutes), leucovorin 400 mg/m2 IV (over 120 minutes), 5-FU 400 mg/m2 IVP, and 5-FU 1200 mg/m2/day CIVI x 2 days, every two weeks. If oxaliplatin has been discontinued then leucovorin will be administered over 30 minutes. In an effort to prevent adverse events, all patients will be premedicated with antiemetics as per institutional guidelines prior to the first dose of treatment. All other anti-emetics and supportive agents may be administered at the discretion of the primary oncologist. Treatment will be performed on the scheduled day ± 7 days. In case of discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off. The 3 weeks on/1 week off schedule is supported by the single agent regorafenib data in colon cancer and GIST.

All patients must be able to provide informed consent prior to enrollment.

See Section 10 for treatment table.

4.2 Intervention

Up to 36 patients will be enrolled on this clinical trial. Patients will receive regorafenib 160 mg daily on days 4 to 10 and days 18 to 24 as four 40 mg tablets + FOLFOX on Day 1 and Day 15 of each cycle until disease progression, unacceptable toxicity or serious intercurrent illness develops or if patient consent is withdrawn. Each cycle consists of 28 days. Patients must have evaluable or measurable disease and will undergo a computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis within 28 days of start of therapy, at eight weeks, and every eight weeks thereafter (every 2 cycles), with a scheduling window of up to one to fourteen (1-14) days. Response assessment will be by RECIST 1.1 criteria[22].The same imaging modality performed at baseline (CT or MRI) will be repeated at subsequent imaging. Intrapatient dose reduction to regorafenib will be allowed depending on the type and severity of toxicity encountered provided that criteria for patient withdrawal from study treatment have not been met. Once regorafenib is dose reduced, the patient should not go back to the starting dose. In case of discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off. The 3 weeks on/1 week off schedule is supported by the single agent regorafenib data in colon cancer and GIST. Therapy will be administered in the outpatient setting, with each cycle consisting of 28 days of continuous therapy. The cycle start date will coincide with the physician visit date. A study diary will be completed by patients to ensure compliance with the study drug (see APPENDIX A).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

For dose modification and management of adverse events see Section 11.0

5.1 Regorafenib (Bay 73-4506)

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.

Dosage and administration

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.
Four 40-mg regorafenib tables should be taken in the morning with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) breakfast. Some examples of low fat breakfasts are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
- One cup of cereal 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.)Patients with emesis should not take a replacement dose. A study diary will be completed by patients to ensure compliance with Regorafenib

Drug logistics and accountability

All study drugs will be stored at the investigational site 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.

Accountability

The investigator, 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.)

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

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 principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits or study drug.

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 CRDB (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 ketoconazole are expected to decrease metabolism of regorafenib and thus increase regorafenib plasma concentrations. There are no clinical data evaluating the effect of chronically coadministered CYP3A4 inhibitor on regorafenib 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.
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.
- 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
- For subject receiving regorafenib in combination with chemotherapy consider adding the following:
    - *A standard antiemetic regimen for the prophylaxis of acute emesis is recommended on the day of chemotherapy at least 30 minutes prior to the administration of chemotherapy. Such a regimen may include a serotonin (5-HT_3) antagonist (e.g. granisetron or ondansetron) with or without a corticosteroid (e.g. dexamethasone). The investigators should also consider providing subjects with a standard antiemetic regimen for treatment of delayed or breakthrough emesis as needed.*

5.2 5-FU, leucovorin and oxaliplatin

Qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.
The total administered dose of cytotoxic chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.
It is not necessary to change the doses of 5-FU, leucovorin or oxaliplatin due to changes in weight unless the calculated dose changes by ≥10%.

5.2.1 Oxaliplatin
Oxaliplatin will prepared and administered as per MKSCC guidelines. Please refer to the FDA-approved package insert for additional information.

Toxicity

The most commonly observed oxaliplatin toxicities include neurotoxicity, GI toxicity, and myelosuppression. Three neurotoxicity syndromes have been seen: acute sensory neuropathy develops within hours to 2 days after oxaliplatin administration. Symptoms include paresthesias, dysesthesias, and hypothesia of the hands, feet and perioral region. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain and a sensation of chest pressure have also been noted. Acute sensory neuropathy symptoms may be exacerbated by exposure to cold temperature or cold objects. Symptoms are reversible, usually resolving within 14 days and commonly recurring with further dosing. This syndrome has been observed in about 56% of patients receiving oxaliplatin with 5-FU and leucovorin.

Acute pharyngolaryngeal dysesthesia is reported to occur in 1-2% of patients. This syndrome is characterized by a subjective sensation of difficulty breathing or swallowing without laryngospasm or bronchospasm or objective evidence of hypoxia. Avoidance of cold drinks, food and air is suggested in order to minimize pharyngolaryngeal dysesthesia. Antianxiety agents (e.g., lorazepam) may be used to treat pharyngolaryngeal dysesthesias once oxygen saturation has been documented to be normal.

Peripheral neuropathy persisting > 14 days is characterized by paresthesias, dysesthesias, and hypothesia. Abnormalities in proprioception may also be seen. Symptoms of persistent neuropathy may improve upon discontinuation of oxaliplatin.

Various agents have been used in an attempt to minimize neurotoxicity of oxaliplatin (e.g. carbamazepine, Mg+, Ca++). Calcium and magnesium infusions appear to be beneficial in preventing neurotoxicity. Contrary to preliminary findings described in 2007, calcium and magnesium do not appear to interfere with tumor response to FOLFOX. Calcium and magnesium infusions are generally given before and after oxaliplatin, and should not be prepared in the same infusion solution as FOLFOX components.

Gastrointestinal toxicities include nausea, vomiting (oxaliplatin is considered to be moderately emetogenic) and diarrhea.

Neutropenia is reported in 73% of patients receiving oxaliplatin with 5-FU and leucovorin (44% grade 3 or 4). Grade 3 or 4 thrombocytopenia is reported to occur in 4% of patients receiving the combination.

Allergic reactions, similar to those seen with other platinum compounds, have also been observed in patients treated with oxaliplatin. Reactions range from rash to anaphylaxis.

Rarely, oxaliplatin has been associated with pulmonary fibrosis, which may be fatal. Oxaliplatin should be discontinued in the presence of unexplained pulmonary symptoms (e.g. nonproductive cough, dysphagia) or pulmonary infiltrates until interstitial lung disease or pulmonary fibrosis have been ruled out.

Recent reports of oxaliplatin extravasation suggest that tissue necrosis may result and that oxaliplatin should be considered a vesicant. No standard treatment exists for oxaliplatin extravasation although heat and sodium thiosulfate have both been suggested.

Veno-occlusive disease (VOD) of the liver is a rare complication associated with oxaliplatin and 5-FU. Clinical manifestations of VOD include hepatomegaly, ascites, and jaundice. Histologically, VOD is characterized by diffuse damage in the centrilobular zone of the liver. Sequelae of VOD include hepatomegaly, splenomegaly, portal hypertension, and esophageal varices. A recent analysis of resected liver metastases in 153 patients indicated histological findings consistent with VOD in 6/27 patients who received 5-FU alone, 4/17 patients who received 5-FU and irinotecan, 20/27 patients who received 5-FU and oxaliplatin, and 14/16 who received 5-FU, oxaliplatin and irinotecan. The remaining 66 patients had not received chemotherapy prior to resection. There were no such findings in these patients.

For more information on toxicities associated with oxaliplatin, please see the package insert.

5.2.2 5-Fluorouracil (5-FU; fluorouracil)

5-FU will prepared and administered as per MKSCC guidelines. Please refer to the FDA-approved package insert for additional information.

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Toxicity

Nausea, diarrhea, vomiting (mild); stomatitis: 5-8 days after treatment initiation; myelosuppression: granulocytopenia (9-14 days); thrombocytopenia (7-14 days); Alopecia; loss of nails; hyperpigmentation; photosensitivity; maculopapular rash; palmar–plantar erythrodysesthesia: (42-82% receiving continuous infusion); CNS effects: cerebral ataxia (rare); cardiotoxicity: MI, angina; asymptomatic S–T changes 68%; ocular effects: excessive lacrimation and less commonly, tear duct stenosis.

Drug Interactions

Leucovorin enhances the cytotoxicity of 5-FU by forming a more stable tertiary complex with thymidylate synthase. Concomitant Adminstration of 5-FU with warfarin has been reported to result in increased INR/prolonged prothrombin time. Patients on warfarin should be converted to enoxaparin or rivaroxaban therapy.

5.2.3 Leucovorin Calcium (Folinic Acid) (calcium folinate; citrovorum factor; N 5-formyltetrahydrofolate; 5-formyl-FH4; folinic acid)

Leucovorin will beprepared and administered as per MKSCC guidelines. Please refer to the FDA-approved package insert for additional information.

Toxicity

The only adverse reactions associated with leucovorin are allergic reactions. These are extremely uncommon.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Patient must have histologically or cytologically confirmed metastatic or unresectable esophageal, gastroesophageal junction or gastric adenocarcinoma.
- Patient must have disease that can be evaluated radiographically. This may be measurable disease or non-measurable disease. Minimum indicator lesion size = 10 mm by helical CT or = 20 mm by conventional techniques. Pathological nodes must be = 15 mm by the short axis to be considered measurable.
- Subject must be able to swallow and retain oral medication
- Age 18 years or older.
- Karnofsky performance status $\geq$ 70%
- Peripheral neuropathy $\leq$ grade 1
- Hematologic (minimal values)
  - White blood cell count $\geq$ 3000/mm$^{3©}$
  - Absolute neutrophil count $\geq$ 1500 cells/ mm^3
  - Hemoglobin $\geq$ 8.0 g/dl
  - Platelet count $\geq$ 90,000 / mm^3
- Total bilirubin $\leq$ 1.5 x the upper limits of normal (ULN)
- Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) $\leq$ 2.5 x ULN ($\leq$ 5 x ULN for subjects with liver involvement of their cancer)
- Alkaline phosphatase limit $\leq$ 2.5 x ULN ($\leq$ 5 x ULN for subjects with liver involvement of their cancer). Patients with alkaline phosphatase elevation secondary to the bony metastases rather

than liver dysfunction may proceed with treatment on protocol after discussion with the principal investigator.
- Serum creatinine ≤ 1.5 x the ULN
- 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.
- Patients with prior deep vein thrombosis (DVT) or pulmonary embolism (PE) currently on an anticoagulation regimen with low molecular weight heparin (LMWH) or rivaroxaban will be permitted..

6.2 Subject Exclusion Criteria

- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg on repeated measurement) despite optimal medical management.
- Active or clinically significant cardiac disease including:
  - Congestive heart failure – New York Heart Association (NYHA) > Class II.
  - Active coronary artery disease.
  - Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
  - Unstable angina (anginal symptoms at rest), new-onset angina within 3 months before randomization, or myocardial infarction within 6 months before randomization.
- Evidence or history of bleeding diathesis or coagulopathy.
- Any hemorrhage or bleeding event ≥ NCI CTCAE version 4.0 Grade 3 within 4 weeks prior to start of study medication.
- Unwillingness to give written informed consent, unwillingness to participate, or inability to comply with the protocol for the duration of the study.
- Active hepatitis B infection, active hepatitis C infection or known HIV carrier.
- Patient may not have received prior chemotherapy for metastatic or unresectable disease. Patients may have received prior adjuvant therapy (chemotherapy and/or chemoradiation) if more than 6 months have elapsed between the end of adjuvant therapy and registration.
- Patient may not have received prior 5-Fluorouracil, Leucovorin, Oxaliplatin or regorafenib. Patient may have received prior radiosensitizing doses of 5Fu if more than 6 months have elapsed between the end of adjuvant therapy and registration.
- Patient may not have had major surgical procedure within 4 weeks of registration.
- Patient may not have had radiation within 2 weeks of registration.

7.0 RECRUITMENT PLAN

This will be a single institution, phase II study. Patients with metastatic or recurrent esophageal, gastric and gastroesophageal (GE) junction cancer that are eligible will be identified for enrollment from MSKCC clinical practice and clinic lists. All patients with metastatic or recurrent disease that have not received prior chemotherapy for metastatic disease will be offered the study. The study information will be posted on clinicaltrials.gov and the MSKCC website. No additional measures, e.g. advertisement, payment to patients, will be employed to recruit patients. Patients will be accrued to this study without regard for gender or minority status.

Inclusion of women and minorities
The investigators take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. There will be no limitation with regards to race or gender.

Our institutional demographics for accrual of patients on esophageal, gastric and GE junction cancer trials reflect the national incidence of this disease: 10-15% of our patients have been women; African-American males comprise 3-5% of patients treated on protocol. Given that our protocol accrual closely reflects the national incidence of this disease, no specific strategy will be undertaken to recruit women or persons of color on this trial.

This protocol does not include children because the number of children with esophageal, gastric and GE junction cancer is very small and because the majority are already accessed by a nation-wide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

8.0 PRETREATMENT EVALUATION

Pretreatment evaluation will be performed within 2 weeks (14 days) of study entry and will include:

- History, concomitant medications, and toxicity assessment.
- Physical exam, vital signs (blood pressure, weight, heart rate, temperature), and performance status.
- Serum pregnancy test for women of childbearing potential (WOCP)
  In addition, all WOCP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g. late or missed period) at any time during study participation.
- Laboratory evaluation including complete blood count, and comprehensive chemistry panel (includes BUN, creatinine, ALT, AST, albumin, glucose, total protein, calcium, bilirubin, bicarbonate, sodium, chloride, potassium, alkaline phosphatase), , Thyroid function test (TSH, T3, T4)Urinalysis
- Electrocardiogram
- CT scan or MRI of all relevant disease sites within 28 days of study entry.

Correlative studies

The patients will be asked to consent to provide archived tissue (at MSKCC or an outside institution) and/or tissue from an upcoming clinically indicated biopsy for molecular analysis of their tumors, which will be stored for future correlative analysis. The patients will be asked to provide matched normal blood sample for normal DNA comparison.

9.0 TREATMENT/INTERVENTION PLAN

A standard antiemetic regimen for the prophylaxis of acute emesis is recommended on the day of chemotherapy, as per MSKCC guidelines.

All patients that meet the eligibility criteria who have signed informed consent and have enrolled on the trial will be treated with regorafenib 160mg (flat dose), on days 4 to 10 and days 18 to 24 as four 40 mg coprecipitate tablets + FOLFOX on Day 1 and Day 15 of each cycle (Table 1). Each cycle consists of 28 days. In case of discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off. The 3 weeks on/1 week off schedule is supported by the single agent regorafenib data in colon cancer and GIST. A given treatment or follow up visit may be moved +/- 4 days for specific administrative reasons, in particular clinic closure for holidays.

9.1 Modified FOLFOX-6 (mFOLFOX-6).

Patients ≤65 years old: Oxaliplatin 85 mg/m^2 IV on day 1, followed by or concurrent with leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2) IV, followed by 5FU 400 mg/m^2 IV bolus, followed by 5FU 2400 mg/ m^2 IV infusion over 48 hours

Patients > 65 years old: Oxaliplatin 70 mg/m^2 on day 1, followed by or concurrent with leucovorin 300 mg/m^2 (or levoleucovorin 150 mg/m^2) IV, followed by 5FU 300 mg/m^2 IV bolus, followed by 5-FU 2000 mg/m^2 infusion over 48 hours.

The patients will be seen weekly for the first three weeks on study. After first three weeks, weekly visits are no longer required and patients can be seen every 2 weeks.

Table 1: Regorafenib + mFOLFOX6 Study Treatment

			Day									
Study Drug[c]	Doses and Route of Administration		1	2	3	4-10	11-14	15	16	17	18-24	25-28
Oxaliplatin	85 mg/m^2	2-hour i.v. infusion	X					X				
Folinic acid	see footnote[a]	2-hour i.v. infusion	X					X				
5-Fluorouracil	400 mg/m^2	i.v. bolus injection	X					X				
	2400 mg/m^2	46-hour i.v. infusion	X	X	X			X	X	X		
Regorafenib[b]	160 mg od	oral tablets				X					X	

[a] Either D/L-folinic acid 400 mg/m2 or L-folinic acid 200 mg/m2.
[b] If regorafenib is administered as a monotherapy during the study, 160 mg daily will be administered for 3 weeks on/ 1 week off
[c] Chemotherapy doses reduced for patients >65 years old: Oxaliplatin 70 mg/m^2 on day 1, followed by or concurrent with leucovorin 300 mg/m^2 (or levoleucovorin 150 mg/m^2) IV, followed by 5FU 300 mg/m^2 IV bolus, followed by 5-FU 2000 mg/m^2 infusion over 48 hours.

9.2 Regorafenib

Regorafenib 160mg (flat dose), on days 4 to 10 and days 18 to 24 as four 40 mg coprecipitate tablets. Each cycle consists of 28 days. In case of permanent discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off. The 3 weeks on/1 week off schedule is supported by the single agent regorafenib data in colon cancer and GIST. Dose reductions described in section 11.

The following assessments should be performed every 2 weeks (14 days) prior to receiving study treatment (+/- 7 days)

- Record concomitant medications
- Vitals (temperature, HR, BP and RR), physical examination (including height and weight) and performance status assessment (KPS)
- Laboratory evaluation including complete blood count, and comprehensive chemistry panel (includes BUN, creatinine, ALT, AST, albumin, glucose, total protein, calcium, bilirubin, bicarbonate, sodium, chloride, potassium, alkaline phosphatase)
- Record Adverse Events (CTCAE v4.0)

Radiological imaging studies to evaluate tumor status will be repeated every two cycles (8 weeks) while on study regardless of treatment delays. 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. A given CT or MRI assessment may be moved +/- 7 days for specific administrative reasons, in particular clinic closure for holidays or patient's preference.

End of Treatment Visit

- Record concomitant medications
- Vitals (temperature, HR, BP and RR)
- Laboratory evaluation including complete blood count, and comprehensive chemistry panel (includes BUN, creatinine, ALT, AST, albumin, glucose, total protein, calcium, bilirubin, bicarbonate, sodium, chloride, potassium, alkaline phosphatase)
- Record Adverse Events (CTCAE v. 4)

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 2: Study Flow Chart

Procedure	Screen [a]	Cycle 1 (28 days)									Cycle 2 (28 days)									Sub-sequent Cycles	EOT [c]	Safety FU [d]	Survival FU [e]
		1	2	3	4-10	15	16	17	18-24	28	1	2	3	4-10	15	16	17	18-24	28				
Medical hx/demographics	X																						
Urine/serum pregnancy test	X																						
Tumor biopsy samples for biomarkers [f]																							
Physical exam [b]	X	X [g]			X	X			X		X			X	X					X [h]	X		
Performance status	X	X									X									X [h]	X	X	
Toxicities/AE assessment	Reported from screening throughout all subsequent cycles																				X	X [i,j]	
TSH, FT_3, FT_4	X		TSH, T3/4 testing should be performed during treatment if clinically inidicated																				
Hematology [b]	X	X [g]			X	X			X		X			X	X			X		X [h]	X		
Chemistry [b]	X	X [g]				X					X				X					X [h]	X		
Urinalysis	X																						
MRI/CT assessment [m]	X																		X [n]	X [n]	X	X [o]	
Concomitant medication	X [p]	All medications taken during the study will be documented																		X	X		
12-lead ECG	X																						
ECHO/ MUGA	X	LVEF assessment should be performed if clinically indicated																					
mFOLFOX6 [q]		X	X			X	X	X			X	X	X		X	X	X			X [h]			
Regorafenib [r]					X				X					X				X		X [h]			
BP monitoring		Weekly for the first 3 weeks of treatment																					
Regorafenib dispensing				X				X					X				X			X [h]			

Regorafenib compliance		Compliance will be assessed at every cycle	X[n]			

BP = blood pressure; chemo = chemotherapy; ECG = electrocardiogram; ECHO = echocardiogram; EOT = end of treatment; FU = follow-up; LVEF = left ventricular ejection fraction; h = hour(s); hx = history; MUGA = multiple gated acquisition scan; 1° = primary.

a Radiological imaging studies within 28 days of start of study treatment, other screening evaluation within 2 weeks prior to start of study treatment.

b Physical exam (vital signs [BP, heart rate, temperature], weight, and a review of body systems), chemistry, Hematology and physical exam will be done weekly for the first 3 weeks and on the intended days 1 and days 15 of each cycle prior to the chemo or ≤ 72 h prior to dosing thereafter. After the end of the cytotoxic regimen (mFOLFOX6 or 5-FU/folinic acid alone), day 15 assessments can be done at the discretion of the investigator.

c Within 1-14 days of tumor progression or study treatment discontinuation.

d Assessment by treating medical oncologist

e For those patients no longer followed by MSKCC MD, the study research assistant will make a follow up phone call every 3 months to assess patient's vital status.

f A sample of archival tumor biopsy, or other available tumor biopsy, should be submitted for biomarker analysis during screening. Tumor biopsy samples may also be submitted for biomarker analysis at any other time during the course of the clinical study.

g For physical exam/lab assessments, not required if screening assessments were done within 72 hours of first dose. For ECG, not required if screening ECG was done within 7 days of first dose.

h Cycles ≥3: Procedures will be performed identical to cycle 2 radiologic tumor assessment will be at the end of every second cycle (cycles 4, 6, etc) before the next cycle (cycles 5, 7, etc). For subjects on monotherapy regorafenib, no day 15 visit after the first 4 cycles is required.

i AE monitoring should continue for at least 4 weeks following the last dose of study treatment.

j Only applies to AEs that occur within 30 days following the last study treatment. Those AEs will be followed until resolution.

l Proteinuria has to be assessed with lab value at screening and continue only if clinically indicated. Urinalysis must not show 1+ or more protein in urine or the subject will require a repeat urinalysis.

m The baseline and subsequent scans to assess response must be performed using identical technique. Radiological imaging studies to evaluate tumor status will be repeated every 2 Cycles (8 weeks) while on study regardless of treatment delays. 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.

n Starting in cycle 2, done at the end of every 2nd cycle (cycles 2, 4, 6, etc) before the next cycle (cycles 3, 5, 7, etc).

o For subjects who have entered the survival follow-up period and have not yet experienced PD, every effort should be made to follow-up for tumor evaluation (by CT or MRI) until progression of their malignancy every 8 weeks, or until a new anticancer treatment is started.

p All medication given within 2 weeks prior to the start of study treatment.

q Doses of chemotherapy regimen should be recalculated prior to each cycle if there has been a change of ≥ 10% in body weight. Use actual weight.

r Regorafenib as a monotherapy will be administered for 3 weeks on/ 1 week off and should be dispensed on day 1 of every cycle.

s If screening evaluations are done within 14 days of start of treatment, Cycle 1 Day 1 evaluations need not be repeated

11.0 TOXICITIES/SIDE EFFECTS

11.1 Regorafenib

The starting dose of regorafenib is 160 mg once daily on days 4 to 10 and days 18 to 24 as four 40 mg coprecipitate tablets + FOLFOX on Day 1 and Day 15 of each cycle. Each cycle consists of 28 days. In case of discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off. The 3 weeks on/1 week off schedule is supported by the single agent regorafenib data in colon cancer and GIST.

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 0 (standard starting dose)	160 mg by mouth daily	Four 40-mg tablets of regorafenib
Dose level - 1	120 mg by mouth daily	Three 40-mg tablets of regorafenib
Dose level - 2	80 mg by mouth daily	Two 40-mg tablets of regorafenib

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.

If more than 2 dose reductions are required, regorafenib only will be discontinued and the rest of the study treatment may be continued. The following tables outline dose adjustments for toxicities related to study drug except hand-foot skin reaction, hypertension and liver function test abnormalities.

Table 11.1.1: 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	
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

Table 11.1.2 : Grading for Hand-Foot-Skin-Reaction

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

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.

Suggested regorafenib (Bay73-4506) dermatologic toxicity modification

Table 11.1.3 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 there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
c. Subjects requiring > 2 dose reductions should go off protocol therapy.
d. The maximum daily dose is 160 mg.

(For studies with combination therapy, consider including the following statement –The other study treatment may be continued‖).

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.

Table 11.1.4: Management of Treatment-Emergent Hypertension

Grade (CTCAE v4.0)	Antihypertensive Therapy	Regorafenib Dosing
1 Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg, OR Symptomatic increase by > 20 mm Hg (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 mm Hg or diastolic BP ≥ 100 mm Hg 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.[c]
4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy

a. Patients requiring a delay of >4 weeks should go off protocol therapy
b. Patients requiring >2 dose reductions should go off protocol therapy.

- 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 at MD visits weeks 1 to 3 and additional BP monitoring per investigator discretion. 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, **Table 11.1.4** outlines suggested dose reductions.

Liver Function Abnormalities

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

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

Table 11.1.5: 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 serum 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 serum 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 monitored weekly.

Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib (Bay 73-4506). 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 FOLFOX

Initiation of the next cycle of therapy may be delayed by no more than 4 weeks to allow recovery from toxicity. Treatment delay of > 4 weeks due to toxicity may lead to removal from study.

Dose reduction of oxaliplatin or 5-FU/folinic acid should be based on the worst toxicity demonstrateddurin the preceding cycle.. Subjects who require more than 2 dose-reduction steps must permanently discontinue either oxaliplatin, or 5-FU/folinic acid, or both depending on the specific toxicity. Regorafenib may continue at investigator's discretion.

If cycle start date is delayed due to toxicity related to FOFLOX, regorafenib will be held and resume on Day 4 of the cycle. In case of discontinuation of FOLFOX due to cumulative toxicity and administration as a single agent during the study, regorafenib for patient convenience will be administered 160 mg daily for 3 weeks on/1 week off.

11.2.1 Dose Modifications of FOLFOX

11.2.1.1 Hematologic Toxicity

Colony stimulating factors: Patients should not routinely receive prophylactic colony stimulating factors (e.g., G-CSF, GM-CSF) during cycle 1. Subsequent use will be at the discretion of the treating physician.

Neutropenia

For ≥ grade 3 ANC on the day of treatment, delay treatment until ANC improves to ≤ grade 2, then resume treatment with:

- One dose level reduction of oxaliplatin for all subsequent cycles.
- One dose level reduction of 5-FU (bolus & infusion) and leucovorin for all subsequent cycles.
- If treatment is delayed for neutropenia for 4 consecutive weeks, discontinue all protocol treatment.

Thrombocytopenia

For platelets 74,000 to 50,000 on day of treatment, delya treatment until platelets improve ≥75K then resume treatment as follows:

- One dose level reduction of oxaliplatin for all subsequent cycles.
- One dose level reduction of 5-FU (bolus & infusion) and leucovorin for all subsequent cycles.
- *For platelets 74 – 50,000 persisting > 7 days, resume treatment with oxaliplatin with two dose level reductions when platelets improve to ≥ 75,000.*

For platelets 49,000– 25,000 on day of treatment, delay treatment until platelets improve to ≥ 75,000, then resume treatment as follows:

- One dose level reduction of oxaliplatin for all subsequent cycles.
- One dose level reductions of 5-FU (bolus & infusion) and leucovorin for all subsequent cycles.
- *For platelets < 49,000 - 25,000 persisting > 7 days, resume treatment with oxaliplatin with 2 dose level reductions when platelets improve to ≥ 75,000.*

For platelets < 25,000 on day of treatment, delay treatment until platelets improve to ≥ 75,000, then resume treatment as follows:

- Two dose level reductions of oxaliplatin for all subsequent cycles.
- Two dose level reductions of 5-FU (bolis & infusion) and leucovorin for all subsequent cycles.
- *For platelets < 25,000 persisting > 7 days, resume treatment with oxaliplatin with 2 dose level reductions when platelets improve to ≥ 75,000.*

11.2.1.2 Neurologic Toxicities

For grade 2 peripheral sensory neuropathy (moderate paresthesia or dysesthesia, or limiting instrumental activities of daily living)

Skip oxaliplatin. When toxicity resolves to ≤ grade 1, resume oxaliplatin with one dose level reduction, for all subsequent cycles. Continue 5-FU and leucovorin.

If oxaliplatin is skipped for 4 weeks (2 consecutive doses) for neurologic toxicity, discontinue oxaliplatin. Continue 5-FU and leucovorin.

For grade 3 or greater peripheral sensory neuropathy (severe paresthesia or dysesthesia, or limiting self-care activities of daily living)

Discontinue oxaliplatin. Continue 5-FU/leucovorin.

11.2.1.3 Gastrointestinal Toxicities

For grade ≥ 2 diarrhea, skip mFOLFOX6 until diarrhea improves to ≤ grade 1.

- Following grade 3 or 4 diarrhea at any time during a cycle: continue mFOLFOX6 with one dose level reduction of 5-FU for all subsequent cycles and the previous dose level of oxaliplatin.
- If FOLFOX is skipped for diarrhea for 4 weeks (2 consecutive cycles), discontinue mFOLFOX6.

For ≥ grade 2 oral mucositis present on Day 1 of a cycle: delay mFOLFOX6 until mucositis improves to < grade 2. Decrease 5-FU by 1 dose level for all subsequent cycles.

If a subject requires a dose delay of oxaliplatin/5-FU/folinic acid > 4 weeks from the intended next dose, then treatment of the specific drug will be permanently discontinued.

Subjects who have had their treatment cycle delayed must be evaluated by those evaluations defined for the intended day 1 of that cycle ≤ 72 hours prior to actual dosing.

Subjects may also discontinue oxaliplatin following multiple cycles if in the investigator's judgment cumulative toxicity is likely to increase over time and become problematic.
If oxaliplatin treatment only should be discontinued in the investigator's judgment, the subjects should continue to receive other protocol-specified treatments.
General dose reductions for mFOLFOX6 are outlined in Table 11.2.1

Table 11.2.1

	Drug	Age (Years)	Starting Dose	Dose Modification	
				Dose Level -1	Dose Level -2
	Oxaliplatin	< 65	85 mg/m^2	70 mg/m^2	50 mg/m^2
		≥ 65	70 mg/m^2	50 mg/m^2	35 mg/m^2
	5 FU	< 65	Bolus 5FU: 400 mg/m^2 Leucovorin: 400 mg/m^2 Infusion 5FU: 2400 mg/m^2/48 hours	Bolus 5FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5FU: 2000 mg/m^2/48 hours	Bolus 5FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5FU: 1600 mg/m^2/48 hours
		≥ 65	Bolus 5FU: 300 mg/m^2 Leucovorin: 300 mg/m^2 Infusion 5FU: 2000 mg/m^2/48 hours	Bolus 5FU: 200 mg/m^2 Leucovorin: 200 mg/m^2 Infusion 5FU: 1600 mg/m^2/48 hours	Bolus 5FU: 150 mg/m^2 Leucovorin: 150 mg/m^2 Infusion 5FU: 1300 mg/m^2/48 hours

11.3 FOFLOX and Regorafenib

The expected toxicities of FOLFOX and Regorafenib are fatigue, mucositis, myelosuppression, diarrhea, neuropathy, liver function abnormalities, hand foot syndrome, hypertension

11.4 Definitions of Adverse Events.

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.
Serious adverse event
A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which

may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Severity of adverse event

The severity of the AE should be judged based on the following:
The severity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4 in the CRDB.

Causal relationship of adverse event

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Causality will be reported as either -Yes‖ or –No‖.

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

11.5 Malignant disease progression

Expected fluctuations or expected deterioration of the underlying disease should not be recorded as an AE unless at least one of the following criteria is met:

- Worsening of the disease constitutes an SAE,
- Additional treatment is required, i.e. concomitant medication is added or changed.
- An unexpected deterioration from baseline has occurred in the opinion of the investigator.

11.6 Worsening of pre-existing conditions

A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as adverse event. Any worsening of any pre-existing baseline condition should be reported as an adverse event. Examples of worsening of a preexisting condition that should be recorded as an AE are given below;

- Worsening of condition meets the criteria for an SAE
- Action is taken with the investigational drug (i.e. dose is reduced or treatment is discontinued)
- Treatment is required (concomitant medication is added or changed)
- The investigator believes a patient has shown a clear deterioration from baseline symptoms

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

All patients who receive at least one dose of FOLFOX and began regorafenib therapy will be evaluable for toxicity and response. Patients who are did not begin regorafenib therapy will not be evaluated for toxicity or response and will be replaced by a new patient.

The primary endpoint of the study is the efficacy of the combination of FOLFOX and regorafenib in terms of progression free survival (PFS) at 6 months. Secondary endpoints include best overall clinical benefit defined as stable disease (SD), complete response (CR), or partial response (PR). Confirmatory scans should be obtained no less than four weeks following initial documentation of

objective response. This is defined as the percentage of patients who have achieved either an objective complete or partial target lesion response that is confirmed on the RECIST 1.1 criteria. Complete or partial responses will be confirmed with repeat CT evaluation after 4 weeks. Target lesions must have a minimum size of at least one diameter of 10mm for liver, soft tissue lesions, lung, and skin. Pathological nodes must be at least 15mm in the short axis to be considered target lesions. The primary tumor is not considered measurable disease. Recurrent or metastatic lesions within a prior radiation field are acceptable as long as disease has progressed in the radiation field by RECIST 1.1 criteria. The same imaging modality performed at baseline (CT or MRI) will be repeated at subsequent imaging.

Secondary endpoints include toxicity, safety and tolerability. The type, frequency, severity, timing, and relationship of each adverse event will be determined as per the NCI Common Toxicity Criteria, version 4.0. Toxicity during cycle 1 and subsequent cycles will be reported.
Assessment of stable disease will be based on RECIST 1.1 criteria.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient develops progressive disease he/she will be taken off study and referred for alternative therapy. If at any time the patient develops unacceptable toxicity that fails to resolve after a maximum treatment delay of 4 weeks, he/she will be removed from study. Before being removed from the study, patients will be scanned to assess the response. If the off study scan shows progression of disease then the patient will be considered as a non responder, while a CR or PR will be considered as response.

A patient will be withdrawn from the study treatment in the following circumstances:

● the patient is no longer able to participate in the study (e.g., AE, surgery, concomitant diagnoses, concomitant therapies or administrative reasons); in such a case the Investigator‘s reason for a patient‘s removal must be recorded in CRDB.
● Patient withdrawal of consents or election to discontinue participation in the trial
● Significant deviation from the protocol or eligibility criteria; such patients will be considered protocol violations and removed from study
● Non-compliance with study or follow-up procedures
● Drug related AE(s) have not resolved after 4 weeks of treatment interruption. Exception to this in patients who derive obvious clinical benefit according to the investigator‘s judgment could be considered upon discussion with Principal Investigator. The dose reduction scheme provided should be followed in this case.
● repeated episodes of drug related toxicity despite dose reduction as indicated in Section 11.
● documented progressive disease

As soon as a patient is withdrawn from the study treatment, the End of Treatment (EOT) visit has to be performed within 1-14 days after off study date. Every effort should be made to follow-up patients in case an adverse event has still ongoing at the time of withdrawal. Patients who show a clinical benefit from treatment with regorafenib (i.e., with either an objective tumor response or the absence of disease progression), may continue to receive additional treatment courses. Patients with radiologically documented progressive disease should be removed from the study unless the investigator judges it to be of clinical benefit for the patient to continue on trial therapy.

14.0 BIOSTATISTICS

The primary endpoint is progression free survival (PFS), as measured from the start of the treatment to the date of either documentation of disease progression or death. We will define progression of disease as per RECIST 1.1 criteria. Patients with measurable disease and with evaluable radiographically but non-measurable disease will be eligible for study entry. As per RECIST 1.1 criteria, any evidence of progression in non-measurable lesions, measurable lesions, or the development of new lesions, would qualify as disease progression. Using an exact single stage binomial design, we will accrue 36 Stage IV or unresectable esophagogastric adenocarcinoma patients to differentiate between 6-month PFS of 40% and 61% with type I of 5% and power of 80%. If 20 or more patients are progression free at 6 months, FOLFOX +Regorafenib will be considered worthy of further investiagaion. Patients who come off study before 6 months without documented progression will be considered as events for the primary endpoint of 6 months PFS. We anticipate enrollment to be 2-3 patients/ months with completion of accrual in approximately 18 months. Patients that come off study due to toxicity before 6 months without documented progression will continue to be scanned to obtain 6 months assessment of progression. Patients that were lost to follow up or withdrew consent before 6 months without documented progression will be counted as events for the primary endpoint; however this is expected to be a rare occurrence. The patients who completed at least one cycle of FOFLOX and regorafenib will be considered evaluable.

Previous clinical trial has reported the frequency of adverse events attributable to treatment with

Toxicity	# of toxicities needed to stop the study	Toxicity rate	Probability boundary is crossed
Gr 4+ Neutropenia	5 within the first 10 patients 7 within the first 20 patients 11 within 36 patients	.19	.11
		.45	.98
Gr 3+ Diarrhea	4 within the first 10 patients 6 within the first 20 patients 8 within 36 patients	.12	.08
		.35	.97
Gr 3+ Neuropathy	2 within the first 10 patients 3 within the first 20 patients 5 within 36 patients	.05	.13
		.25	.98
Gr 4+ LFT	5 within the first 10 patients 8 within the first 20 patients 11 within 36 patients	.19	.09
		.4	.92
Gr 3+ HFS	4 within the first 10 patients 6 within the first 20 patients 8 within 36 patients	.12	.08
		.3	.9
Gr 3+ persistent hypertension	2 within the first 10 patients 3 within the first 20 patients 4 within 36 patients	.04	.1
		.2	.96

FOLFOX[5] A similar frequency of adverse events will be considered attributable to the FOLFOX plus Regorafenib used in this trial and therefore acceptable. In order to reduce patient risk, the study design includes early termination of the trial in the event of excessive grade 4+ neutropenia, grade 3+ diarrhea despite adequate antidiarrheal management (loperamide and diphenoxylate/atropine) or grade 3+ neuropathy. In addition, the safety analysis will assess the

toxicity rates that may arise related to regorafenib of grade 4+ LFT abnormality, grade 3 hand food syndrome (HFS) (despite adequate skin management) or persistent grade 3+ hypertension despite adequate medical management. Furthermore, presence of grade 3+ events which in the clinical judgment of the principal investigator are felt to be serious, unexpected, and a side effect likely due to regorafenib, will give evidence to reduce the dose as well. Only adverse events (possibly, probably, or definitely) related to the study treatment in the first 2 cycles (i.e. 8 weeks) will count towards the excessive toxicity boundaries below. The stopping rules are derived using repeated significance testing are given in the table below.

Secondary endpoints: Overall survival will be measured from the start of treatment to death or last follow-up and will be estimated using the Kaplan-Meier method. Response rate will be estimated using binomial proportions along with 95% confidence intervals. Toxicity will be summarized using descriptive statistics.

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.

16.0 DATA MANAGEMENT ISSUES

The data collected for this study will be entered into MSKCC's Clinical Research DataBase (CRDB), a secure database. Source documentation will be available to support the computerized patient record. Anonymization will take place at the point of entry into the database. Subsequent laboratory analysis will take place on the anonymized samples.

Tumor slides will be stored in the MSKCC pathology laboratory. Results from laboratory studies will include photomicrographs of IHC studies, computer files of sequencing data, and computer files from microarray analyses. These files will be stored on the Department of Medicine server. Documentation linking patient identifiers and patient samples results will be securely maintained in the CRDB with access limited to study investigators.

16.1 Quality Assurance

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

16.2 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://mskweb2.mskcc.org/irb/index.htm*

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.

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.

For IND/IDE protocols:
The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.3

Definitions

The following standard text should be used:

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).

The clinical manifestation of any failure of expected pharmacological action (lack of efficacy) is not recorded as an AE if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria of an SAE, it must be recorded as and AE and reported as an SAE.

- 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.

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.

Serious adverse events
In addition to the SAE criteria specified in the standard text above, further criteria may be defined; e.g. all Grade-4 laboratory toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE, version to be specified) may have to be recorded as SAEs.

Classifications for adverse event assessment

The following classifications should be used:

- *Seriousness*

- *Intensity*
  As an alternative to the grading system described in the standard text below (mild, moderate, severe), other systems for intensity may be used (e.g. CTCAE, Grade 1 to Grade 5). If used, this needs to be stated and definitions of the grades should be provided. If applicable, a "translation" between the CTCAE system and the standard system of intensity grading may have to be provided.

- *Causal relationships to study drug:*

To be assessed separately for concomitant agents

Example 1 *Doxorubicin (open* *regorafenib (blinded)* *Versus* *Doxorubicin (open label)* *+ matching placebo* *(blinded)*	*The relationship to study drug will assume that both active entities (regorafenib or doxorubicin) are suspect drugs if both drugs are given in combination. Due to regorafenib, regorafenib and placebo being blinded, the assumption is that both compounds could be in causal relationship as long as doxorubicin and regorafenib /placebo (blinded) are given in combination. In exceptional cases, the investigator can state in the comment field that he/she believes that the event is more likely to be caused by doxorubicin.*
Example 2 *Dose-escalation trial,* *open-label study* *regorafenib +* *bevacizumab*	*The assessment of the relationship of an AE to the administration of study drug is the investigator's clinical decision based on all available information at the time of the completion of the CRF. Study drug refers to regorafenib and/or bevacizumab and the assessment of relationship to study drug will be done for each drug separately. If the investigator feels such a distinction cannot be made (e.g. due to a suspected underlying interaction) the same assessment will be documented for both drugs*

- *Study treatment action*

- *Other specific treatment of AE*

- *Causal relationship to protocol-required procedures(s)*
- *Outcome*

All AEs will be assessed and documented by the investigator according to the categories detailed below.

Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 0.

Intensity

The intensity of the AE is classified according to the CTCAEv4.0. Grade refers to the severity (intensity) of the AE:

CTCAEv 4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv 4 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

CTCAEv 4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv 4 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv 4 Grade 5: death due to an AE.

Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information.

If applicable for trials with more than one study agent, the following sentence should be included.

The causality assessment should be done separately for each study treatment.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no".

An assessment of "no" would include:

1. The existence of a clear alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):
- Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.

[Causal relationship to protocol-required procedure(s)]

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

If applicable for trials with more than one study agent, the following sentence should be included.

The study treatment action should be recorded separately for each study treatment.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

Assessments and documentation of adverse events

Reporting of serious adverse events

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

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

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

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

An ADEERS form (Adverse Event Expedited Reporting System) available at

http://ctep.cancer.gov/reporting/adeers.html

OR

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

All reports shall be sent electronically to:

Electronic Mailbox: DrugSafety.GPV.US@bayer.com

Facsimile: (973) 709-2185

Address: Global Pharmacovigilance - USA

Mail only: Bayer HealthCare Pharmaceuticals Inc.

P.O. Box 1000

Montville, NJ 07045-1000

Address: 340 Changebridge Road

FDX or UPS only Pine Brook, NJ 07058

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

Phone: 1-888-842-2937

Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) / summary of product characteristics.

If applicable, the following sentence should be included.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by Bayer according to the applicable reference document and according to all local regulations.

Adverse events of special safety interest

This optional subsection may be used to pre-define certain AEs that are of particular interest for a given drug development program. All pertinent details (e.g. reporting procedures) are to be specified as appropriate.

If not needed, this subsection should be deleted.

As with any new chemical entity, there is always potential for unexpected adverse events, including hypersensitivity reactions.

Based on data studies with regorafenib and from current knowledge of the pharmacological properties of other small molecule tyrosine kinase inhibitors in this drug class, as soon as there is reasonable suspicion of any of the following AEs, the investigator should immediately notify the sponsor.

Reportable adverse events include:

- Acute renal failure (NCI-CTCAE version 4.0 ≥ grade 3) or severe proteinuria (NCI-CTCAE version 4.0 ≥ grade 3)
- Interstitial lung disease
- Acute cardiac failure
- Clinically significant bleeding (NCI-CTCAE version 4.0 ≥ grade 3)

- Stevens-Johnson Syndrome and erythema multiforme
- Hepatic failure
- Reversible posterior leukoencephalopathy syndrome
- Gastrointestinal perforation or fistula

Pregnancies

The investigator must report to Bayer any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used.

Further safety

Consider adding following additional language:

Progressive disease

If progressive disease leads to signs and symptoms that meet the criteria for an SAE (i.e., hospitalization, disability, death, or important medical event), the signs and symptoms should be reported as an SAE and not the underlying progressive disease.

Death

If any subject dies during the trial or within 30 days of the end-of-treatment visit, the investigator will inform Bayer and record the cause of death in detail (using the SAE Form) within 24 hours.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

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

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

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

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: Pill Diary For Regorafenib Days 4 through 10 and 18 through 24

Appendix B: Pill Diary For Regorafenib Days 1 through 21