Title: A phase II study of regorafenib in metastatic medullary and differentiated RAI refractory thyroid cancer

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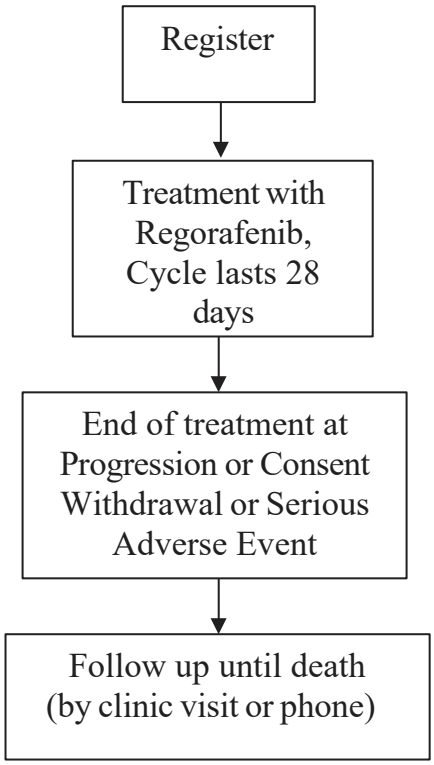
Agent: Regorafenib, supplied by Bayer HealthCare Pharmaceuticals

IND #: IND Exempt

SCHEMA OF THE STUDY



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1. OBJECTIVES

1.1 Study Design

This is an open label, non-randomized, phase II study designed to evaluate the efficacy and safety of regorafenib in subjects with progressive, metastatic medullary thyroid carcinoma (M T C) and in subjects with differentiated thyroid cancer (DTC) with or without prior therapy. A total of up to 32 patients could be enrolled in this study (8 with medullary thyroid cancer, and up to 24 with RAI refractory thyroid cancer) which is similar to the overall accrual goal from when the trial originally opened. Given the changing treatments for medullary thyroid cancer, enrollment to the medullary thyroid cancer cohort is held and up to 24 patients with RAI refractory thyroid cancer will be enrolled. Eligible subjects with RAI refractory thyroid cancer will be enrolled on a dose escalation schedule that has been established recently (starting at 80mg and escalation weekly to 120 and 160mg if no severe SAE occur and continuing on the individual MTD from cycle 2 onward) with regorafenib daily on a three weeks on and one week off schedule.

1.2 Primary Objectives

- To evaluate proportion progression-free at 10 months in patients with MTC
- For RAI refractory thyroid cancer: Response rate by RECIST criteria.

1.3 Secondary Objectives

- To evaluate the safety and tolerability.
- To evaluate radiographic response per RECIST v1.1 (medullary TC only).
- To assess Quality of Life.
- To evaluate candidate biomarkers and associate with response (Calcitonin and CEA in MTC, Thyroglobulin in RAI refractory DTC).
- Whole exome sequencing will be performed on tumor and normal genomic DNA on all responders.

2. BACKGROUND

2.1 Study Disease

Medullary thyroid cancer (MTC) comprises 3% to 4% of all thyroid cancers. These tumors usually present as a mass in the neck or thyroid, often associated with lymphadenopathy [1] or they may be diagnosed through screening family members. MTC can also be diagnosed by fine-needle aspiration biopsy. Cytology typically reveals hypercellular tumors with spindle-shaped cells and poor adhesion [2].

The overall survival of patients with MTC is 86% at 5 years and 65% at 10 years. Poor prognostic factors include advanced age, advanced stage, prior neck surgery, and associated multiple endocrine neoplasia (MEN) 2B [2-4].

Approximately 25% of reported cases of MTC are familial. Familial MTC syndromes include MEN 2A, which is the most common; MEN 2B; and familial non-MEN syndromes. Any patient with a familial variant should be screened for other associated endocrine tumors, particularly parathyroid hyperplasia

and pheochromocytoma. MTC can secrete calcitonin and other peptide substances. Determining the level of calcitonin is useful for diagnostic purposes and for following the results of treatment.

Family members should be screened for calcitonin elevation and/or for the *RET* proto-oncogene mutation to identify other individuals at risk for developing familial MTC. All patients with MTC (whether familial or sporadic) should be tested for *RET* mutations, and if they are present, family members should also be tested. Whereas modest elevation of calcitonin may lead to a false-positive diagnosis of medullary carcinoma, DNA testing for the *RET* mutation is the optimal approach.

Family members who are gene carriers should undergo prophylactic thyroidectomy at an early age [5,6].

Patients with MTC should be treated with a total thyroidectomy, unless there is evidence of distant metastasis. In patients with clinically palpable MTC, the incidence of microscopically positive nodes is more than 75%; routine central and bilateral modified neck dissections have been recommended [7]. When cancer is confined to the thyroid gland, the prognosis is excellent.

External radiation therapy has been used for palliation of locally recurrent tumors; however, no evidence exists that it provides any survival advantage [8]. Radioactive iodine has no place in the treatment of patients with MTC.

Differentiated thyroid cancer (DTC) includes papillary and follicular thyroid cancer as well as poorly differentiated histologies. Papillary thyroid cancer (PTC) is the most frequent type of thyroid cancer, is more frequent in women. The prognosis is generally good; however, 7–23% of patients develop distant metastastatic disease; further treatment with RAI can eradicate the disease in only one third of these cases while two thirds develop radioiodine refractory (RAIR) disease. For these patients, treatment options are limited with only 2 targeted drugs currently approved by the FDA: Lenvatinib and Sorafenib. Therefore, more treatment options are urgently needed.

There are no data about the activity of regorafenib in differentiated thyroid cancer (DTC). However, the biochemical properties of this drug are very similar to that of sorafenib, an FDA approved standard in RAI refractory thyroid cancer with similar or stronger inhibition of individual kinases.

Furthermore, clinical activity in all other cancer types that have been studies so far was at least as good as Sorafenib, in some cases clearly better. For example, Regorafenib has received FDA approval in metastatic colorectal cancer where sorafenib has shown some but limited activity.

Both drugs are FDA approved in hepatocellular carcinoma based on phase 3 data. Regorafenib improved overall survival with a hazard ratio of 0.63 (95% CI 0.50–0.79; one-sided $p<0.0001$); median survival was 10.6 months (95% CI 9.1–12.1) for regorafenib versus 7.8 months (6.3–8.8) for placebo. For sorafenib, median overall survival was 10.7 months in the sorafenib group and 7.9 months in the placebo group (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; $P<0.001$). In renal cell cancer, sorafenib is FDA approved based on phase 3 data (median progression-free survival was 5.5 months in the sorafenib group and 2.8 months in the placebo group) but regorafenib has recenly demonstrated significant, perhaps superior activity with a median (duration of treatment was 7.1 months (range 0.7–34.4, IQR 2.5–18.0) 19/48 patients (39.6%, 90% CI 27.7–52.5) had partial responses versus 10% partial responses with sorafenib.

The purpose of this amendment is to assess efficacy in differentiated thyroid cancer. Based on the kinase-inhibitory profile and clinical data in other cancer types including renal cell cancer, activity should at least be similar, if not superior to sorafenib, a FDA approved standard in DTC.

2.2 FDA approved Treatment options for locally advanced and metastatic disease Vandetanib is an oral inhibitor of RET kinase, vascular endothelial growth-factor receptor, and epidermal growth-factor receptor signaling. It was tested in a placebo-controlled, prospective trial (NCT00410761) in 331 patients with locally advanced and metastatic disease with a 2:1 ratio in assignment to the study drug [9]. Subjects with 0, 1 or more than 1 prior therapies were included in this study. With a median follow-up of 24 months, progression-free survival (PFS) favored vandetanib (hazard ratio = 0.46; 95% confidence interval, 0.31–0.69; $P < .001$) with a median PFS estimated at 30.5 months for vandetanib versus 19.3 months for placebo [9].

Overall survival (OS) was not different at 24 months; longer follow-up will be required since only 47 patients had died at the time of analysis, and there was a crossover to the study drug on progression from placebo, making analysis of OS problematic. Vandetanib has significant side effects, including diarrhea, rash, hypertension, and QT prolongation. Quality of life was not formally assessed in this trial [9].

Cabozantinib, another, similar TKI with RET and VEGFR inhibitory properties was tested in a randomized double blinded study. In this trial, documented disease progression within 14 months prior to enrollment in the trial was required. Median PFS was superior for patients on the experimental arm vs the control arm 11.2 versus 4.0 months (HR 0.28 95%CI 0.19-0.4 p<0.0001). Cross over was allowed for patients on the placebo arm and no difference in OS was detected. In this trial, there was no limit on number of prior therapies even though the majority of patients were treated as first line. Cabozantinib has a manageable AE profile in patients with progressive metastatic MTC, including those previously treated with TKIs [10]. Based on these studies, Vandetanib and Cabozantinib were approved by the FDA for treatment of metastatic medullary thyroid cancer. However, little information is available about the use of these drugs after failure of another TKI.

Sorafenib and Lenvatinib are FDA approved for the treatment of RAI refractory disease based on randomized phase 3 studies (DECISION and SELECT studies, respectively). In the DECISION study, Sorafenib was tested in a double-blind, randomized, multicenter phase III in patients with locally advanced/metastatic RAI-refractory DTC which had progressed within 14 months prior to enrollment and the primary endpoint was progression-free survival (PFS). 417 patients were randomized (207 to sorafenib and 210 to placebo). In the sorafenib arm, PFS was 10.8 months vs 5.8 months (HR 0.58, 95% CI 0.45–0.75, p<0.0001). Overall response rate (ORR) was 12.2% (n=24/196) versus 0.5% (n=1/201) with sorafenib versus placebo, respectively (P<0·0001). There was no difference in overall survival [11].

In the SELECT study, Lenvatinib was tested using a similar design: 392 pts randomized (2:1), the trial was double-blind, placebo controlled and patients had documented disease progression within 13 months. Crossover to open-label lenvatinib was allowed upon progression and the primary endpoint was also PFS. PFS was 18.3 months (15.1-NR) in the lenvatinib arm and 3.6 months (2.2-3.7) in the placebo arm. Response rate was 64.8% in the lenvatinib group (4 complete responses and 165 partial responses). As in the DECISION study, no difference in overall survival between treatment and control arms was detected. Interestingly, there was no difference between cases that had received a prior line of treatment with a TKI

[12].

In both trials, dose modifications due to adverse events were necessary in the majority of cases. Since none of these treatments are curative and tumors will eventually develop resistance to these drugs, more lines of treatment are needed.

2.3 IND Agent 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 *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 *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. [13] Regorafenib has potent preclinical antitumor activity and long-lasting anti- angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI).

2.3.1 Preclinical Summary

In *in vivo* studies, 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). [13] Immunohistochemical ex-vivo studies with a phospho–specific monoclonocal anti-ERK 1 / 2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB 231 and BxPC-3), but not in NSCLC (H460).

In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody. [13] These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

2.3.2 Clinical experience

In the phase I dose escalation study of regorafenib, 53 patients were enrolled in 8 cohorts at dose levels ranging from 10 mg to 220 mg daily. [14] The recommended dose for further studies was determined to be 160 mg daily on a 3 week on / 1 week off scheduled repeating in 28 day cycles. The most common drug-related AEs occurring in 30% or more of patients were voice changes, hand-foot skin reaction, mucositis, diarrhea, and hypertension. The most common drug-related grade 3 or 4 AEs were dermatologic AEs (hand-foot skin reaction, rash), hypertension and diarrhea. When treated with 220 mg daily of regorafenib, 5 of 12 patients had DLTs in cycle 1, compared with 2 of 12 at the 160 mg daily dose. The most common DLT was hand-foot skin reaction and rash/desquamation. Pharmacokinetic analysis revealed a similar exposure at steady state for the parent compound and two pharmacologically advice metabolites. The unbound plasma concentration of the pharmacologically active species at the 160 mg dose level exceeded the IC50 of many target kinases including mVEGFR2, RET, and c-KIT. The initial t_{max} was 1 to 5 hours and secondary and tertiary maxima at about 6 to 8 and 24 hours. The observed

terminal half-life ranged from 20 to 40 hours, with 2- to 4- fold increases in $C_{max,md}$ (multiple dose) compared with $C_{max,sd}$ (first dose). Pharmacodynamic assessments of plasma angiogenic cytokines and tumor perfusion analysis by DCE-MRI assessments showed biologic activity of regorafenib. DCE-MRI results showed a 40% or more decrease in tumor perfusion at dose levels of 120 mg or above. Evidence of anti-tumor activity was seen in 3 of 47 evaluable patients who achieved partial response.

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

At a preplanned second interim analysis, there was a statistically significant survival benefit for regorafenib. The estimated hazard ratio for overall survival was 0.773 (95% confidence interval [CI], 0.635 to 0.941; 1-sided $p = .0051$). Patients treated with regorafenib had a median overall survival of 6.4 months, compared with 5.0 months for placebo — a 29% increase in survival. In addition to improved overall survival, progression-free survival was superior; median progression- free survival was 1.9 months (95% CI, 1.88 to 2.17) for regorafenib and 1.7 months (95% CI, 1.68 to 1.74) for placebo. The estimated hazard ratio for progression-free survival was 0.493 (95% CI, 0.418 to 0.581; 1-sided $p< .000001$). There was a substantial difference in disease control rate in the regorafenib and placebo groups (44% vs. 15%; p<.000001). Regorafenib demonstrated comparable efficacy benefits across patient subgroups analyzed including age, number of metastases, 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. The study involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib. Patients were randomized 2:1 to regorafenib (160 mg orally once daily on a 3 weeks on/1 week off cycle) or placebo, plus best supportive care.

The results showed that treatment with regorafenib led to a statistically significant 3.9-month improvement in progression-free survival (PFS), compared with placebo (4.8 months vs. 0.9 months; hazard ratio [HR] = 0.27; $p <.0001$). Overall survival was statistically similar between groups as expected due to a trial design that allowed crossover to regorafenib for disease progression (85% for placebo and 31% regorafenib randomized patients). The median survival period without tumor growth among patients on regorafenib was 4.8 months while for the control group on placebo it was less than a month. The overall disease control rate combining partial responses with durable stable disease for at least 12 weeks was 53% with regorafenib compared with 9% in the control group. The most common grade 2:3 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.

Due to the severity of the side effects at full dose, a similar protocol with Regorafenib in recurrent or metastatic adenoid cystic carcinoma (ACC) at Memorial Sloan Kettering required a reduction of the starting dose to 120 mg and escalation to 160 mg was allowed (Ho et al, ASCO 2016, abstract 6096). In order to reduce the risk for severe side effects at the full dose of 160 mg and to avoid frequent dose reductions in this study, patients start at 120 mg initially and if the drug is well tolerated, escalation to 160 mg is allowed at the PI's discretion.

To ameliorate side effects of regorafenib, an escalating dosing schedule was tested recently in a randomized phase 2 study. On this schedule, patients start at 80mg for one week and if no significant toxicity occurs, the dose is escalated to 120mg on week 2 and 160mg on week 3 followed by one week off in a 28 day cycle. The study met its primary endpoint and showed that a greater number of patients were able to enter cycle 3 of treatment (43%vs 24%, p=.028) with a trend towards improved overall survival on the escalating dose regimen (Median OS 9 months vs 5.9 months, p=.094). The protocol treatment for the DTC cohort will follow this dosing regimen. [Regorafenib Dose Optimization Study (ReDos). A Phase II Randomized Study of Lower Dose Regorafenib Compared to Standard Dose Regorafenib in Patients With Refractory Metastatic Colorectal Cancer (mCRC) Abstract 611Bekaii-Saab TS, Ou FS, Anderson DM, Ahn DH, Boland PM, Ciombor KK, Jacobs NL, DesnoyersRJ, Cleary JM, Meyers JP, ChioreanEG, Pedersen K, BarziA, Sloan J, McCune JS, LacoutureME, Lenz HJ, GrotheyA] [15].

2.4 Rationale

There is no established standard of care for patients following progression after first line tyrosine kinase inhibitor (TKI) in medullary thyroid cancer and with only 2 drugs approved by the FDA in both medullary and RAI refractory DTC, more treatment options are needed. The response to second line therapies following resistance to first-line treatment is unknown. However, a relatively small number of cases who had received and failed treatment with a different tyrosine kinase inhibitor prior to treatment with Vandetanib or Cabozantinib were reported in subset analyses in the randomized phase III trials and it appears that the clinical benefit was similar compared to those who received either drug as first line treatment. In both trials, these numbers were small, however, limiting interpretation of these results. Moreover, first-line molecularly targeted therapies have yet to show improvement in survival and are associated with toxicities. Similarly, the benefit for patients treated first or second line with lenvatinib appeared similar in the SELECT phase 3 study [12].

Therefore, there is an unmet medical need for patients who progress after first line therapy. Since no difference in overall survival has been established in medullary and DTC for patients treated with a TKI, patients with DTC with be eligible for this protocol for any line of treatment including first line.

Regorafenib is a multikinase inhibitor of RET, VEGFR 1-3, TIE2, RAF-1, BRAF, PDGFR, KIT, DDR2, Eph2A and Abl. Given the high prevalence in MTC of driver mutations in RET and oncogenic mutations in RAS, there is strong rationale that combined inhibition of both targets, with additional inhibition of angiogenesis (VEGF, TIE2), is a very promising therapeutic strategy in advanced MTC. Further, combined targeting of the three most prevalent activated pathways in MTC (RET, RAS/BRAF and VEGF) with regorafenib may overcome clinical resistance to the first-line FDA-approved therapies, vandetanib and cabozantinib, which primarily target RET and VEGFR. Given the activity of regorafenib in other diseases and its similarity with lenvatinib and other TKI tested in DTC, it is likely that regorafenib has comparable activity.

2.5 Rationale for Correlative Studies – Use of Genomic Sequencing Technologies

Mutations in the RET proto-oncogene are key pathogenic events in the majority of patients with MTC.

Virtually all patients with the hereditary MTC carry a germline RET mutation. Approximately 65-80% of sporadic MTC tumors harbor a somatic RET mutation. Almost all (98%) MEN2A cases involve point mutations affecting the extracellular cysteine-rich domain (codons 609, 611, 618, 620, 630 or 634). About 95% of MEN2B cases possess the kinase domain mutation, M918T, which is also found in up to 80% of sporadic MTC cases and is associated with poorer prognosis. Although rare, RET V804M and V804L gatekeeper mutations have been identified in sporadic and hereditary MTC and have been shown in vitro to confer resistance to clinically approved RET inhibitors such as vandetanib. In patients with RET *wild-type* sporadic MTC, Ras mutations (HRAS and KRAS) have been identified in 60-80% of cases. Ras mutations could represent alternative genetic events in sporadic MTC tumorigenesis and the prognostic significance of Ras mutations is unclear. Presently there are no validated predictors to select MTC patients for TKI therapy. In this protocol we aim to provide a descriptive analysis of the utility of genomic sequencing and correlation to response to TKI therapy.

In DTC, the relevant targets for lenvatinib or sorafenib are unknown. It is suspected that the anti-VEGF properties of the drugs might be responsible for clinical activity but this has never been shown conclusively and no good predictors of treatment response have been established. More recently, it has been argued that immune modulating effects could contribute to clinical efficacy.

Whole exome sequencing will be performed and comparing the genomic signature with responders versus non-responders could provide important clues what the relevant targets might be help to establish predictive markers for response.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

- Subjects must be able to understand and be willing to sign the written informed consent form. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure.
- Age $\geq$18 years.
- Eastern Cooperative Oncology Group performance status of $\leq$ 1.
- Histologically or cytologically confirmed diagnosis of metastatic medullary thyroid cancer or histologically or cytologically confirmed diagnosis of RAI refractory differentiated thyroid cancer for which no curative treatment option exists.
- Documented disease progression as defined by RECIST criteria within 6 to 12 months prior to study registration for patients with MTC and within 12 months prior to study registration for patients with RAI refractory DTC.
- Must have at least 1 site of measurable disease by RECIST criteria, by version 1.1.
- Archival tissue block or unstained slides (from primary or metastatic site) must be available, otherwise fresh tissue biopsy sample will be collected for patients with accessible tumors.
- Any number of prior chemotherapies and targeted therapies are allowed.

- Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements within 3 weeks prior to study registration:
    - Total bilirubin: ≤ 1.5 x the upper limits of normal (ULN)
    - Alanine aminotransferase (ALT) and aspartate amino-transferease (AST): ≤ 2.5 x ULN (: ≤ 5 x ULN for subjects with liver involvement of their cancer)
    - Alkaline phosphastase limit: ≤ 2.5 x ULN (: ≤ 5 x ULN for subjects with liver involvement of their cancer)
    - Serum creatinine: ≤ 1.5 x the ULN
    - International normalized ratio (INR)/ Partial thromboplastin time (PTT): ≤ 1.5 x ULN. (Subjects who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care. (See Section 3.3)
    - Platelet count ≥ 100000 /mm3, hemoglobin (Hb) ≥ 9 g/dL, absolute neutrophil count (ANC) ≥ 1500/mm3. Blood transfusion to meet the inclusion criteria will not be allowed.
- Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to study registration. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test. The definition of adequate contraception will be based on the judgment of the investigator.
- Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least 2 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the principal investigator or a designated associate.
- Subject must be able to swallow and retain oral medication.

3.2 Exclusion Criteria

- Prior treatment with regorafenib.
- Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.
- Uncontrolled hypertension (systolic pressure >140 mm Hg or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] 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 v4.0 Grade 3 within 4 weeks prior to study registration.
- Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months prior to study registration.
- Subjects with any previously untreated or concurrent cancer that is distinct in primary site or histology except cervical cancer in-situ, treated basal cell carcinoma, or superficial bladder

tumor. Subjects surviving a cancer that was curatively treated and without evidence of disease for more than 3 years before registration are allowed. All cancer treatments must be completed at least 3 years prior to study registration.

- Patients with pheochromocytoma.
- Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.
- Ongoing infection > Grade 2 NCI-CTCAE v4.0.
- Symptomatic metastatic brain or meningeal tumors.
- Presence of a non-healing wound, or non-healing ulcer, (that is not tumor related) or bone fracture.
- Major surgical procedure or significant traumatic injury within 28 days prior to study registration.
- Other investigational treatment during or within 4 weeks prior to study registration.
- Use of any approved tyrosine kinase inhibitors within 2 weeks or 6 half-lives of the agent, whichever is shorter, prior to study registration.
- Prior radiation within 14 days prior to study registration.
- Renal failure requiring hemo-or peritoneal dialysis.
- Dehydration Grade ≥1 NCI-CTCAE v4.0.
- Patients with seizure disorder requiring medication.
- Persistent proteinuria > Grade 3 NCI-CTCAE v4.0
- Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
- Pleural effusion or ascites that causes respiratory compromise (2: NCI-CTCAE version 4.0 Grade 2 dyspnea).
- History of organ allograft (including corneal transplant).
- Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial.
- Any malabsorption condition.
- Women who are pregnant or breast-feeding.
- Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation.
- Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

3.3 Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment (regorafenib, other agents being investigated in combination with regorafenib).
- Prior use of regorafenib.

Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks prior to study registration. Subjects are allowed to participate in trials involving investigational agents used for the treatment of PPE symptoms.

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- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and

heparinoids.
    - However, prophylactic anticoagulation as described below is allowed:
        - Low dose warfarin (1 mg orally, once daily) with PT-INR ≤ 1.5 x ULN is permitted. Infrequent bleeding or elevations in PT-INR have been reported in some subjects taking warfarin while on regorafenib therapy. Therefore, subjects taking concomitant warfarin should be monitored regularly for changes in PT, PT-INR or clinical bleeding episodes.
        - Low dose aspirin (≤ 100 mg daily).
        - Prophylactic doses of heparin.
- Use of any herbal remedy (e.g. St. John's Wort [Hypericum perforatum])

3.4 Inclusion of Women and Minorities
Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied. An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI), Kartik Sehgal, MD. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions
DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites
Eligible participants will be entered on study centrally at Dana-Farber Cancer Institute by the Study Coordinator. All sites should call the Study Coordinator to verify dose level availabilities. Following registration, participants should begin protocol therapy within 5 days.
Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites
To register a participant, the following documents should be completed by the research nurse or data manager and faxed or e-mailed to the Study Coordinator:

- Copy of required laboratory tests, please refer to section 10.

- Signed participant consent form
- HIPAA authorization form
- Eligibility checklist completed by the treating physician, assistant, nurse practitioner, and/or registered nurse.

The research nurse or data manager at the participating site will then call or e-mail the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site and verbally confirm registration

5. TREATMENT PLAN

5.1 Treatment Regimen

Regorafenib will be administered as monotherapy during the study. Subjects will take one dose daily for 3 weeks on /1 week off. One cycle is 28 days.

During cycle 1, patients will start taking 80mg for one week. If no significant drug related toxicities (SDRT's) occur, the dose will be escalated to 120mg daily starting day8. If no SCRT's occur, the dose will be escalated to 160mg daily.
From cycle 2 onward, the highest tolerated dose will be the treatment dose level.

Dose Escalation Plan:

Cycle	Week	Daily Dose	
Cycle 1	Week 1	80 mg	Two 40-mg tablets of regorafenib
	Week 2	120 mg	Three 40-mg tablets of regorafenib
	Week 3	160 mg	Four 40-mg tablets of regorafenib
	Week 4	No dosing	
Cycle 2-onwards	Week 1-3	Highest tolerated dose	
	Week 4	No dosing	

Regorafenib tablets should be taken once a day with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat) meal. Some examples of lowfat meals are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
- One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

5.2 Agent Administration

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 28 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.

5.3 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.

5.3.1 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.)

5.3.2 Destruction and Return

At the end of the study, unused supplies of regorafenib 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: OR
Mail: (VP of Medical Affairs named in contract) at Bayer HealthCare Pharmaceuticals
100 Bayer Boulevard
Whippany, NJ 07981

5.4 Treatment compliance

An adequate record of receipt, distribution, and return of the study drug must be kept on the NCI 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.

5.5 Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study and during the study must be recorded in the subject's source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication). Specific caution should be taken when considering or administering a concomitant medication that is metabolized

by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

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

Co- administration of a strongCYP3A4 inhibitor (ketoconazole) with a single 160mg dose of regorafenib increased the mean exposure of regorafenib and decreased the mean exposure of the active metabolites M-2 and M-5. Avoid concomitant use of regorafenib with strong inhibitors of CYP3A4 activity (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole, nefazadone, posaconazole, telithromycin, and voriconazole).

5.6 Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates
- Subjects who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (day 5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

5.7 The following are not permitted:

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

5.8 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. Treatment must discontinue regorafenib if any of the following criteria are met:

Disease progression by clinical evaluation or as documented by RECIST v 1.1.

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Drug is held for 28 days or longer
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Kartik Sehgal, MD

5.9 Duration of Follow Up

Participants will be followed through scans and visits until first progression or start of new cancer treatment regimen. Participants will be followed for survival for two years from study entry or until death-whichever occurs first.

5.10 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Disease Progression by clinical evaluation or as documented by RECIST v1.1
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/ProtocolDevelopment/electronic_applications/ctc.htm.

The starting dose of regorafenib is 80 mg once daily. Regorafenib will be administered on a 3 weeks on/1week off schedule [3 weeks out of every 4]. The dose will be escalated in the first cycle to 160 mg at the investigator's discretion if toxicities observed are <grade2. The maximum tolerated dose in cycle 1 will be given in cycle 2 and onwards.

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:		
	160 mg daily	Four 40-mg tablets of regorafenib
	120 mg daily	Three 40-mg tablets of regorafenib
	80 mg daily	Two 40-mg tablets of regorafenib
	40 mg daily	One 40-mg tablet 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.

The following tables outline dose adjustments for toxicities related to study drug except hand-foot skin reaction, hypertension and liver function test abnormalities.

Table 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 :S Grade 2[c]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated
			and toxicity (2: Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until :S 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.

The table above outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except HFSR, hypertension and ALT/ST/bilirubin.

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.

Table 2: Grading for Hand-Foot-Skin-Reaction

	Grade 1	**Grade 2**	**Grade 3**
NCI-CTCAE v4.0 Palmar-plantar erythrodysesthesia syndrome [a]	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
	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.			

Table 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 toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.

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

6.1 Recommended prevention/management strategies for skin toxicities consistent with HFSR are summarized below:

6.1.1 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.

6.1.2 Use of creams

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

6.1.3 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

6.2 Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at visits 1,2,3,4, and 5 during the first 6 weeks of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is > 140 mm Hg systolic or > 90 mm Hg diastolic (NCI CTCAE v4.0), then the subject must contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, Table 6-4 outlines suggested dose reductions.

Table 4: Management of Treatment-Emergent Hypertension		
Grade (CTCAE v4.0)	**Antihypertensive Therapy**	**Regorafenib Dosing**

1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	• Treat with the aim to achieve diastolic BP :S 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 :S 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
3 Systolic BP 2: 160 mmHg or diastolic BP 2: 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP :S 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 :S 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Patients requiring a delay of >4 weeks should go off protocol therapy b. If BP remains controlled for at least one cycle, dose re-escalation permitted per investigator's discretion. c. Patients requiring >2 dose reductions should go off protocol therapy.		

6.3 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 *5* should be followed.

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

Table 5: Dose Modification/interruption for alanine aminotransferase and/or aspartate aminotransferase increases related to study drug

Increases in ASL/ALT (per NCI-CTCAE v 4.0)	1st Occurrence	Restart	Recurrence
AST and/or ALT < 5 X ULN (<Grade 3)	Continue dosing, with weekly monitoring of liver function until transaminases return to < 3 X ULN (< Grade 1) or baseline.		
ALT and/or AST > 5 X ULN (> Grade 3)	Interrupt dosing, with weekly monitoring until transaminases return to < 3 X ULN or baseline.	If the potential benefit of reinitiating regorafenib is considered to outweigh the risk of hepatotoxicity: reduce 1 dose level and measure serum transaminases weekly for at least 4 weeks.	Discontinue
ALT and/or AST > 20 X ULN (> Grade 4)	Discontinue		
ALT and/or AST > 3 X ULN (> Grade 2) with concurrent bilirubin > 2 X ULN	Discontinue treatment and measure serum transaminases weekly until resolution. Exception: subjects with Gilbert's syndrome who develop elevated transaminases should be managed as per the recommendations outlined above for ALT/AST elevations.		

6.4 Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. 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.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Reported and/or potential AEs

The most common adverse reactions (2:30%) are asthenia/fatigue, decreased appetite and food intake, hand-foot skin reaction (HFSR) [palmar-plantar erythrodysesthesia (PPE)], diarrhea, mucositis, weight loss, infection, hypertension, and dysphonia.

Investigators should refer to the Safety Information section of the current Investigator's Brochure (IB) for regorafenib, including the DCSI (development core safety information), for the expected side effects of, regorafenib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

Therapeutic monitoring should be performed following dose selection or modification of regorafenib, in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.

All concomitant medications must be recorded in the subject's source documentation.

Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol- Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.

Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Safety

All subjects who receive at least one dose of study treatment will be valid for the safety analysis. All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: AEs, laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation), changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature) and ECG and, in some instances, changes in chest x-ray images, as produced at the investigator's discretion (e.g., for evaluation for pneumonia).

All AEs whether considered drug-related or not, will be reported in with a diagnosis, start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, outcome, and other possible causes. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator.

This trial will use the NCI-CTCAE v4.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

7.5 Adverse events

Investigators should refer to the Safety Information section of the current IB for regorafenib, including the DCSI (development core safety information), for the expected side effects of regorafenib. As with any agent, there is always the potential for unexpected AEs, including hypersensitivity reactions. The IB will be updated if any new relevant safety data are obtained.

Therapeutic monitoring should be performed following dose selection or modification of regorafenib, in a manner consistent with the local clinical standard of care. In general, subjects should be closely monitored for side effects of all concomitant medications regardless of the path of drug elimination.
All concomitant medications must be recorded in the subject's source documentation.

Subjects must be carefully monitored for AEs. This monitoring also includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug, or other chemotherapy/treatment.

7.5.1 Guidelines for Participating Institutions

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the same manner described above, and again below:

- Fatal and Life Threatening SAEs: within 24 hours but no later than 4 calendar days of the participating institution's observation or awareness of the event.
- All other serious (non-fatal/non life threatening) events: within 4 calendar days of the participating institution's observation or awareness of the event.

Criteria for SAEs remain the same as described in protocol section 7.6.1.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

7.6 Definitions

7.6.1 Definition of adverse event (AE)

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

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

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

7.6.2 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.

7.6.3 **Classifications for adverse event assessment**

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

7.6.3.1 **Seriousness**

For each AE, the seriousness must be determined according to the criteria given in Section 7.6.

7.6.3.2 **Intensity**

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

CTCAEv4 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv4 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).

CTCAEv4 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to selfcare ADL (selfcare ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv4 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv4 Grade 5: death due to an AE.

7.6.3.3 **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.

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 subject's 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.

7.6.3.4 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".

7.6.3.5 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.
- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

7.6.3.6 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

7.6.3.7 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

7.6.3.8 **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 institutional policies and regulations, serious adverse events must be reported to the IRB within 10 business days.

All serious adverse events should be reported to Bayer by DF/HCC within 24 hours of notice of the SAE. 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:

Reports can also be phoned in via Clinical Communications Dept Phone:

Address: Global Pharmacovigilance - USA Bayer HealthCare Pharmaceuticals Inc.
P.O. Box 915
Whippany, NJ 07981-0915

Address: 100 Bayer Boulevard, Whippany, NJ 07981 *(FDX or UPS only)*

7.6.3.9 **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.

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. 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 as outlined in Section 7.6.3.8.

7.6.3.10 **Reportable adverse events include:**

- Acute renal failure (NCI-CTCAE version 4.0 2: grade 3) or severe proteinuria (NCI- CTCAE version 4.0 2: grade 3)
- Interstitial lung disease
- Acute cardiac failure
- Clinically significant bleeding (NCI-CTCAE version 4.0 2: grade 3)
- Stevens-Johnson Syndrome and erythema multiforme
- Hepatic failure
- Reversible posterior leukoencephalopathy syndrome
- Gastrointestinal perforation or fistula

7.6.3.11 **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.

7.6.3.12 **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.

7.6.3.13 **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.

7.6.3.14 **Appropriateness of procedures / measurements**

The assessments described in the previous sections are widely used and generally recognized as reliable, accurate, and relevant for determining the safety and efficacy of therapies in this disease.

8. PHARMACEUTICAL INFORMATION

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.

8.1 Regorafenib

8.1.1 Description

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 tablets (for randomized studies) or 28 tablets (for open-label studies) 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.

8.1.2 Availability

Regorafenib will be supplied free-of-charge, by Bayer HealthCare Pharmaceuticals.

8.1.3 Administration

Regorafenib will be administered as monotherapy during the study. In cycle 1; 80 mg daily will be administered in week 1, 120 mg in week 2 and 160 mg in week 3 (depending on the toxicity and investigator's discretion). In cycle 2 and onwards, maximum tolerated dose in cycle 1 will be given. The dosing will be 3 weeks on /1 week off. One cycle is 28 days. There will be no doing in week 4 of all cycles.

Regorafenib tables should be taken once a day with approximately 8 fluid ounces (240 mL) of water after a low-fat (<30% fat meal. Some examples of lowfat meals are:

- Two slices of white toast with 1 tablespoon of low-fat margarine and 1 tablespoon of jelly and 8 ounces (240 mL) of skim milk (approximately 319 calories and 8.2 g of fat).
- One cup of cereal (i.e. Special K), 8 ounces (240 mL) of skim milk, one piece of toast with jam (no butter or marmalade), apple juice, and one cup of coffee or tea (2 g fat, 17 g protein, 93 g of carbohydrate, 520 calories.

If the subject vomits after taking regorafenib, do not attempt to retake dose and wait until the next dose. If the subject forgets to take regorafenib for the day and it is after 6 PM, do not take the missed dose and wait until the next dose.

8.1.4 Ordering

8.1.5 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 Institutional Drug Accountability Record/Log.

8.1.6 **Destruction and Return**

At the end of the study, unused supplies of regorafenib should be destroyed according to institutional policies. It is acceptable for site to remove excess if needed and destroy per institutional standard practice while dispensing the needed quantity in original container. 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: OR
Mail: (VP of Medical Affairs named in contract) at Bayer HealthCare Pharmaceuticals
100 Bayer Boulevard
Whippany, NJ 07981

9. BIOMARKER STUDIES

Patients will be asked for permission to obtain and store either a tumor tissue block from previous biopsy and/or undergo sequential biopsies. Patients who do not have archival tumor tissue will be asked to provide a fresh pre-treatment tumor biopsy. All patients will have tumor tissue collected (40 unstained slides or one tumor block) if deemed safe and feasible at baseline, on treatment and post-treatment. A vial of EDTA blood will also be obtained. All patients consented to Dana-Farber Cancer Institute Protocol# 11-104 will undergo Oncopanel testing which analyzes 300 cancer relevant genes. Paired tumor specimens will be analyzed for genotyping utilizing next-generation sequencing techniques and receptor phospho-tyrosine kinase activity utilizing kinome assays according to already established methods. We will evaluate tumor *RET* and *RAS* mutation status, and phospho-tyrosine kinase activity, and correlate with outcomes.

Whole exome sequencing will be performed on tumor and normal genomic DNA on all responders.

Whole-exome sequencing is a diagnostic test for patients with nonspecific or unusual disease presentations of possible genetic cause and for patients with clinical diagnoses of different and unrelated genetic conditions. The purpose is also to study how DNA, genes, proteins, and other molecules in the tumor may affect response to treatment. Whole exome sequencing will be performed/coordinated at Broad Institute. The goal is to obtain 100-500ng of genomic DNA from FFPE blocks. To obtain sufficient amount of DNA, we need one of the following:

a) 5-10 unstained 10 micron FFPE slides (10 ideal)
b) 2-3 30 micron scrolls (3 ideal)
c) 2 x 1mm cores or equivalent (3 x 0.6mm cores, 1 x 2mm core, etc)

In addition, one tube of whole blood (frozen at – 80°C or fresh) needed for isolation of normal blood.

Protocol for sending biological sample (blood or fresh tissue biopsy)

1. Samples will be stored a -80°C the day of collection. They can be stored together.
2. During the first week of each month, biological samples will be sent on dry ice to:

Protocol for sending archival tissue sample collection

When the archival tissue samples are available, one block will be shipped ambient to:

10. STUDY CALENDAR

Screening evaluations are to be conducted within 3 weeks prior to study registration. Scans and x-rays must be done ≤4 weeks prior to study registration. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Procedures	Screening	Treatment Cycle 1 Day 1 of			Treatment Cycle 2 Day 1 of		Treatment Cycle 3 and beyond Day 1 of	End Of Treatment	Follow up until first progression	After first progression. Follow up by phone until death[i]
		Week 1	Week 2	Week 3	Week 1	Week 3	Week 1			
Clinic Visit	X	X	X	X	X	X	X			
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X	X	X	X	X	X	X		
Physical exam	X	X	X	X	X	X	X	X		
Vital signs	X	X	X	X	X	X	X	X		
Height	X									
Weight	X	X	X	X	X	X	X	X		
Performance status	X	X	X	X	X	X	X	X		
CBC w/diff, plts	X	X	X	X	X	X	X	X		
Serum chemistry[a]	X	X	X	X	X	X	X	X		
B-HCG[b]	X	X			X		X	X		
Urinalysis[k]	X	X	X	X	X	X	X	X		
UPCR[n]	X									
EKG	X	X						X		
CT/MRI/PET[d]	X	Xc						Xe	Xf	
Archival or fresh tumor biopsy	X			Xm				Xm		
Tumor measurements	X						Xc	Xe	Xf	

Tumor markers[g]	X	X			X		X	X		
QOL questionnaire[h]		X[l]		X	X	X	X	X	X	
Regorafinib		Once daily, weeks 1-3 in each cycle								
Adverse Events[j]		X								

a) Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, INR, PT and PTT.

b) Serum pregnancy test (women of childbearing potential). b-HGG testing for women of childbearing potential should be done prior to the initiation of each cycle.

c) Every 8 weeks until first progression, death, or 24 months from study registration whichever occurs first (also obtain a survival status update at each visit).

d) The same imaging modality should be used throughout the study.

e) In subjects who discontinue study therapy without confirmed disease progression, a tumor assessment should be performed at end of treatment (i.e. date of discontinuation +/- 4 week window). If a previous scan was obtained within 4 weeks prior to end of treatment date then a scan at end of treatment is not mandatory.

f) Post end of protocol treatment, if first progression has not yet been confirmed, tumor assessments are to continue every 2 months (+/- 7 days) until first progression, start of new cancer treatment regimen, death, or 24 months from study registration, whichever occurs first.

g) Serum calcitonin, carcinoembryonic antigen (CEA), CA 19-9 for MTC, Thyroglobulin, TSH and free T4 in DTC.

h) MD Anderson Symptom Inventory – Thyroid (MDASI-Thy)

i) After first progression, participants will be followed by phone only, every 3 months (+/- 2 weeks) for 24 months from study registration or until death whichever occurs first.

j) Patients will be assessed monthly for adverse events; until first disease progression.

k) Full urinalysis (dipstick plus microscopic evaluation) at the Screening and End-of-Treatment visits and a basic urinalysis (dipstick only) at each visit indicated prior to administration of trial drug. If the basic urinalysis is abnormal, then a full urinalysis should be performed.

l) Patient needs to complete this timepoint prior to starting protocol therapy.

m) For patients with accessible tumors. Optional but strongly encouraged.

n) Patients with persistent proteinuria $\geq$ Grade 3 NCI-CTCAE v4.0 are excluded.

Assessments must be performed prior to study registration. Study assessments and agent should be administered within + 3 days of the protocol-specified date, unless otherwise noted. Biological Sample Collection:

Sample Type	Screening	Cycle 1, Day 1 of Week 3	End of Treatment
Blood (whole blood with EDTA)	X	X	X
Archived tumor	X		
Fresh Biopsy	X[a]	X[b]	X[b]

a) Fresh screening biopsy required for patients without sufficient archival tumor tissue.
b) For patients with accessible tumors. Optional but strongly encouraged.
c) For participating sites that are not Dana-Farber Cancer Institute, fresh biopsy and blood will be stored at -80°C until they can be sent to Dana-Farber Cancer Institute.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 **Definitions**

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

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

11.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as 2: 20 mm by chest x-ray or 2:10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be 2:15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with 2:10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic

lesions are all considered non- measurable.

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

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

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

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

11.1.3 Methods for Evaluation of Disease

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

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and 2:10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET/CT Imaging.

Patient Preparation
Patients should avoid any strenuous exercise for 24 hours prior to the PET scan and fast for no less than 4 hours prior to the injection of FDG. Patients must have a fasting blood glucose level :S 200 mg/dL prior to FDG injection. An attempt should be initially made to control the blood glucose level, which will require the rescheduling of the injection. If the glucose level cannot be controlled (i.e. > 200 mg/dL), the patient will not be included in the FDG-PET/CT imaging. Patients should be adequately hydrated with plain water. Weight (kg), height (cm), and blood glucose (mg/dL) will be measured and recorded prior to the injection of FDG. Sedation (alprazolam, 0.5-1 mg, po, 30 minutes pre-FDG injection) is allowed, but not mandatory and should be used consistently by the patient for all scans. Filgrastim, pegfilgrastim, and epoetin are known to affect FDG uptake, and their use by the patient should be recorded. Patients should wait in a warm room to avoid false positive brown fat FDG uptake. Patients will lie supine in a quiet room during the FDG uptake period. FDG will be synthesized and prepared in accordance with the institution's standard procedures or obtained from a commercial supplier.

FDG Dosing and Administration
The administered activity of FDG should be based on the PET/CT system manufacturer's recommendation. The recommended FDG dose is 0.14-0.21 mCi/kg. The actual FDG dose should be a bolus of 8-20 mCi, followed by a saline flush (per institutional procedure). Preinjection FDG Syringe dose, FDG dose injected and Post-injection FDG dose residual and corresponding time should be documented.

FDG-PET/CT Imaging Acquisition
Whole body PET/CT acquisition at both pre-therapy (baseline) and on follow ups MUST start **70 (± 10) minutes** after FDG injection. The timing should stay the same for follow- up PET/CT scans from the baseline (**no more than a ± 10 minute difference**). It is **critical** that follow-up PET/CT scans will be performed in an identical way to the baseline scan, with the same scanner, same scan direction (skull to thighs or thighs to skull), and consistent arm positioning (arms up or arms down). Preferably, schedule the patient for both baseline and follow-up scans at the same time of day (AM or PM) to

improve reproducibility. The field of view is to encompass the region between the scalp and toes. Patient will be scanned supine with arms positioned comfortably above the head, if possible. Oral and/or IV contrast is optional. Patient should empty his/her bladder immediately before the acquisition of images. For the emission scanning, the acquisition should be performed in 2D or 3D mode in accordance with the manufacturer's recommendations. The emission scan must be corrected for scatter, random events, and dead-time losses using the manufacturer's recommended procedure. The image reconstruction will be performed using the manufacturer recommended parameters. Images should be attenuation corrected using CT data (note that if IV contrast is used, blood FDG SUV may be altered; therefore attenuation correction must be done without contrast).

11.1.4 **Response Criteria**

11.1.4.1 **Evaluation of Target Lesions**

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

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

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

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

11.1.4.2 **Evaluation of Non-Target Lesions**

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

11.1.4.3 **Evaluation of New Lesions**

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 **Evaluation of Best Overall Response**

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

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

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**

CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

11.1.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.6 **Progression-Free Survival**

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12. DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Data Reporting

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix B.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

Original Primary Endpoint (when trial opened).
The primary endpoint of this trial was to evaluate the proportion progression-free at 10 months in patients with MTC. A Simon two-stage design was used to minimize the number of patients exposed to this regimen and the specific sample size and operating characteristics were chosen to be able to rule out a proportion progression-free at 10 months of 20%. The rate chosen for this null hypothesis was based on the following considerations:

Elisei et al (10) trial showed a proportion progression-free at 10 months of approximately 60% vs 20% on the cabozantinib vs. placebo arms respectively. The population in that trial was a mix of patients receiving treatment in the 1st and second line setting. This current trial is for a similar patient population, but is for patients who have received any prior number of lines of therapy, including at least on targeted therapy. Regorafenib may also have a similar or a more favorable toxicity profile.

Original Statistical Design for patients with MTC (when the trial opened).:

A two-stage design was used where if ≥10 patients were alive and disease was progression-free at 10 months among 31 evaluable (eligible and began protocol treatment) patients (assuming that ≥4 patients among 18 evaluable patients accrued in the first stage were alive and disease is progression-free at 10 months), further testing of this regimen was to be considered. The probability of concluding the regimen was effective was 85% if the true proportion progression-free was 40%. The probability of concluding the regimen as effective was 7% if the true proportion progression-free was 20%. Allowing 2 patients to not begin protocol treatment or be classified as ineligible, a total of 33 patients were to be entered.

Revised Statistical Design for patients with MTC (2018).:

Changes to the statistical design were needed to be in line with the rarity of the MTC as well as the corresponding observed slow accrual.

A two-stage Simon optimal design was used where if ≥7 patients were alive and disease was progression-free at 10 months among 21 evaluable (eligible and began protocol treatment) patients (assuming that ≥2 patients among 8 evaluable patients accrued in the first stage were alive and disease progression-free at 10 months), further testing of this regimen was to be considered. The probability of concluding the regimen was effective was 81% if the true proportion progression-free was 42%. The probability of concluding the regimen as effective was 10% if the true proportion progression-free was 20%. Allowing 2 patients to not begin protocol treatment or to be classified as ineligible, a total of 23 patients with MTC were to be entered.

Rationale for Patient Population and Design Changes (2019).
A total of 8 patients with MTC have been enrolled. Due to the changing treatment landscape/other treatment options for patients with MTC, the trial will no longer enroll patients with MTC. Patients with DTC will now be enrolled in order to obtain preliminary information on efficacy using regorafenib in this patient population.

Revised Endpoint and Statistical Design for patients with DTC

With only 2 treatment options currently FDA approved for RAIR DTC and their corresponding response rates, the study chair felt that an overall response rate >25% by using regorafenib would be worth further study. The below design and specific operating characteristics were chosen to rule out a best overall response rate of 25% by studying approximately n=22 patients with DTC. Therefore ,keeping within the original overall accrual goal from when the trial opened (approximately 31 (n=8 MTC plus n=22 DTC)) and that only large improvements in response will be able to be detected statistically.

A two-stage Simon optimal design will be used to stop the trial early if there is minimal activity in this patient population. In the first stage, accrual will continue until 9 evaluable patients (eligible and begin protocol treatment) with DTC are entered. If there are ≤2 patients with disease in response, accrual to the trial will be closed with the conclusion that there is little evidence that the response rate would reach 49%. The probability that the trial will close early is 60% if the true response rate is 25%.

If there are ≥3 patients with disease in response among 9 evaluable patients, the trial will continue to accrue patients until a total of 20 evaluable patients are entered. If there are ≥ 8 patients with disease in response among 20 evaluable patients, further testing of this regimen will be considered. The probability of concluding the regimen as effective is 81% if the true response rate is 49%. The probability of concluding the regimen as effective is 9 % if the true response rate is 25 %. Allowing 2 patients to not begin protocol treatment or be classified as ineligible, a total of 22 patients could be entered.

The primary efficacy population includes all eligible patients who begin protocol treatment. The proportion progression-free at 10 months for patients with MTC and the response rate for patients with DTC will be summarized as a proportion with a corresponding exact 95% binomial confidence interval. Safety will be assessed via the CTCAE and frequencies of adverse events will be summarized. Time-to-event endpoints will be estimated using the Kaplan-Meier method and 95% confidence intervals for the median or time-specific event time will be summarized. Another endpoint is to assess quality of life (QOL). QOL will be assessed via self-report questionnaires at the timepoints outlined in the Study Calendar. Descriptive statistics from the responses from the questionnaires will be summarized across timepoints of assessment. Rates of drop-out/non-response to QOL assessments and corresponding reason will also be summarized across timepoints of assessment.

With an estimated monthly accrual of 1 - 2 patients with DTC, the first stage is estimated to complete accrual in approximately 6-8 months. As is customary with this type of design, accrual will be suspended after the first stage (n=9 evaluable patients) in order to assess outcome, however, this suspension is also dependent on the actual observed accrual rate and the number of patients' disease confirmed in CR or PR while the first stage of the trial is accruing.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

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