Protocol Title

A Randomized, Phase II Trial to Evaluate the Efficacy of Supportive Therapy with Ginseng for Patients on Treatment with Regorafenib: HCRN GI14-191

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PROTOCOL SIGNATURE PAGE

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

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SYNOPSIS

TITLE	A Randomized, Phase II Trial to Evaluate the Efficacy of Supportive Therapy with Ginseng for Patients on Treatment with Regorafenib
SHORT TITLE	Efficacy of Ginseng for Patients on Regorafenib
PHASE	Phase II
OBJECTIVES	Primary Objective: Assess fatigue with the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and Patient-Reported Outcomes Measurement Information System (PROMIS) form for each group (Regorafenib + No Ginseng vs. Regorafenib + Ginseng) to determine if 2000 mg of American Ginseng for 8 weeks has an impact on the fatigue score Secondary Objectives: 1) Assess the effect of Ginseng on adherence to Regorafenib for CRC subjects with good performance status 2) Assess the toxicities of the combination of Regorafenib and Ginseng for CRC subjects with good performance status 3) Assess the retention of subjects to the combination of Regorafenib and Ginseng for CRC subjects with good performance status 4) Evaluate response rate and overall survival
STUDY DESIGN	Randomized
ESTIMATED NUMBER OF SUBJECTS	90: 60 randomized to regorafenib + ginseng and 30 to regorafenib + no ginseng
KEY ELIGIBILITY CRITERIA	Inclusion criteria: 1. Subjects must be able to understand and be willing to sign the written informed consent and HIPAA authorization for release of personal health information. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately. 2. Age ≥ 18 years at the time of consent. 3. Life expectancy of at least 12 weeks (3 months). 4. ECOG Performance Status of 0 or 1 within 28 days prior to registration. 5. Histological or cytologically confirmed stage IV adenocarcinoma of the colon. 6. Adequate bone marrow, liver and renal function as assessed by the following laboratory values obtained within 7 days prior to registration for protocol therapy. a. Absolute neutrophil count (ANC) count > 1,500/mm^3 b. Hemoglobin (Hgb) > 9g/dL c. Platelet count > 100,000/mm^3 d. Total bilirubin ≤ 1.5 × the upper limit of normal (ULN). e. Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 × ULN for subjects with liver involvement of their cancer) f. Alkaline phosphatase limit ≤ 2.5 × ULN (≤ 5 × ULN for subjects with liver involvement of their cancer) g. Serum creatinine ≤ 1.5 × the ULN

h. International normalized ratio (INR)/ Partial thromboplastin time (PTT) < 1.5 × ULN. (Subjects who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate if 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.)

7. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test. The definition of adequate contraception will be based on the judgment of the site investigator.
8. 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 treating physician or a designated associate.
   Examples of adequate contraception may include but are not limited to a combination of any two of the following:
   - Use of oral, injected or implanted hormonal methods of contraception
   - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
   - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
   - Total abstinence
   - Male/female sterilization
9. All subjects must have radiographically assessable disease per RECIST v1.1 obtained by imaging within 28 days prior to registration.
10. Must be able to swallow and retain oral medication.
11. Subject must be deemed a suitable candidate for regorafenib as per their treating physician

Exclusion Criteria

1. Subject should not be receiving any agent for fatigue including steroids or megace.
   NOTE: Subjects who have a contrast-induced allergy are allowed to receive steroids for their scans.
2. Radiotherapy within 2 weeks prior to randomization. Subjects must have recovered from all therapy-related toxicities.
3. Prior treatment with regorafenib.
4. Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.
5. Congestive heart failure > New York Heart Association (NYHA) class 2.
   i. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of study medication.
   ii. Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
   iii. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).

	6. Evidence or history of bleeding diathesis or coagulopathy. 7. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to start of study medication. 8. Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks) deep vein thrombosis or pulmonary embolism within 6 months of start of study treatment or within 6 months of informed consent. 9. Previous or concurrent cancer that is distinct in primary site or histology from colorectal cancer within 3 years prior to randomization EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (Non-invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)]. 10. Subjects with pheochromocytoma. 11. Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy. 12. Ongoing infection > Grade 2 NCI-CTCAE v4.0. 13. Metastatic brain or meningeal tumors (symptomatic or asymptomatic). 14. Major surgical procedure or significant traumatic injury within 28 days before start of study medication 15. Renal failure requiring hemo- or peritoneal dialysis. 16. Dehydration Grade > 1 NCI CTCAE v4.0. 17. Subjects with seizure disorder requiring medication. 18. Persistent proteinuria ≥ Grade 3 NCI CTCAE v4.0 (> 3.5 g/24 hours, measured by urine protein: creatinine ratio on a random urine sample). 19. Interstitial lung disease with ongoing signs and symptoms at the time of informed consent. 20. Pleural effusion or ascites that causes respiratory compromise (≥ NCI CTCAE version 4.0 Grade 2 dyspnea). 21. History of organ allograft (including corneal transplant). 22. 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. 23. Any malabsorption condition. 24. Women who are pregnant or breast-feeding. 25. Any condition, which, in the site investigator's opinion, makes the subject unsuitable for trial participation. 26. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the study or evaluation of the study results. 27. Treatment with any investigational agent within 28 days prior to registration.
STATISTICAL CONSIDERATIONS	Ninety (90) subjects will be enrolled and randomized using a 2:1 allocation with 60 subjects enrolled in the Regorafenib + Ginseng group and 30 enrolled in the Regorafenib + placebo No Ginseng group. Expected standard deviations for the outcome of interest are 27.0 for the Ginseng group and 26.1 for the no ginseng group. Using a two group Satterthwaite t-test with a 0.050 two-sided significance level, there is 80% power to detect a difference between groups if the change in the No

	Ginseng group is 10 and the change in the Ginseng group is 27 (or greater). A two-sided 95.0% confidence interval for the difference of the two means (change in fatigue score for Ginseng group vs change in fatigue score for no ginseng group) will extend 11.833 from the observed difference in means, assuming that the common standard deviation is 27.0 (conservatively choosing the standard deviation from the Ginseng group since it is larger than the no ginseng standard deviation) when the sample sizes are 60 and 30 respectively (a total sample size of 90) and the confidence interval is based on the large sample z statistic.
ESTIMATED ENROLLMENT PERIOD	12 months
ESTIMATED STUDY DURATION	18 months

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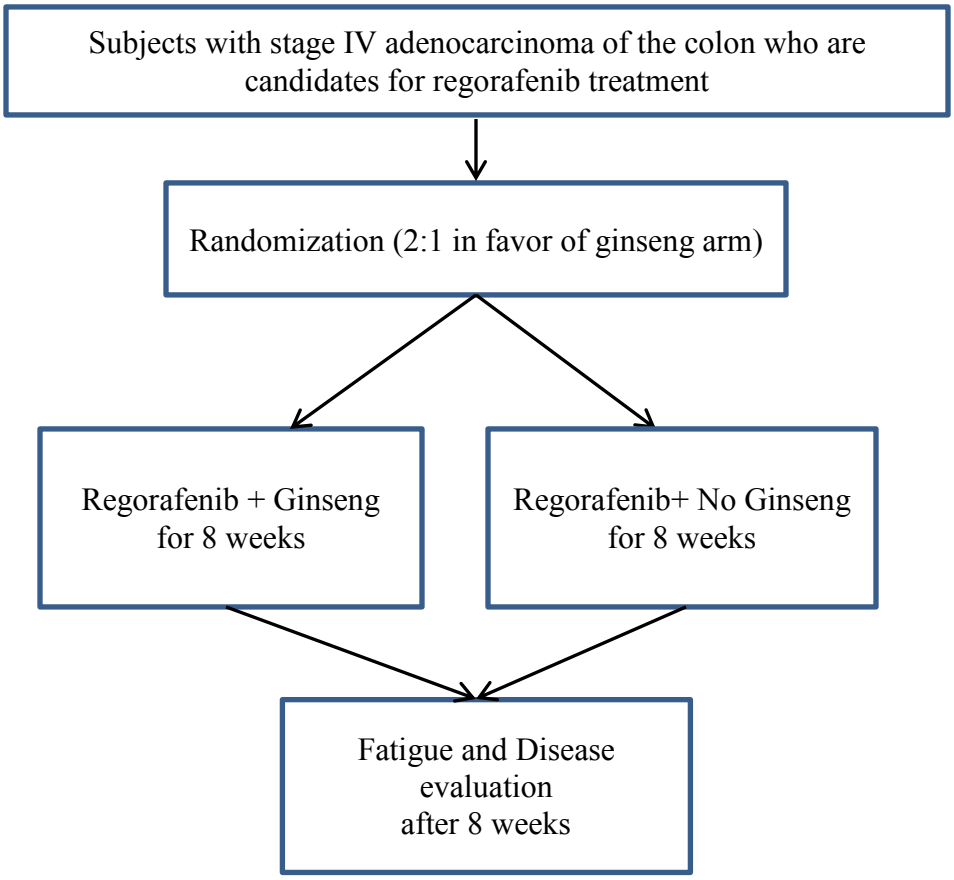
LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse event
ALT	Alanine aminotransferase
Ang	Angiopoietin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCRP	Breast Cancer Resistance Protein
BID	*bis in die*, twice daily
BP	Blood pressure
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CCCWFU	Comprehensive Cancer Center of Wake Forest University
CFR	Code of Federal Regulations
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CRC	Colorectal cancer
CRF	Cancer-related fatigue
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DCE	Dynamic Contrast Enhanced
DMSO	Dimethyl sulfoxide
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOT	End of treatment
ERK	Extracellular Signal-regulated Kinases
FACT-F	Functional Assessment of Cancer Therapy: Fatigue
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular carcinoma
HCRN	Hoosier Cancer Research Network
HFSR	Hand-foot-skin reaction
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act of 1996

HPA	Hypothalamic-pituitary-adrenal
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IND	Investigational New Drug
IL-1β	Interleukin 1 beta
IL-2	Interleukin 2
IL-6	Interleukin 6
IL-8	Interleukin 8
INR	International normalized ratio
IR	Immediate Release
IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
MFSI-SF	Multidimensional Fatigue Symptom Inventory-Short Form
mL	Milliliter
NCI	National Cancer Institute
NM	Nanomolar
NYHA	New York Heart Association
PBMC	Peripheral blood mononuclear cell
PD	Progressive Disease
PDGFR-β	Platelet Derived Growth Factor Receptor-beta
PFS	Progression free survival
po	*per oris*, oral
PR	Partial Response
PROMIS	Patient Reported Outcomes Measurement Information System
PS	Performance Status
PTT	Partial thromboplastin time
QC	Quality control
QOL	Quality of life
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria for Solid Tumors
RET	Rearranged during transfection
rpm	Revolutions per minute
RPMI-1640	Roswell Park Memorial Institute medium 1640
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
SPM	Study Procedures Manual
SUSARs	Suspected Unexpected Serious Adverse Reactions
TIE2	Tyrosine kinase with Immunoglobulin and Epidermal Growth Factor (EGF) homology domain 2
TK	Tyrosine Kinase

TK	Tyrosine Kinase
TNF-α	Tumor necrosis factor alpha
TTP	Time to Progression
UGT1A1	UDP-glucuronosyltransferase 1-1
UGT1A9	UDP-glucuronosyltransferase 1-9
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
WBC	White blood cell

SCHEMA


Subjects with stage IV adenocarcinoma of the colon who are candidates for regorafenib treatment
Randomization (2:1 in favor of ginseng arm)
Regorafenib + Ginseng for 8 weeks
Regorafenib+ No Ginseng for 8 weeks
Fatigue and Disease evaluation after 8 weeks

1. BACKGROUND AND RATIONALE

Safe, effective interventions to improve cancer-related fatigue (CRF) are needed because it remains a limiting factor for quality of life as well as a prevalent, distressing, and activity-limiting symptom. In addition, patients impacted by low levels of fatigue are not candidates for active anticancer therapies. Furthermore, patients have difficulty remaining on active anticancer therapies because of declines in performance status. Fatigue is a major component of declining performance and many times, it is difficult to estimate if it is drug related or cancer related. The prevalence of fatigue in patients undergoing chemotherapy is reported to be between 59% and 96% and, in patients receiving radiation therapy, between 65% and 100%. Therefore, improving energy level could increase adherence and eligibility to active anticancer therapies. A phase III trial was developed to evaluate the efficacy of American ginseng (Panax quinquefolius) on cancer related fatigue and reported that 2,000mg daily of American Ginseng significantly decreased the level of fatigue in the treatment group [1].

Regorafenib is a recently approved active treatment for good performance status patients with colorectal cancer (CRC) as a third line. 47% of the patients in the regorafenib group had fatigue of any grade compared with 28% in the placebo group. 9% of patients in the regorafenib group had grade 3 fatigue versus 5% in the placebo group. Most adverse events occurred early in the course of treatment (during cycles 1–2) [2] .Fatigue can be significant and debilitating in the first few cycles, and symptoms, which are most prominent toward the end of dosing in each cycle, can begin early (e.g., hoarseness within the first 3–4 days) [3].

We hypothesize that Ginseng will decrease fatigue and increase adherence to chemotherapy for patients receiving regorafenib for colon cancer.

We propose a randomized phase II study of Ginseng in colorectal cancer patients treated with Regorafenib to determine if Ginseng will reduce fatigue in this patient population and improve adherence to Regorafenib.

Specific Hypothesis: Regorafenib is a recently approved active, third line treatment for good performance status patients with CRC. One of the potential treatment-limiting toxicities is fatigue, observed in approximately 50% of the patients. We hypothesize that Ginseng will decrease fatigue and increase adherence to chemotherapy for patients receiving regorafenib for colon cancer. The fatigue level will be evaluated with 2 different scales: MFSI-SF (multidimensional fatigue symptom inventory-short form) and PROMIS (Patient-Reported Outcomes Measurement Information System) Short Form v1.0 – Fatigue 8a [4] . The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative is an example of an effort to develop a standard battery of valid and reliable measures that can be used in symptom management and QOL research [5].We will use the MFSI-SF tool that was used in the original ginseng study by Barton et.al and compare its results with the PROMIS scale which represents the NCI recommended tool to evaluate symptoms in oncology clinical trials [6].

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

Assess the difference in fatigue scores using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF) and Patient-Reported Outcomes Measurement Information System (PROMIS Short Form v1.0 – Fatigue 8a) for each group (Regorafenib+ No Ginseng vs. Regorafenib + Ginseng) to determine if 2000 mg of American Ginseng for 8 weeks has an impact on the fatigue score.

2.2. Secondary Objectives

1) Assess the difference in adherence to regorafenib between the two groups. Pill counts will be used to assess adherence. The hypothesis is that Ginseng may increase adherence by decreasing fatigue.

2) Assess the difference in toxicities between the two arms.

3) Assess the difference in retention between the two arms. Retention is the proportion of subjects who complete the study. Note that they may not completely adhere to the study medication, but as long as they come in for the last measurements, they are considered retained.

4) Assess response rate and overall survival

2.3 Endpoints

Fatigue score, adherence, toxicity and retention

3. ELIGIBILITY CRITERIA

3.1. Inclusion Criteria

1. Subjects must be able to understand and be willing to sign the written informed consent and HIPAA authorization for release of personal health information. A signed informed consent form must be appropriately obtained prior to the conduct of any trial-specific procedure. **NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.

2. Age ≥ 18 years at the time of consent.

3. Life expectancy of at least 12 weeks (3 months) as determined by the treating physician.

4. ECOG Performance Status of 0 or 1 within 28 days prior to registration.

5. Histological or pathologically confirmed stage IV adenocarcinoma of the colon.

6. Adequate bone marrow, liver and renal function as assessed by the following laboratory values obtained within 7 days prior to registration for protocol therapy.
    - Absolute neutrophil count (ANC) count > 1,500/mm^3
    - Hemoglobin (Hgb) > 9g/dL
    - Platelet count > 100,000/mm^3
    - Total bilirubin ≤ 1.5 × the upper limit of normal (ULN).
    - Alanine aminotransferase (ALT) and aspartate amino-transferase (AST) ≤ 2.5 x ULN (≤ 5 × ULN for subjects with liver involvement of their cancer)
    - Alkaline phosphatase limit ≤ 2.5 × ULN (≤ 5 × ULN for subjects with liver involvement of their cancer)
    - Serum creatinine ≤ 1.5 × the ULN
    - International normalized ratio (INR)/Partial thromboplastin time (PTT) < 1.5 × ULN. **NOTE**: Subjects who are prophylactically treated with an agent such as warfarin or heparin will be allowed to participate if 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. Warfarin dose should not exceed 1 mg

7. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study drug. Post-menopausal women (defined as no menses for at least 1 year) and surgically sterilized women are not required to undergo a pregnancy test.

8. Subjects (men and women) of childbearing potential must agree to use adequate contraception beginning at the signing of the ICF until at least2 months after the last dose of study drug. The definition of adequate contraception will be based on the judgment of the treating physician or a designated associate.
   NOTE: Examples of adequate contraception may include but are not limited to a combination of any two of the following:
    - Use of oral, injected or implanted hormonal methods of contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
    - Total abstinence
    - Male/female sterilization

9. All subjects must have radiographically assessable disease per RECIST v1.1 obtained by imaging within 28 days prior to registration.

10. Must be able to swallow and retain oral medication.

11. Subject must be deemed a suitable candidate for regorafenib as per their treating physician

3.2. Exclusion Criteria

1. Subject should not be receiving any agent for fatigue including steroids or megace.
   NOTE: Subjects who have a contrast-induced allergy are allowed to receive steroids for their scans.

2. Radiotherapy within 2 weeks prior to study registration. Subjects must have recovered from all therapy-related toxicities.

3. Prior treatment with regorafenib.

4. Previous assignment to treatment during this study. Subjects permanently withdrawn from study participation will not be allowed to re-enter study.

5. Congestive heart failure > New York Heart Association (NYHA) class 2.
   - Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before study registration.
   - Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
   - Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).

6. Evidence or history of bleeding diathesis or coagulopathy.

7. Any hemorrhage or bleeding event ≥ NCI CTCAE Grade 3 within 4 weeks prior to study registration.

8. Subjects with thrombotic, embolic, venous, or arterial events, such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months of study registration.

9. Previous or concurrent cancer that is distinct in primary site or histology from colorectal cancer within 3 years prior to randomization EXCEPT for curatively treated cervical cancer in situ, non-melanoma skin cancer and superficial bladder tumors [Ta (Non-invasive tumor), Tis (Carcinoma in situ) and T1 (Tumor invades lamina propria)].

10. Subjects with pheochromocytoma.

11. Known history of human immunodeficiency virus (HIV) infection or current chronic or active hepatitis B or C infection requiring treatment with antiviral therapy.

12. Ongoing infection > Grade 2 NCI-CTCAE v4.0.

13. Metastatic brain or meningeal tumors (symptomatic or asymptomatic).

14. Major surgical procedure or significant traumatic injury, as defined by the site investigator, within 28 days before study registration.

15. Renal failure requiring hemo- or peritoneal dialysis.

16. Dehydration Grade > 2 NCI CTCAE v4 within 7 days prior to registration.

17. Subjects with seizure disorder currently requiring medication.

18. Persistent proteinuria ≥ Grade 3 NCI CTCAE v4.0 as defined as > 3.5 g/24 hours, measured by urine protein: creatinine ratio on a random urine sample.

19. Interstitial lung disease with ongoing signs and symptoms at the time of study registration.

20. Pleural effusion or ascites that causes respiratory compromise (≥ NCI CTCAE version 4.0 Grade 2 dyspnea).

21. History of organ allograft (including corneal transplant).

22. 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.

23. Any malabsorption condition which, in the opinion of the treating physician, will affect the absorption of any of the agents used in this study.

24. Women who are pregnant or breast-feeding.

25. Any condition, which, in the site investigator's opinion, makes the subject unsuitable for trial participation.

26. Substance abuse, medical, psychological, or social conditions that may interfere with the subject's participation in the study or evaluation of the study results.

27. Treatment with any investigational agent within 28 days prior to registration.

3.3. Excluded therapies and medications, previous and concomitant

1. 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)
   NOTE: Steroids for contrast related allergy or pain management are allowed.

2. Subjects on therapeutic anticoagulation will be excluded form study.
   NOTE: 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. 40 mg daily

3. Subjects with prior history of a bleeding disorder will be excluded from study.

4. Concurrent use of any herbal remedy or preparation other than ginseng (e.g. St. John's wort [Hypericum perforatum])

3.4. Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible for participation in this study.

4. SUBJECT REGISTRATION

All subjects must be registered and randomized through the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system.

Subjects must be registered and randomized prior to starting protocol therapy. Subjects must begin therapy **within 5 business days** of randomization.

5. TREATMENT PLAN

Regorafenib will be administered 160 mg once daily for the first 21 days of each 28-day cycle. Subjects that randomize to receive Ginseng will take 2,000 mg orally once daily every day for 8 weeks (2 cycles). Subjects that randomize to NOT receive Ginseng will not be given Ginseng. Subjects will be instructed to take regorafenib with a low-fat meal.

Subjects will undergo the fatigue assessments, using the MFSI-SF instrument and PROMIS according to the study calendar. Subjects will have a pill count C2D1 and at the end of treatment visit. Subjects will have the re-staging scan (CT of chest/abdomen/pelvis) at the end of Cycle 2/ week 8 (±5). See Study Procedures Manual for questionnaire administration and pill count instructions.

5.1. Study Drug Administration

Table 1: Study Drug Administration; One cycle is 28 days.

Drug	Dose	Frequency of administration	Route of administration	Number of cycles
Regorafenib	160 mg	Days 1-21 of each 28-day cycle	Orally	2
Ginseng	1,000 mg	Twice a day (total of 2,000 mg per day) for 4 weeks (28 days)	Orally	2

5.1.1 Treatment Schedules

5.1.1.1 Regorafenib

Regorafenib 160 mg PO once daily will be taken for 3 weeks on/1 week off for 2 cycles. Four 40-mg 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 a low-fat meal 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.

5.1.1.2 Ginseng

Ginseng 2,000 mg per day will be taken for 4 weeks on for 2 cycles. **Dosing will be 1,000 mg PO twice a day.** The (4) 500 mg capsules consist of pure ground root of Wisconsin ginseng and should be swallowed whole. Do not chew, crush or break. May be taken with or without food. For subjects that randomize to ginseng, if regorafenib is held due to toxicity the ginseng may continue per protocol schedule.

5.1.2 Missed Doses

Missed doses can be within 4 hours of the time that the dose was scheduled. If the timing is beyond 4 hours, the subject will skip the dose and take the next dose as scheduled. Under no circumstances should a subject take two doses on the same day to make up for a missed dose from the previous day.

5.1.3 Pre-medications

Premedication is not required, but can be implemented per site investigator discretion.

5.1.4 Concurrent 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 site 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 strong CYP3A4 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, nefazodone, posaconazole, telithromycin, and voriconazole).

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- 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 site 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 if they do not interfere with the study endpoints, in the opinion of the site investigator.
- Bisphosphonates

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 (other than testosterone supplements used to treat erectile dysfunction).
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cyclosporine, and digoxin). Warfarin is metabolized by the cytochrome enzyme CYP2C9 and its levels may be especially affected by regorafenib
- Use of any herbal remedy or preparation other than ginseng (e.g. St. John's wort [Hypericum perforatum])

5.2. Dose Modifications

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study.

A treatment-limiting adverse event is any adverse event related to study drug experienced during the study resulting in treatment termination.

5.2.1 Dose Modifications for Ginseng

For subjects randomized to receive ginseng there are no dose delays or reductions. If regorafenib is held due to toxicity, the ginseng may continue if the toxicity is attributed to regorafenib only.

5.2.2 Dose Modifications for Regorafenib

5.2.2.1 Dose Reduction Levels

The starting dose of regorafenib is 160 mg once daily. Study medication will be administered on a 3 weeks on/1 week off schedule [3 weeks out of every 4].

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

The modifications of regorafenib will follow the following predefined dose levels:		
Dose level 0 (standard starting dose)	160 mg orally every day	Four 40-mg tablets of regorafenib
Dose level - 1	120 mg orally every day	Three 40-mg tablets of regorafenib
Dose level - 2	80 mg orally every day	Two 40-mg tablets of regorafenib

If a subject experiences more than one toxicity, dose reduction should be according to the toxicity with the highest grade.

In the case of two or more toxicities of the same grade, the site investigator may dose reduce according to that deemed most causally related to study treatment.

If more than 2 dose reductions are required, regorafenib only will be discontinued and the rest of the study treatment may be continued. If a dose reduction has been performed, intra-subject dose re-escalation can be considered (up to the maximal 160 mg daily dose) at the discretion of the treating physician, provided that the toxicity(ies) has resolved to baseline.

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

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

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

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

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

Grade of event	**Occurrence**	**Suggested Dose Modification**

(NCI-CTCAE v4.0)		
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 site investigator.
b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the site investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 2 dose reductions should go off protocol therapy.
e. The maximum daily dose is 160 mg.

The other study treatment may be continued.

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

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

Control of calluses
Before initiating treatment with regorafenib:

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

During regorafenib treatment:

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

Use of creams

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

Tender areas should be protected as follows:

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

Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at every clinic visit or more frequently if clinically indicated. 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 site investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, the table below outlines suggested dose reductions.

Management of Treatment-Emergent Hypertension		
Grade (CTCAE v4.0)	**Antihypertensive Therapy**	**Regorafenib Dosing**
1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 – 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	• Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: • If BP previously within normal limits, start anti-hypertensive monotherapy • If subject already on anti-hypertensive medication, titrate up the dose.	• Continue regorafenib • If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.

3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	• Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, reduce another dose level.[c]
4 Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy
a. Subjects 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 site investigator's discretion. c. Subjects requiring >2 dose reductions should go off protocol therapy.		

Liver Function Abnormalities

Liver function tests should be obtained before initiation of regorafenib and monitored at least every 2 weeks during first 2 months of treatment. Thereafter liver function should be monitored monthly or more frequently as clinically indicated.

For subjects 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 the table below should be followed.

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

Dose Modification/interruption for alanine aminotransferase and/or aspartate aminotransferase increases related to study drug			
Increases in AST/ALT (per NCI CTCAE v 4)	**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.		

5.2.3 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., antidiarrheals 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.

6 TREATMENT DISCONTINUATION

6.2 Reasons for Discontinuing Study Drug

In the absence of treatment delays due to adverse events, treatment may continue for up to 2 cycles or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of study drug
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the site investigator

6.3 Reasons for Withdrawal from Study

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

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the site investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Subject is lost to follow-up.
- Death.

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

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Severe allergic reaction to regorafenib (such as exfoliative erythroderma or Grade 3 or 4 hypersensitivity reaction) or ginseng.
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the site investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to 4.
- Use of illicit drugs or other substances that may, in the opinion of the site investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

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

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

7 STUDY SCHEDULE OF EVENTS

Cycle = 28 days

Examination	Screening		Cycle 1		Cycle 2		After completion of Cycle 2	End of Treatment Visit [7]	Follow up[8]
	-28 days	-7 days	Day 1	Day 15 (±3)	Day 1 (±3)	Day 15 (±3)	(±5)	30 days (± 7) after last dose of Cycle 2	(±7)
REQUIRED ASSESSMENTS									
Informed Consent	X								
Medical history	X								
Height	X								
Physical examination	X		X	X	X	X		X	
Vital signs including BP, weight and ECOG performance status	X	X[9]	X	X	X	X		X	
CBC w/ differential		X		X	X	X		X	
Complete Metabolic Profile[1]		X		X	X	X		X	
PT/INR and aPTT [2]		X	[D5]		[X]			X	
Pregnancy test[3]		X							
Urinalysis[10]		X	X		X				
AEs & concomitant medications	X		X	X	X	X		X	
DISEASE ASSESSMENT									
Pathology Review	X								
CT chest/abdomen/pelvis[4]	X						X[4]		
TREATMENT									
Regorafenib[5]			X	X	X	X			
Ginseng[5]			X	X	X	X			
OTHER									
MFSI-SF, PROMIS[6]			X		X[6]			X	
Pill count[6]					X			X	
FOLLOW-UP									
For progression, start of additional cancer treatment, and survival									X

Footnotes:
CBC=complete blood count; CT=computed tomography; D=days; ECOG=Eastern Cooperative Oncology Group; ICS = informed consent; MFSI-SF= Multidimensional Fatigue Symptom Inventory-Short Form

1. Serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
2. All subjects will have PT/INR/aPTT at screening and End of Treatment Visit. ONLY subjects who are prophylactically treated with an agent such as warfarin or heparin must have close monitoring on Cycle 1 Day 5 and Day 1 of each cycle. If either of these values is above the therapeutic range, subjects should have at least weekly evaluations until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
3. Complete only for women of childbearing potential
4. Baseline CTs must be completed within 28 days prior to registration. CTs for re-staging will be performed after Cycle 2 (8 weeks) is complete and may be performed ± 5 days of scheduled clinic visit. Regardless of randomization, all subjects will follow up with their physician to discuss results.
5. Regorafenib 160 mg PO once daily will be administered for 3 weeks on/1 week off. If subject randomizes to receive Ginseng: 2,000 mg PO per day (1,000 mg BID), every day of each 28-day cycle. For subjects that randomize to ginseng, if regorafenib is held due to toxicity the ginseng may continue per protocol schedule.
6. See Study Procedures Manual for MFSI-SF and PROMIS questionnaires and additional information. The research nurse will provide the questionnaires to the subject as well as instructions on completion of the questionnaires. These instructions should include the importance of the subject completing the surveys without family assistance. The first set of surveys will be administered by the research nurse in the clinic via interview. The remainder of the surveys will be self-administered by the subject in clinic. If the subject has a question regarding the surveys the research nurse or physician will be available to respond. For pill count, please ask the subject to bring their pill bottle to verify number of doses taken at the time of clinic visit.
7. The End of Treatment visit should occur 30 days after completion of Cycle 2 (± 7 days). Subjects who stop treatment prior to completion of Cycle 2 should have the EOT 30 days after discontinuation of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.
8. Follow up will occur in all subjects after completion of Cycle 2 every 3 months for 18 months. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.
9 Day -7 only ECOG performance status need be obtained.
10 Urinalysis should be done if proteinuria is suspected as per site investigator's discretion.

7.1 Screening

Within 28 days of study registration
- Informed consent statement
- Complete medical history
- Complete physical examination
- Vital signs including blood pressure (BP), height, weight and ECOG performance status
- Adverse event and concomitant medication assessment
- Local pathology review for confirmation of adenocarcinoma
- CT scans of the chest, abdomen, and pelvis to assess all measurable or non-measurable sites of disease

Within 7 days of study registration
- ECOG performance status
- Laboratory testing:
  - Complete Blood Count (CBC) with differential and platelet count
  - Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium)
  - PT/INR and aPTT
  - Urine pregnancy test or serum HCG (only for women of child bearing potential)
  - Urinalysis should be done if proteinuria is suspected as per site investigator's discretion.

7.2 On Treatment

7.2.1 Cycle 1 Day 1

NOTE: Cycle 1 Day 1 testing need not be repeated if completed within 7 days of starting protocol therapy.
- Complete physical examination
- Vital signs including BP, weight and ECOG performance status
- Adverse event and concomitant medication assessment
- MFSI-SF and PROMIS questionnaires
- Drug administration as outlined in Section 5 and Study Calendar

7.2.2 Cycle 1 Day 15 (± 3 days)
- Complete physical examination
- Vital signs including BP, weight and ECOG performance status
- Laboratory testing:
  - Complete Blood Count (CBC) with differential and platelet count
  - Complete metabolic profile (CMP)
- Adverse event and concomitant medication assessment
- Drug administration as outlined in Section 5 and Study Calendar
- Administer MFSI-SF and PROMIS questionnaires

7.2.3 Cycle 2 Day 1 (± 3 days)

- Complete physical examination
- Vital signs including BP, weight and ECOG performance status
- Laboratory testing:
  - Complete Blood Count (CBC) with differential and platelet count
  - Complete metabolic profile (CMP)
  - PT/INR and aPTT
  - Urinalysis should be done if proteinuria is suspected as per site investigator's discretion.
- Adverse event and concomitant medication assessment
- Drug administration as outlined in Section 5 and Study Calendar
- Administer MFSI-SF and PROMIS questionnaires
- Pill Count

7.2.4 Cycle 2 Day 15 (± 3 days)

- Complete physical examination
- Vital signs including BP, weight and ECOG performance status
- Complete metabolic profile (CMP)
- Adverse event and concomitant medication assessment
- Drug administration as outlined in Section 5 and Study Calendar
- Administer MFSI-SF and PROMIS questionnaires

7.2.5 After completion of Cycle 2/ 8 weeks (± 5 days)

- CT scans of the chest, abdomen, and pelvis to assess all measurable or non-measurable sites of disease. Regardless of randomization, all subjects will follow up with their physician to discuss results.

7.3 End of Treatment: At least 30 days (±7) after the last dose of Cycle 2

- Complete physical examination
- Vital signs including BP, weight and ECOG performance status
- Laboratory testing:
  - Complete Blood Count (CBC) with differential and platelet count??
  - Complete metabolic profile (CMP)
  - PT/INR and aPTT
- Adverse event and concomitant medication assessment
- Administer MFSI-SF and PROMIS questionnaires
- Pill count

7.4 Follow-Up (±7)

Subjects will be followed every 3 months for 18 months after completion of Cycle 2:

- Disease progression
- Type and start date of additional cancer treatment
- Survival status

8 CRITERIA FOR EVALUATION

8.1 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

8.1.1 Measurable disease

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

8.1.2 Measurable lesions

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

8.1.3 Non-measurable lesions

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

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

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

8.1.4 Malignant lymph nodes

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

8.1.5 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, recorded, and measured at baseline. Target lesions should be selected based on 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.

8.1.6 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 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.

8.1.7 Response Criteria

8.1.7.1 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

8.1.7.2 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 subject 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 later by the sponsor-investigator.

8.1.7.3 Evaluation of best overall response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/ Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

8.2 Definitions for Response Evaluation – RECIST version 1.1

8.2.1 First Documentation of Response

The time between initiation of therapy and first documentation of PR or CR.

8.2.2 Confirmation of Response

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

8.2.3 Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

8.2.4 Duration of Overall Complete Response

The period measured from the time that measurement criteria are met for complete response until the first date that recurrent disease is objectively documented.

8.2.5 Objective response rate

The objective response rate is the proportion of all subject with confirmed PR or CR according to RECIST v.1.1, from the start of treatment until disease progression/recurrence (taking as

reference for progressive disease the smallest measurements recorded since the start of treatment).

8.2.6 Time to Progression
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

8.2.7 Progression Free Survival
A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

8.2.8 Overall Survival
Overall survival is defined by the date of randomization to date of death from any cause.

8.3 Measurement of Fatigue

8.3.1 Multidimensional fatigue symptom inventory-short form (MFSI-SF)
The MFSI-SF tool that was used in the original ginseng study by Barton et.al will be used in this clinical trial. Please see document entitled "Information about the Fatigue Symptom Inventory (FSI) and the Multidimensional Fatigue Symptom inventory (MFSI)" in the SPM for detailed information.

8.3.2 Patient –Reported Outcomes Measurement Information System (PROMIS)
The Patient-Reported Outcomes Measurement Information System (PROMIS) initiative is an example of an effort to develop a standard battery of valid and reliable measures that can be used in symptom management and QOL research [5]. Please see the document entitled "PROMIS Fatigue Scoring Manual" in the SPM for detailed information.

9 DRUG INFORMATION
The two drugs used in this trial are Regorafenib and Ginseng.

9.1 American Ginseng (Panax quinquefolius)
Ginseng's proposed mechanism based on preclinical and clinical data is by down regulating inflammatory pathways , decrease inflammation and modulate cortisol and the impact of chronic stress on the hypothalamic pituitary adrenal axis [7-12] .

Formulation
Because ginseng is not regulated by the FDA and is a plant that is subject to all of the variables relevant to any agricultural crop, this study will use American Ginseng manufactured in Wisconsin, which was also used in the phase 3 clinical trial (Barton et al 2013) (Ginseng Board of Wisconsin, and Wausau, WI), and which is manufactured using good manufacturing practices by Beehive Botanicals (Hayward, WI).

Administration
Subjects will take four 500-mg opaque capsules consisting of pure ground root of Wisconsin ginseng. Dosing will be twice a day at 1000 mg (around meal and at lunch or noon). Total dose is 2,000 mg per day.

Precautions
Ginseng is known to interfere with blood coagulation and some components of ginseng can elevate plasma insulin levels, causing hypoglycemia. Treating physicians should closely monitor persons with hypoglycemia or those on anticoagulants per local standard of care.

Side Effects
May cause insomnia, nervousness, restlessness, increased heart rate, increased blood pressure or nausea.

9.2 Regorafenib

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

The study drug must be exclusively used for the investigation specified in this protocol and it will only be accessible to authorized staff.

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.

Storage and Handling
Store all study drugs at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [See USP Controlled Room Temperature].

Store study drugs in the original bottle.

Do not remove the desiccant from the original bottle. Keep the bottle tightly closed after first opening. Discard any unused tablets 28 days after opening the bottle.

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

Destruction and Return
At the end of the study, unused supplies of regorafenib and ginseng should be destroyed according to institutional policies. Destruction will be documented on the Drug Accountability Record Form. A certificate of destruction should be sent to HCRN (or designee).

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

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

Adverse Events
Site investigators should refer to the Safety Information section of the current IB or prescribing information 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.

10 ADVERSE EVENTS
The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov. All forms for AE/SAE recording and reporting can be found in the Study Procedure Manual or in OnCore (Documents and Information Tab).

10.1 Definitions

10.1.1 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 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. An adverse event may include the following: an adverse event occurring in the course of the use of a drug in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug withdrawal and any failure of expected pharmacological action.

10.1.2 Serious Adverse Event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria:

- Results in death, other than death related to disease progression
- Is life-threatening.
  - The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- 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 24 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.
- Results in persistent or significant disability/incapacity.
  - Disability means a substantial disruption of a person's ability to conduct normal life's functions.
- Is a congenital anomaly/birth defect.
- Is another medically important serious event.
  - An event may be considered an important medical event when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

10.1.3 Adverse Drug Reaction

Adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

10.1.4 Serious Adverse Drug Reaction

A serious adverse drug reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drugs.

10.2 Adverse Event Reporting

10.2.1 Site Requirements for Recording Adverse Events

Adverse events (AEs) will be recorded from the time of consent and for 30 days after the last dose of study drugs, regardless of whether or not the event(s) are considered related to the study drugs. The descriptions and grading scales found in the revised NCI Common Terminology

Criteria for Adverse Events (CTCAE) v4 will be utilized for AE reporting. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov.

All AEs considered related to study drug will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

10.2.2 Site Requirements for Reporting Serious Adverse Events to HCRN

Site investigators and other site personnel must report any SAEs occurring from the time of informed consent to 30 days after the last dose of study drugs. This includes events both related and unrelated to the study drugs.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

Unrelated	The Adverse Event is ***clearly not related*** to the study drug(s)
Unlikely	The Adverse Event is ***doubtfully related*** to the study drug (s)
Possible	The Adverse Event ***may be related*** to the study drug (s)
Probable	The Adverse Event is ***likely related*** to the study drug (s)
Definite	The Adverse Event is ***clearly related*** to the study drug (s)

The completed SAE Submission Form (see SPM) must be sent to HCRN **within 24 hours** of discovery of the event. The form may be sent to HCRN either electronically to safety@hoosiercancer.org or by fax to 317-921-2053. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Submission Form and the fax confirmation sheet/email must be kept within the site study file.

Follow-up information should be submitted to HCRN either electronically to safety@hoosiercancer.org or by fax to 317-921-2053, using a SAE Submission Form stating that this is a follow-up to the previously reported SAE and providing the follow-up number if appropriate. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

10.2.3 HCRN Requirements for Reporting Serious Adverse Events to Bayer

HCRN will report all SAEs to Bayer **within 24 hours** of receipt of the SAE Submission Form from the site and to regulatory authorities (FDA) per federal guidelines.

HCRN will report SAEs using a MedWatch form available at http://www.fda.gov/medwatch/ for SAEs reportable to FDA; all other SAEs will be reported using the HCRN SAE Submission Form. All SAE reports must include the following minimum information:

1. The name and contact information of the reporter
2. The name of the study drug(s)
3. A description of the reported SAE

4. A subject identified by one or more of the following:
    a. Subject initials
    b. Subject number
    c. Knowledge that a subject who experienced the adverse event exists
    d. Age
    e. Sex
5. An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.

Additional data which would aid the review and causality assessment of the case include but are not limited to:

The date of onset
The severity
The time from administration of study drug(s) to start of the event
The duration and outcome of the event
Any possible etiology for the event
The final diagnosis or syndrome, if known
Action(s) taken, if any

All reports shall be sent electronically to:

Electronic Mailbox:	DrugSafety.GPV.US@bayer.com
Facsimile:	(973) 709-2185
Address:	Global Pharmacovigilance - USA
Mail only:	Bayer HealthCare P.O. Box 915 Whippany, NJ 07981-0915
Address:	**100 Bayer Boulevard, Whippany, NJ 07981**
FDX or UPS only	**67 Whippany Road, Whippany NJ 07981 for UPS**

Reports for all Bayer products can also be phoned in via our Medical Communications Department

Phone: 1-888-842-2937

10.2.4 Expedited Reporting of Other Safety Information:

Sites will report to HCRN **within 24 hours** of discovery of event and HCRN shall report to Bayer **within 24 hours** of receipt of report:

- An adverse event related to study specific procedures which the site investigator reasonably believes impacts subject safety (For Non-SAEs: site investigator decision whether to file to Bayer and other regulatory authorities).
- Any new and important event related to treatment with the study drug(s) which the site investigator reasonably believes impacts subject safety (this is up to the site investigator to determine what is new and important and related to the study drug. Site investigator decision whether to file to Bayer and other regulatory authorities).

- Any pregnancy during which a female patient was exposed to the study drug(s). Any pregnancy in the partner of a male subject, where the male subject was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).

Any communication, other than communication provided by Bayer, concerning safety related information to regulatory authorities or ethics committees including but not limited to: Development Safety Update Reports (DSUR) / relevant parts of IND reports for study drugs. Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees.

10.2.5 HCRN Reporting to the Food and Drug Administration (FDA)

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the IND (73,088) sponsored by Charles L Loprinzi MD at Mayo Clinic.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report.

10.2.6 IND Safety Reports Unrelated to this Trial

IND safety reports not occurring on this trial but involving the trial treatment (outside SAEs) received from Bayer will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. IND safety reports will also be available in HCRN electronic data capture system.

11 STATISTICAL CONSIDERATIONS

Power/Sample Size:

The pilot study will enroll 90 total subjects and randomize them using a 2:1 allocation with 60 subjects enrolled in the Regorafenib + Ginseng group and 30 enrolled in the regorafenib + no ginseng group. The sample size is calculated based on the MFSI-SF fatigue endpoint. Based on the data published in Barton et al (2013), the expected standard deviations for the outcome of interest are 27.0 for the Ginseng group and 26.1 for the no ginseng group. Using a two group Satterthwaite t-test with a 0.050 two-sided significance level, there is 80% power to detect a difference between groups if the change in the no ginseng group is 10 and the change in the Ginseng group is 27 (or greater) (a group difference of 17 units). In addition, with this sample size, a two-sided 95.0% confidence interval for the difference of the two means (change in fatigue score for Ginseng group vs. change in fatigue score for no ginseng group) will extend 11.833 from the observed difference in means, assuming that the common standard deviation is 27.0 (conservatively choosing the standard deviation from the Ginseng group since it is larger than the no ginseng standard deviation) when the sample sizes are 60 and 30 respectively (a total sample size of 90) and the confidence interval is based on the large sample z statistic.

Based on previous published data [1] we believe that the Ginseng mean change in fatigue score will likely be closer to 20 (rather than 27); thus, we do not anticipate that this trial will reach

statistical significance. However, we will be able to refine our estimate of the standard deviation for the fatigue score in this subject population and provide a 95% confidence interval to estimate the likely boundaries for the true effect size. This information, along with estimates of retention and adherence, can be used to determine the sample size for further evaluation.

Furthermore, if the observed difference between groups is 12 or larger then this trial will provide both statistically significant and clinically meaningful evidence that Ginseng can help reduce fatigue in subjects taking regorafenib and a follow-up trial would not be needed. If the observed difference between groups at the end of the trial is 8-12 (expected difference based on previous study of Ginseng's impact on fatigue), then this study will have provided strong support for the potential efficacy of Ginseng and the follow-up trial designed to detect an effect of that magnitude would be justified. If at the end of this trial the observed difference between groups is close to zero then this would provide evidence to suggest that the potential beneficial effects of Ginseng may be less than expected and would warrant further discussion about whether a future trial should be performed.

Analyses:
The primary objective is to assess the effect of Ginseng on fatigue using the multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF) and PROMIS Short Form v1.0 – Fatigue 8a. Subjects will have fatigue assessed at baseline and at weeks 2, 4, and 8. Repeated measures analysis of covariance will be used to assess the effect of Ginseng on fatigue. An unstructured covariance matrix will be used initially to account for the within subject correlation in fatigue over time. Additional covariance structures (exchangeable, autoregressive, Toeplitz, etc.) will be considered to reduce the number of fitted parameters, and the final structure will be chosen based on likelihood ratio tests for nested structures and the AIC statistic for non-nested structures. The primary hypothesis will be assessed using a linear contrast at the end of cycle 1. Additional contrasts will be used to assess the difference in fatigue at each time as well as the average difference in fatigue over time.

The secondary objectives are as follows:
(1) To assess the difference in adherence to regorafenib between the 2 groups. We will assess regorafenib adherence at three times, at the end of the 3rd week of each cycle. Since the recommended dose is once daily for 21 days, a measure of adherence would be the number of pills (out of 21) that each subject takes during each cycle. Using this measure for each subject, we will first compare groups using a 2-sample t-test for cycle 1, cycle 2 and then overall. Next, we will define subjects as being adherent based on having taken their pills on 17 (or more) days out of 21 (i.e. over 80% adherence). Using this definition of adherence, we will fit a 2x2 table comparing adherence rates between groups using a 1 degree of freedom Chi-square test. In addition, the statistician will compare mean daily doses using a t test and median daily doses by using Mann-Whitney test. Our hypothesis for these analyses is that Ginseng will reduce fatigue and thus lead to greater adherence to regorafenib in subjects who are in the Ginseng arm when compared to the no ginseng arm

(2) To assess the difference in toxicities between the two arms. Fisher exact tests will be used to assess the difference in toxicities between the two groups as well as the proportion of subjects

who experience grade 3 or higher toxicities of any kind according to the data safety monitoring plan described below.

(3) To assess the difference in retention between the two arms. As subjects can drop out of the study at various times, we will use Kaplan-Meier methods to estimate the retention distributions in each group and a log-rank test to assess the difference in distributions between the two groups.

(4) Response rate and overall survival are secondary objectives for the trial. Overall survival (OS) as an endpoint is defined in section 8.2.8 of the protocol. OS will be estimated using the Kaplan-Meier method[13] and 90% confidence intervals derived as described in Brookmeyer and Crowley[14]. The median will be provided along with the corresponding 95% CI. Additionally, the 25% and 75% percentiles for these endpoints will also be provided.

Response rate (RR) as an endpoint is defined in section 8.2.5 of the protocol. Objective response (complete response + partial response) rate defined as the proportion of patients who achieve an objective response out of all patients treated on that arm will be estimated along with a 95% confidence interval.

12 TRIAL MANAGEMENT

12.1 Data and Safety Monitoring Plan

The study will be conducted in accord with the Comprehensive Cancer Center of Wake Forest University's Data and Safety Monitoring Plan.

HCRN oversight activities include:

- Review all adverse events requiring expedited reporting as defined in the protocol
- Notify participating sites of adverse events requiring expedited reporting
- Provide trial accrual progress and safety information to the sponsor-investigator
- Provide data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee for review as per their DSMP.

12.2 DSMP Reporting Guidelines

HCRN will compile data summary reports for this trial and submit these reports monthly to the sponsor-investigator. HCRN will submit data summary reports at a minimum twice a year to a Data and Safety Monitoring Committee (DSMC) associated with this protocol for review.

12.3 On-Site Monitoring

Monitoring visits to the trial sites will be made periodically during the trial, to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data as submitted via the data collection system. The site investigator/Institution guarantee access to source documents by HCRN or its designee and appropriate regulatory agencies. The trial site may also be subject to quality assurance audit by Bayer Pharmaceutical or its designee as well as inspection by appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

13 DATA HANDLING AND RECORD KEEPING

13.1 Case Report Forms and Submission

This study will utilize electronic case report form (eCRF) in the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system. The EDC system is a comprehensive database used by HCRN. Access to the data through EDC system is restricted by user accounts and assigned roles. Once logged into the EDC system with a user ID and password, the EDC system defines roles for each user, which limits access to appropriate data. User information and passwords can be obtained by contacting HCRN at (317) 921-2050.

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is housed at HCRN and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and HCRN.

13.2 Record Retention

It is the expectation that all data has source documentation available at the site. The site must implement processes to ensure this happens.

Inspections by regulatory health authority representatives (i.e. FDA and IRB[s]) are possible. The site investigator should notify Bayer immediately of any such inspection.

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all participating subject (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the site investigator in compliance with regulations.

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request. Subject (hospital) files will be archived according to local regulations and in accordance with the maximum period permitted by the hospital, institution, or private practice.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs

will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Bayer, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

13.4 Changes to the Protocol

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, HCRN, and Bayer Pharmaceuticals.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the HCRN and must be approved by each IRB, Bayer Pharmaceuticals, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Bayer Pharmaceuticals' willingness to supply study drug is predicated upon the review of the protocol. HCRN agrees to provide written notice to Bayer Pharmaceuticals of any modifications to the protocol or informed consent.

14 ETHICS

14.1 Ethics Review

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by an IRB. The site investigator must submit written approval to the HCRN office before he or she can enroll any subject into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subject for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.
The site investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Bayer Pharmaceuticals will provide this information to the sponsor-investigator. These reports will be reviewed by the sponsor-investigator and those considered unexpected and possibly related to protocol therapy and all deaths within 30 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

14.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

14.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subject must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the subject.

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Appendix 1

List of medications to be used with caution during study drug treatment

Category	Drug Name
Moderate CYP3A4/5 inhibitors	Amprenavir, atazanavir, casopitant, cimetidine, darunavir, diltiazem, fosamprenavir, lomitapide, netupitant, tofisopam, verapamil
Moderate CYP3A4/5 inducers	Bosentan, efavirenz, etravirine, genistein, lersivirine, modafinil, nafcillin, talviraline
Sensitive CYP3A4/5 substrates[1]	Alpha-dihydroergocryptine, almorexant, alpaviroc, apixaban (doses <2.5 mg only), atazanavir, atorvastatin, avanafil, bosutinib, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, darifenacin, darunavir, ebastine, eletriptan, eplerenone, felodipine, fluticasone, ivacaftor, lomitapide, lumefantrine, lurasidone, maraviroc, midazolam, perospirone, quetiapine, ridaforolimus, sildenafil, ticagrelor, tilidine, tolvaptan, triazolam, vardenafil, vicriviroc, voclosporin
Strong BSEP inhibitors	Bosentan, fusidate, glibenclamide, sulindac, troglitazone (TGZ-sulfate)
Medications that carry a possible risk for QT prolongation[2]	Alfuzosin, apomorphine, aripiprazole, atazanavir, atomoxetine, bedaquiline, clozapine, dexmedetomidine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, gatifloxacin, gemifloxacin, granisetron, iloperidone, isradipine, lithium, mirabegron, mirtazapine, moexipril, norfloxacin, ofloxacin, olanzapine, ondansetron (4 mg or 8 mg), oxytocin, paliperidone, pasireotide, pipamperone, promethazine, quetiapine, ranolazine, rilpivirine, risperidone, roxithromycin, sertindole, telavancin, tetrabenazine, tizanidine, tolterodine, vardenafil, ziprasidone
MATE1 and OCT2 substrates[3]	Acyclovir, amantadine, amiloride, cephalexin, cephradine, cimetidine, famotidine, fexofenadine, memantine, metformin (also a substrate for OCT1,

	MATE1, and MATE2K), pindolol, procainamide, ranitidine, and varencicline
BCRP substrates	Rosuvastatin, sulfasalazine
1 Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor. 2 Source: www.qtdrugs.org (as of Apr 7, 2015) 3 Source: FDA Draft Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, and implications for Dosing and Labeling (February 2012) and Yonezawa and Inui (2011) Importance of the multidrug and toxin extrusion MATE/SLC47A family to pharmacokinetics, pharmacodynamics/toxicodynamics and pharmacogenomics. Br J Pharmacology 164:1817-25	

Appendix 2

List of prohibited medications during study drug treatment

Category	Drug Name
Strong CYP3A4/5 inhibitors	Voriconazole, boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Strong CYP3A4/5 inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort (hypericum perforatum)
CYP3A4/5 substrates with NTI	Terfenadine, alfentanil, apixaban, aprepitant, astemizole, cisapride, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, lovastatin, nicardipine, nisoldipine, pimozide, quinidine, rivaroxaban, simvastatin, sirolimus, tacrolimus, terfenadine, thioridazine
Medications with a known risk for QT prolongation	Vandetanib, amiodarone, anagrelide, arsenic trioxide, astemizole, azithromycin, bepridil, chloroquine, chlorpromazine, cilostazol, ciprofloxacin, cisapride, citalopram, clarithromycin, disopyramide, dofetilide, domperidone, donepezil, dronedarone, droperidol, erythromycin, escitalopram, flecainide, fluconazole, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl, mesoridazine, methadone, moxifloxacin, ondansetron (i.v. only), pentamidine, pimozide, probucol, procainamide, propofol, quinidine, sevoflurane, sotalol, sparfloxacin, sulpiride, terfenadine, thioridazine, vandetanib, venlafaxine
NTI = narrow therapeutic index drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes). Source: www.qtdrugs.org (as of Apt 7, 2015)	