

PROTOCOL Version 2.2 Dated 08 February 2017

Phase II Study of Perindopril and Regorafenib in mCRC (PARICCA)

A Phase II Trial of the Effect of Perindopril on HFSR Incidence and Severity in Patients Receiving Regorafenib with Refractory Metastatic Colorectal Carcinoma (mCRC)

Short title:

Phase II Study of Perindopril and Regorafenib in mCRC (PARICCA)

Test drugs: COVERSYL® (perindopril erbumine) and Stivarga® (regorafenib) or “regorafenib”

Study purpose: Efficacy and Safety

Clinical study phase: II

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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

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Phase II Study of Perindopril and Regorafenib in mCRC (PARICCA)

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The signatory agrees to the content of the final clinical study protocol as presented.

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Synopsis

Title	A Phase II Trial of the effect of Perindopril on HFSR incidence and severity in patients receiving Regorafenib with Refractory Metastatic Colorectal Carcinoma (mCRC)
Short Title	Phase II Study of Perindopril and Regorafenib in mCRC
Clinical study phase	Phase II
Study Objectives	<p>Primary Objective: To assess the incidence of all grade toxicities for HFSR defined by CTCAE v4.03 criteria.</p> <p>Secondary Study Objective(s);</p> <ul style="list-style-type: none"> • Incidence of (all grade): <ul style="list-style-type: none"> ○ hypertension ○ toxicity • Maximal severity of HFSR • Time course to development of worst grade (stage 3) HFSR • Progression-free survival
Test drugs	COVERSYL® (perindopril erbumine) or “perindopril” Stivarga® (regorafenib) or “regorafenib”
Dose of administration	COVERSYL® (perindopril erbumine) 4 mg will be administered daily for 21 days of a 28-day cycle. Perindopril will be administered orally, first thing in the morning on an empty stomach. Regorafenib will be administered 160 mg daily for 21 days of a 28-day cycle. Regorafenib will be administered with low fat breakfast, one hour after perindopril. A low fat breakfast as defined by the Regorafenib monograph is one that is <30% fat, ~300-550 calories.
Route of administration	Both medications will be administered orally
Duration of treatment	<p>The study will be discontinued if 5 of the first 10 patients exhibit a Grade 3 or higher HFSR. Note that in the CORRECT trial, 47% of patients experienced HFSR of all grades with 17% experiencing HFSR with grade 3 severity.</p> <p>Patients will remain on trial and will receive regorafenib and perindopril until radiological disease progression, based on RECIST v1.1 criteria. If patients progress on regorafenib, both drugs will be stopped. However, after the patient progresses (i.e. is no longer on trial) the medication can be continued if the investigator feels that there is a clinical benefit.</p> <p>Other reasons for patients to discontinue therapy include: death; patient withdraws consent; treating physician determines</p>

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	discontinuation of treatment is in the patient's best interest; substantial non-compliance with the protocol.
Indication	<p>Patients with metastatic colorectal carcinoma (mCRC) who have progressed on/ after, or are intolerant to all approved drugs* for CRC and are eligible for regorafenib will be included in this trial.</p> <p>*fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-vascular endothelial growth factor (anti-VEGF) therapy, and, if RAS wild type, an anti-epidermal growth factor receptor (anti-EGFR) therapy.</p>
Diagnosis and main criteria for inclusion	<p>Patients with metastatic colorectal cancer (mCRC) who have progressed on/after, or are intolerant to all approved drugs for CRC and are eligible for regorafenib.</p> <p>In order to be eligible, <u>all</u> inclusion criteria must be met.</p> <p>A patient must:</p> <ul style="list-style-type: none"> • Understand, be willing to give consent, and sign a written informed consent form prior to undergoing any study-specific procedure • Be male or female and ≥ 18 years of age • Histological or cytological documentation of adenocarcinoma of the colon or rectum. • Patients with metastatic colorectal cancer (Stage IV) previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy. • Progression during or within 3 months following the last administration of approved standard therapies, or have experienced intolerance to previous therapy. • Metastatic CRC patients with measurable or non-measurable disease • Life expectancy of at least 3 months • Have an Eastern Cooperative Oncology Group performance status of 0 or 1 (within 14 days prior to the initiation of study treatment) • Have adequate bone marrow, liver function, and renal function as measured by the following laboratory assessments conducted within 7 days prior to the initiation of study treatment: • Total bilirubin ≤ 1.5 times the upper limit of normal (ULN) <ul style="list-style-type: none"> ○ Alanine aminotransferase (ALT) and aspartate

	<p>aminotransferase (AST) \leq 2.5 times the ULN (<u>< times ULN for patients with liver involvement of their cancer</u>)</p> <ul style="list-style-type: none"> ○ Lipase \leq 1.5 times the ULN ○ Serum creatinine \leq 1.5 times the ULN ○ Glomerular filtration rate \geq 30 mL/min/1.73 m² according to the modified diet in renal disease abbreviated formula ○ International normalized ratio (INR) of prothrombin time (PT; PT-INR) and partial thromboplastin time (PTT) \leq 1.5 times the ULN ○ Platelet count \geq 100000 /mm³, hemoglobin \geq 9 g/dL, absolute neutrophil count \geq 1500/mm³. ○ Alkaline phosphatase limit \leq 2.5 times the ULN (<u>< times ULN for patients with liver involvement of their cancer</u>) <ul style="list-style-type: none"> ● If female and of childbearing potential, have a NEGATIVE result on a pregnancy test performed a maximum of 7 days before initiation of study treatment. ● If female and of childbearing potential or if male, must agree to use adequate contraception (e.g., abstinence, intrauterine device, oral contraceptive, or double-barrier method) based on the judgment of the investigator or a designated associate from the date on which the ICF is signed until 6 months after the last dose of study drug.
<p>Exclusion Criteria</p>	<p>Exclusion Criteria</p> <p>Patients who meet the following criteria at the time of screening will be excluded:</p> <ul style="list-style-type: none"> ● Patients with hypotension (less than 90/60mm Hg) or at risk of symptomatic hypotension (fainting or dizziness) will be excluded. ● Prior treatment with regorafenib or any VEGFR-targeting kinase inhibitor. ● Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study. ● Concurrent cancer requiring treatment that is distinct in primary site or histology from colorectal cancer. ● Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication. ● Unstable/uncontrolled cardiac disease including: congestive heart failure \geq New York Heart Association (NYHA) class 2; unstable angina (angina symptoms at rest), new-onset angina

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	<p>(begun within the last 3 months); myocardial infarction less than 6 months before start of study drug; cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).</p> <ul style="list-style-type: none">● Uncontrolled hypertension. (Systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).● Patients with pheochromocytoma.● Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication.● Ongoing infection > grade 2 NCI-CTCAE version 4.03● Known history of human immunodeficiency virus (HIV) infection.● Known history of chronic hepatitis B or C.● Patients with seizure disorder requiring medication.● Symptomatic metastatic brain or meningeal tumors unless the patient is > 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry. Also the patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for one month prior to and following screening radiographic studies)● History of organ allograft● Patients with evidence or history of bleeding diathesis, including patients who have had a transfusion and/or radiographic endoscopic or elective operative intervention to control the bleeding or hemorrhage event within four weeks prior to the study● Non-healing wound, ulcer, or bone fracture.● Renal impairment or failure requiring hemo- or peritoneal dialysis.● Patients with severe hepatic impairment.● Dehydration NCI-CTC version 4.03 grade > 1.● Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results● Any illness or medical conditions that are unstable or could jeopardize the safety of the study● Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.● Persistent proteinuria of CTC Grade 3 or higher. Quantification of
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	<p>proteinuria done by urinary protein/creatinine ratio on a random urine sample preferably taken at mid-morning. If protein/creatinine ratio is greater than 30g/mol Creat, then a 24-hour urine protein test should be performed to confirm Grade 3 or higher proteinuria (> 3.5 g/24 hours).</p> <ul style="list-style-type: none"> ● Patients unable to swallow oral medications ● Any malabsorption condition ● Unresolved toxicity higher than NCI-CTCAE (version 4.03) Grade 1 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin induced neurotoxicity ≤Grade 2 ● Patients who are hypersensitive to perindopril, as well as those hypersensitive to regorafenib, sorafenib, drugs in the same class or any ingredient in the formulation. ● Patients who cannot tolerate the full dose of perindopril (4 mg) for any reason. ● Patients receiving systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy, hormonal therapy and experimental or approved therapies during this trial or within 14 days before starting to receive study medication. <p>In addition, patients will be excluded for the following reasons (From perindopril monograph).</p> <ul style="list-style-type: none"> ● Patients with a history of hereditary/idiopathic angioedema, or angioedema related to previous treatment with an angiotensin converting enzyme inhibitor. ● Pregnant women or those planning to become pregnant, nursing women. ● Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency. ● Patients with pre-existing anti-hypertension treatment with an ACE inhibitor or angiotensin receptor blocker (ARB) are to be excluded. Co-administration of ACE inhibitors, including COVERSYL[®], with other agents blocking the Renin-Angiotensin System (RAS), such as ARBs or aliskiren-containing drugs, will not be allowed, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.
Study Design	Phase II, open-label, single-arm trial of patients with refractory mCRC treated with regorafenib (160 mg/day) and perindopril (4 mg/day).

	There will be no stratification in this study.
Methodology	<p>This trial will measure the incidence and severity of HFSR and hypertension in patients receiving both perindopril and regorafenib using the CTCAE v4.03 criteria.</p> <p>The incidence of HFSR will be expressed as the number of patients out of study (N=34) who are experiencing HFSR of all grades. The incidence of hypertension will be expressed as the number of patients on study (N=34) who are experiencing hypertension of all grades. Severity will be evaluated using CTCAE v4.03 criteria as the secondary endpoint.</p>
Type of control	This is not a randomized study. All patients in the study will receive perindopril.
Number of subjects	34 subjects, single-arm trial. A total of 38 will be recruited to allow for screen failure
Primary endpoint	To assess the incidence of all grade toxicities for HFSR.
Secondary endpoints	<p>Secondary Outcomes</p> <ul style="list-style-type: none"> • <u>Hypertension</u>: All grades of hypertension will be evaluated using CTCAE v4.03, weekly for the first six weeks while they are on the study drug, then every second week and during the 30-day follow up period (Post therapy). • <u>Toxicity</u>: all grades of AE (including HFSR) will be evaluated using CTCAE v4.03, at baseline and at D1 of each cycle while they are on the study drug and during the 30-day follow up period (Post therapy). • Time course to development of worst grade (stage 3) HFSR. • <u>PFS</u> will be evaluated based on RECIST v1.1 criteria.
Plan for statistical analysis	<p>Statistical & Analytical Plan and Methodology</p> <p>General considerations</p> <p>Statistical analyses will be performed using SAS 9.3. Demographic and other baseline characteristics will be listed and summarized. Qualitative data will be summarized using frequencies and percentages and quantitative data will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum and maximum). Secondary safety variables will be summarized using descriptive statistics and exploratory graphical presentations of the data.</p> <p>Duration of study treatment exposure, cumulative dose and dose</p>

	<p>intensity will be summarized. The number of patients with dose changes/interruptions and withdrawals will be presented along with reasons for the dose change.</p> <p>Variables related to tumor response and disease progression will be evaluated based on investigator assessed RECIST criteria, version 1.1. In cases where radiographic imaging is not possible, clinical progression may be used. Clinical progression is based on the judgment of the investigator.</p> <p>Toxicity related variables will be evaluated using the CTCAE v4.03 criteria.</p> <p>Biomarker and pharmacokinetics will not be performed in this study and no subgroup analysis will be performed.</p> <p>Analysis sets</p> <p>The primary analysis set will consist of all evaluable patients. An evaluable patient is defined as a patient who meets all inclusion/exclusion and who has received at least one dose of study medication. The safety set will consist of all patients who receive at least one dose of study medication.</p> <p>Primary Objectives</p> <p>The primary objective is to determine the proportion of patients that have any grade HFSR toxicity when treated with a combination of regorafenib and perindopril.</p> <p>Secondary Objectives</p> <p>The secondary objectives are to evaluate the time to development of worst (grade 3) HFSR toxicity, proportion of all grades of hypertension, proportion of all grade toxicities and progression-free survival. All toxicities will be evaluated using CTCAE v4.03.</p> <p>Sample Size</p> <p>The alpha level is 0.05 and the power is 80% for the sample size calculation. A total of 34 evaluable patients be needed. 38 patients will be recruited to account for inevaluable patients. The primary endpoint is a 50% reduction in all grades of HFSR based on CTCAE v4.03 criteria (from 47% of patients with any grade of HFSR down to 24% of patients).</p>
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List of abbreviations

ACE	Angiotensin converting enzyme
AE	Adverse Event
ALT	Alanine amino-transferase
ANC	Absolute neutrophil count
ARB	Angiotensin receptor blocker
AST	Aspartate amino-transferase
AUC	Area under the curve
BCCA	BC Cancer Agency
BP	Blood pressure
BSC	Best supportive care
BUN	Blood urea nitrogen
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CRF	Case Report Form (either paper or electronic)
CT	Computed tomography
CYP	Cytochrome P450
CTC(AE)	Common Terminology Criteria (for AEs)
dl	deciliter
EC	Ethical Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Trial
e.g.	<i>Exempli gratia</i> , for example
EGFR	Epidermal growth factor receptor
ERK	Extracellular-signal-related kinase
FGFR	Fibroblast growth factor receptor
FMD	Flow mediated dilation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GFR	Glomerular Filtration Rate

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GMP	Good Manufacturing Practice
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related Quality of Life
ICH	International Conference on Harmonization
i.e.	<i>Id est</i> , that is
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional Review Board
kg	Kilogram
KM	Kaplan-Meier
LD	Longest diameter
LDH	Lactic dehydrogenase
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MEK	MAPK/ERK kinase
mg	Milligram
MI	Myocardial infarction
mL	Milliliter
mm	Millimeter
MRI	Magnetic resonance imaging
MUGA	Multi Gated Acquisition Scan
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NO	Nitrous Oxide
NYHA	New York Heart Association
od	Once a day
OM	Operational manual
OS	Overall survival
PD	Progressive Disease
PDGF	Platelet derived growth factor
PDGFR	Platelet derived growth factor receptor
PFS	Progression-free survival
po	Per os (oral)
PR	Partial response
PRO	Patient Reported Outcome
PS	Performance Status
PT	Prothrombin time
PTT	Partial thromboplastin time
qd	Every day

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RBC	Red blood cell (count)
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiotherapy
SAE	Serious Adverse Event
SD	Stable disease
SOP	Standard operating procedure
SUSARs	Suspected, unexpected, serious adverse reactions
TIA	Transient ischemic attack
TTP	Time to progression
ULN	Upper limit of normal
UPCR	Urinary protein/creatinine ratio
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
vs	Versus
WBC	White blood cell (count)

1.0 Introduction

1.1 Background

We hypothesize that treatment of regorafenib-treated mCRC patients with perindopril may reduce HFSR compared to reported incidence and severity.

We also hypothesize that treatment of regorafenib-treated mCRC patients with perindopril will likely reduce hypertension, a known adverse effect of VEGF/VEGFR inhibition.

According to the 2014 Canadian Cancer Statistics, colorectal cancer is the second most frequently diagnosed cancer in Canadian males and the third most frequently diagnosed cancer in Canadian females, accounting for 13.9% and 11.6% of new diagnoses, respectively. Although mortality rates are declining very slightly, colorectal cancer is the second most frequent cause of cancer deaths in males and the third most frequent cause of cancer death in females, at 12.8% and 11.5% respectively.

Metastatic colorectal cancers are generally not curable. Median overall survival for patients with unresectable mCRC who receive best supportive care (BSC) is five to six months. Palliative treatment with systemic chemotherapy is the best option prolonging survival and maintaining quality of life. Patients who are exposed to all active drugs can sometimes extend survival past two years.

For many years 5 Fluorouracil (FU) was the only treatment, but the approval of irinotecan, oxaliplatin, fluoropyrimidines, as well as various monoclonal antibodies targeting VEGF and EGFR growth factors led to the development of a number of different regimens. The ideal combination and sequence of the different agents is still not determined.

Recently, Regorafenib has shown efficacy in patients pretreated with all these options in a large phase III trial, where it prolonged OS compared with placebo (*Grothey, et al 2013*). In addition, the results were confirmed in a smaller randomised trial in the Asian population, with patients being less intensively pre-treated (*Li et al, 2014*). Therefore, regorafenib is now considered a standard option in pre-treated patients.

1.2 Overview of regorafenib

Regorafenib is a multi-kinase inhibitor (MKI), belonging to a unique class of orally-administered small molecule therapeutics targeting multiple protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, -2, -3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, BRAFV600E),

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and the tumour microenvironment (PDGFR, FGFR). Regorafenib was proven to be efficacious in mCRC in patients who are refractory to standard therapy in the CORRECT trial (*Grothey et al, 2013*). The endpoint of overall survival was met in this pivotal Phase III trial; however the most common grade three adverse event (AE) reported was Hand Foot Skin Reaction (HFSR). 47% of patients experienced HFSR of all grades with 17% experiencing HFSR with grade three severity. 26% of patients in the CORRECT trial experienced rash/desquamation, with 6% reporting the side effect as severe. In addition, 28% of patients in the CORRECT trial experienced hypertension, with 7% reporting severe hypertension.

The subsequent CONCUR trial was designed to evaluate the efficacy and safety of regorafenib in a broader population of Asian patients with mCRC (*Li et al, 2014*). The multicenter study was conducted in 25 centres in mainland China, Hong Kong, South Korea, Taiwan and Vietnam. The study met its primary endpoint of overall survival, 8.8 months on regorafenib as compared to 6.3 months with placebo (HR 0.550, 95% CI [0.395 – 0.765], $P= 0.0002$ (1-sided)). Again, in this trial HFSR was the most common grade 3 adverse event. Results of this trial were consistent with CORRECT. Although 74.3% of patients experienced any grade of HRSF, 16.2% experienced grade 3. Other AEs of note in the CONCUR trial included an increase in blood bilirubin (48.5% increase in all grades, 7.4% increase in grade 3), ALT increased (31.6% all grades, 8.1% grade 3) and an increase in hypertension (25% increase in all grades, 11.8% increase in grade 3).

The pathogenesis of regorafenib-induced HFSR is not yet established; however the capillary endothelium is felt to be the first target in HFSR. Abnormal signaling interruption of the VEGF and PDGF receptors may lead to alteration of small vessels (*Erber R et al. 2004*) which are traumatized by frequent impacts or pressure requiring endothelial repair (*Robert C et al. 2005*). An inflammatory response has also been hypothesized (*Robert C et al. 2005*).

1.3. Overview of perindopril

Perindopril is an Angiotensin Converting Enzyme (ACE) Inhibitor indicated for the treatment of hypertension, congestive heart failure and for the treatment of hypertensive and/or post-MI patients with stable coronary artery disease (*COVERSYL® Product Monograph*). ACE inhibitors protect the vascular endothelium, by decreasing the concentration of angiotensin II, which inhibits NO production and activity, while increasing the concentrations of bradykinin, a vasodilator and stimulator of NO (*Taddei S. 2012*). [ENREF 1](#) Interestingly, different ACE inhibitors have demonstrated differing abilities to improve vascular endothelial function as demonstrated through flow-mediated vasodilation (FMD) (*Anderson TJ, et al. 2000*), with perindopril being most effective (*Taddei S. 2012*). [ENREF 1](#) [ENREF 1](#) [ENREF 1](#) As a vessel dilator, perindopril may be beneficial in preventing or reducing the severity of regorafenib-induced HFSR, possibly by helping to restore the normal balance between angiotensin II and bradykinin, and reducing inflammation (TNF- α) to reverse endothelial dysfunction (*Taddei S. 2012; Ceconi C, et al. 2007a; Ceconi C 2007b; Zhuo JL, et al. 2002*).

1.4 Hand foot skin reaction,

Hand foot skin reaction (HFSR), also called palmar-plantar erythrodysesthesia, is a common side effect of many new targeted therapies (*Miller KK et al., 2014*).

HFSR associated with kinase inhibitor therapy differs in important ways from the classic hand-foot syndrome (HFS) seen with traditional cytotoxic agents such as 5-fluorouracil, capecitabine, doxorubicin, or liposomal doxorubicin. Initial symptoms of HFSR mediated by kinase inhibitor therapies may manifest with early signs of tingling or subtle discomfort, even after only 5–7 days on therapy (*Grothey et al. 2014*). These symptoms may progress in some patients to worsening pain, tenderness, callus formation, redness, and edema (occasionally associated with a burning sensation) in the palms of the hands or soles of the feet and especially in the folds between joints or pressure points of the feet. Other areas that may be involved include the tips of the fingers and toes, heels, and areas of flexure or overlying skin. These pressure areas are where most severe symptoms are typically seen, with formation of blisters that can severely impair the ability to walk. These blisters can burst and discharge serous fluid, although, commonly, thick callus formation may occur. Signs and symptoms may appear concomitantly or sequentially, and can affect both hands and both feet (*Grothey et al. 2014*).

HFSR can significantly impact the quality of life, requiring dose reductions or modifications. All patients in this trial will have experience with previous chemotherapy regimens and may have previous experience with hand-foot syndrome (HFS).

Previous experience with HFS will be collected as per patient recollection only (no chart review). This will be used to determine (as an exploratory analysis only) if this influences the rate and severity of HFSR in this study.

1.5 Rationale for Use in Colorectal Cancer

The intended outcome of successfully and significantly mitigating regorafenib-induced HFSR is that patients will be able to stay on the regorafenib for a longer period to increase efficacy. The hypothesis underlying this trial is that the co-administration of perindopril with regorafenib will mitigate HFSR symptoms.

This may not be the case, and if the HFSR is more severe with the addition of perindopril than with regorafenib alone, the study will be discontinued.

As a secondary endpoint, hypertension will also be followed.

1.6 Clinical experience with Regorafenib

47% of regorafenib treated patients in the CORRECT trial experienced HFSR of all grades, while 17% experienced grade 3 HFSR. Results of the CONCUR Trial were similar. Although 74.3% of patients experienced any grade of HFSR, 16.2% experienced grade 3.

All efforts need to be made to find new therapeutic combinations to reduce HFSR, as it causes a significant decrease in a patient's quality-of-life.

Expected time on trial: In the CORRECT trial (regorafenib versus placebo) overall survival was 6.4 vs 5.0 months (HR=0.77, p=0.0052) and PFS was 1.9 vs 1.7 months (HR=0.49, p<0.000001). In the CONCUR trial, (regorafenib versus placebo) overall survival was 8.8 versus 6.3 months (HR=0.550, 95% CI 0.395-765, p=0.0002 (I sided). PFS was 3.2 versus 1.7 months (HR=0.311, 95% CI 0.222-0.435, p<0.0001 (1 sided)).

Based on CONCUR, expected time patients will stay on trial is four months.

2. Study objectives

This trial will measure the incidence and severity of HFSR and hypertension in patients receiving both perindopril and regorafenib.

The incidence of HFSR will be expressed as the number of patients out of study (N=34) who are experiencing HFSR of all grades. Severity will be evaluated using CTCAE v4.03 criteria.

The incidence of hypertension will be expressed as the number of patients on study (N=34) who are experiencing hypertension of all grades. Severity will be evaluated using CTCAE v4.03 criteria.

2.1 Primary outcome

Incidence of all grade toxicities for HFSR will be evaluated.

Patients will be seen by physician every week for the first six weeks, then every two weeks after (see attached study schedule, APPENDIX A).

Subjects are to be evaluated for symptoms and AEs in a visit **30 days (+7 days)** after permanently stopping study treatment. After the last contact of the Safety Follow-Up Visit (or after the EOT visit if the Safety Follow-Up Visit is not available), subjects will be off study.

2.2 Secondary outcomes

- Hypertension: All grades of hypertension will be evaluated using CTCAE v4.03, weekly for the first six weeks while they are on the study drug, then every second week and during the 30-day follow up period (Post therapy)(see attached study schedule, APPENDIX A).

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- Toxicity: all grades of AE including HFSR will be evaluated using CTCAE v4.03, at baseline and at D1 of each cycle while they are on the study drug and during the 30-day follow up period (Post therapy).
- Time course to development of worst grade (grade 3) HFSR.
- PFS will be evaluated based on RECIST v1.1 criteria, 20% progression or any new lesion.

3. Investigators and other study participants

Study sponsors and PIs:

Dr. Barbara Melosky, Dr. Daniel Renouf
BC Cancer Agency – Vancouver Cancer Centre
600 West 10th Avenue
Vancouver, BC V5Z 4E6

3.1 Data Monitoring Committee

Not applicable – ISS.

3.2 Clinical Trials Nurse Coordinator (CTNC)

Reporting to the Clinical Trials Unit Manager (VCC), Operations Cancer Care Leader (CCSI, VICC and FVCC), or designate, the Clinical Trials Nurse Coordinator (CTNC) receives direction from Principal Investigators or designates, and is professionally accountable to the Professional Practice Leader in Nursing.

The CTNC participates in the coordination of clinical trials from the protocol review and approval stage through to activation, trial closure and follow-up.

The CTNC has principal responsibility for the coordination of the treatment programs, nursing care, monitoring, clinical assessment, and education of patients participating in the assigned clinical trials. The CTNC has formal responsibility for advising or teaching nursing staff in clinic and treatment areas on specialized theory and practice related to clinical trials.

3.3 Clinical Trials Data Coordinator (CTDC)

The Clinical Trials Data Coordinator (CTDC) receives direction from Principal Investigators or designates, and receives general supervision in matters related to Patient Information Management from the Chief Paramedical, PIM.

The CTDC has principal responsibility for clinical trials data management, including designing data capture tools, capturing and recording clinical trials data, monitoring and promoting the quality and integrity of data, and preparing summary reports. Data management is performed in accordance with trial protocol, procedures, guidelines and professional standards of practice.

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3.4.1 Biostatistician

Reporting directly to the Principal Investigator, the biostatistician will provide statistical support as well as some database management support. Statistical support includes: protocol design and development and REB application, support in design of data collection forms, statistical analysis plan, statistical analysis and provision of the final statistical analysis report. Data Management Support includes database design and development, data dictionary, data review, coding and cleaning ready for analysis.

3.5 Location of laboratory and imaging facilities

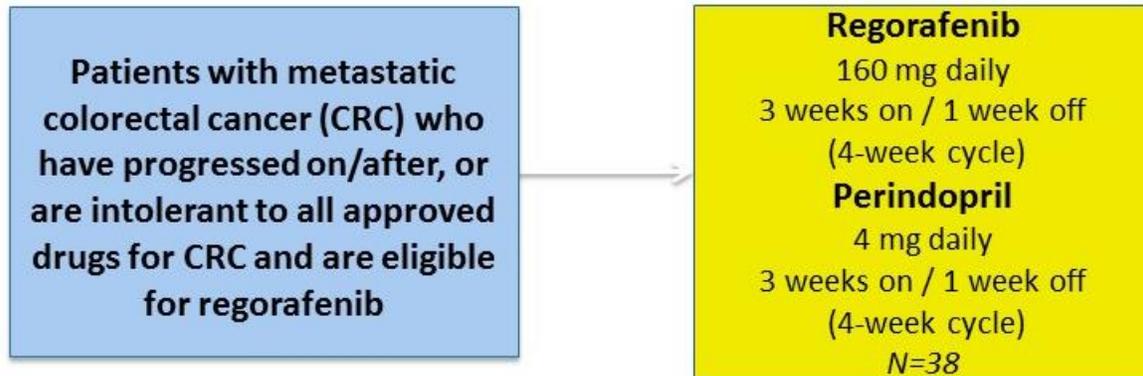
The laboratory and imaging facilities for this study are both located on the 3rd floor of the BC Cancer Agency at 600 West 10th Avenue.

4. Study design

Phase II, open-label, single-arm trial of patients with refractory mCRC treated with regorafenib (160 mg/day) and perindopril (4 mg/day).

This study will be conducted at the BC Cancer Agency (Vancouver Centre) only.

PARICCA trial design



Primary endpoint: Incidence of all grade toxicities for HFSR

Secondary endpoints: Incidence of (all grade) hypertension & toxicity; Severity of HFSR; Time course to development of worst grade (stage3) HFSR; Progression Free Survival.

Treat until progression, unacceptable toxicity, or withdrawal

During the study period, patients will undergo evaluations for safety and drug accountability every cycle. Drug safety will be monitored and evaluated continuously throughout the study, including a 30-day follow up period. Patients will continue on treatment until one of the following occurs (main criteria):

- Progressive Disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1, or clinical progression
- Death
- Unacceptable toxicity
- Patient withdraws consent
- Treating physician determines discontinuation of treatment is in the patient's best interest
- Substantial non-compliance with the protocol

For the full list of criteria refer to section 5.2.1.

If in the Investigator's opinion, treatment with regorafenib is providing clinical benefit to a patient experiencing disease progression, the patient may continue treatment.

Justification of the design

47% of regorafenib treated patients in the CORRECT trial experienced HFSR of all grades, while 17% of regorafenib patients experienced grade 3 HFSR. All efforts need to be made to find new therapeutic combinations to reduce HFSR, as it causes a significant decrease in a patient's quality-of-life.

Although we are assuming that the co-administration of perindopril with regorafenib will mitigate HFSR symptoms, this may not be the case. If the HFSR is more severe with the addition of perindopril than with regorafenib alone, the study will be discontinued.

The choice of dosage and schedule to be used in this trial comes from data accumulated in previous phase III trials with regorafenib (CORRECT, CONCUR). The choice of dosage and schedule for perindopril is from the Coversyl monograph.

End of study

The study will conclude with the last visit of the last patient.

5. Study population

5.1 Eligibility

Patients with metastatic colorectal cancer (mCRC) who have progressed on/after all approved drugs for CRC and are eligible for regorafenib. Specifically, regorafenib is indicated for the treatment of patients with metastatic colorectal cancer (mCRC) who have been previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if *KRAS* wild type, an anti-EGFR therapy (*Stivarga*® (*regorafenib*) *Product Monograph*).

Patients will have been tested for Ras (K- and N- mutations).

5.1.1 Inclusion criteria

In order to be eligible, all inclusion criteria must be met.

A patient must:

- Understand, be willing to give consent, and sign a written informed consent form prior to undergoing any study-specific procedure
- Be male or female and ≥ 18 years of age
- Histological or cytological documentation of adenocarcinoma of the colon or rectum.
- Patients with metastatic colorectal cancer (Stage IV) previously treated with fluoropyrimidine-based chemotherapy, oxaliplatin, irinotecan, an anti-VEGF therapy, and, if *KRAS* wild type, an anti-EGFR therapy.

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- Progression during or within 3 months following the last administration of approved standard therapies, or have experienced intolerance to previous therapy. Patients treated with oxaliplatin in an adjuvant setting should have progressed during or within 6 months of completion of adjuvant therapy. (Please note that in Canada patients are not re-challenged with oxaliplatin in the metastatic setting).
- Metastatic CRC patients with measurable or non-measurable disease
- Life expectancy of at least 3 months
- Have an Eastern Cooperative Oncology Group performance status of 0 or 1 (within 14 days prior to the initiation of study treatment)
- Have adequate bone marrow, liver function, and renal function as measured by the following laboratory assessments conducted within 7 days prior to the initiation of study treatment:
 - Total bilirubin \leq 1.5 times the upper limit of normal (ULN)
 - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) \leq 2.5 times the ULN ($<$ 5 times ULN for patients with liver involvement of their cancer)
 - Lipase \leq 1.5 times the ULN
 - Serum creatinine \leq 1.5 times the ULN
 - Glomerular filtration rate \geq 30 mL/min/1.73 m² according to the modified diet in renal disease abbreviated formula
 - International normalized ratio (INR) of prothrombin time (PT; PT-INR) and partial thromboplastin time (PTT) \leq 1.5 times the ULN
 - Platelet count \geq 100000 /mm³, hemoglobin (\geq 9 g/dL, absolute neutrophil count \geq 1500/mm³).
 - Alkaline phosphatase limit \leq 2.5 times the ULN ($<$ 5 times ULN for patients with liver involvement of their cancer)
- If female and of childbearing potential, have a NEGATIVE result on a pregnancy test performed a maximum of 7 days before initiation of study treatment
- If female and of childbearing potential or if male, must agree to use adequate contraception (e.g., abstinence, intrauterine device, oral contraceptive, or double-barrier method) based on the judgment of the investigator or a designated associate from the date on which the ICF is signed until 6 months after the last dose of study drug.

5.1.2 Exclusion criteria

Patients who meet the following criteria at the time of screening will be excluded (from CORRECT Trial):

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- Patients with hypotension (less than 90/60mm Hg) or at risk of symptomatic hypotension (fainting or dizziness) will be excluded.
- Prior treatment with regorafenib or any VEGFR-targeting kinase inhibitor.
- Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
- Concurrent cancer requiring treatment that is distinct in primary site or histology from colorectal cancer.
- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Unstable/uncontrolled cardiac disease including: congestive heart failure \geq 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 start of study drug; 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).
- Patients with pheochromocytoma.
- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication.
- Ongoing infection $>$ grade 2 NCI-CTCAE version 4.03
- Known history of human immunodeficiency virus (HIV) infection.
- Known history of chronic hepatitis B or C.
- Patients with seizure disorder requiring medication.
- Symptomatic metastatic brain or meningeal tumors unless the patient is $>$ 6 months from definitive therapy, has a negative imaging study within 4 weeks of study entry and is clinically stable with respect to the tumor at the time of study entry. Also the patient must not be undergoing acute steroid therapy or taper (chronic steroid therapy is acceptable provided that the dose is stable for one month prior to and following screening radiographic studies)
- History of organ allograft
- Patients with evidence or history of bleeding diathesis, including patients who have had a transfusion and/or radiographic endoscopic or elective operative intervention to control the bleeding or hemorrhage event within four weeks prior to the study.
- Non-healing wound, ulcer, or bone fracture.
- Renal impairment or failure requiring hemo-or peritoneal dialysis.
- Patients with severe hepatic impairment.
- Dehydration NCI-CTC version 4.03 grade $>$ 1.
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results

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- Any illness or medical conditions that are unstable or could jeopardize the safety of the study
- Interstitial lung disease with ongoing signs and symptoms at the time of informed consent.
- Persistent proteinuria of CTC Grade 3 or higher. Quantification of proteinuria done by urinary protein/creatinine ratio on a random urine sample preferably taken at mid-morning. If protein/creatinine ratio is greater than 30g/mol Creat, then a 24-hour urine protein test should be performed to confirm Grade 3 or higher proteinuria (> 3.5 g/24 hours).
- Patients unable to swallow oral medications
- Any malabsorption condition
- Unresolved toxicity higher than NCI-CTCAE (version 4.03) Grade 1 attributed to any prior therapy/procedure excluding alopecia and oxaliplatin induced neurotoxicity ≤Grade 2
- Patients who are hypersensitive to perindopril, as well as those hypersensitive to regorafenib, sorafenib, drugs in the same class or any ingredient in the formulation.
- Patients who cannot tolerate the full dose of perindopril (4 mg) for any reason.
- Patients receiving systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy, hormonal therapy and experimental or approved therapies during this trial or within 14 days before starting to receive study medication.

In addition, patients will be excluded for the following reasons (From perindopril monograph). Patients with a history of hereditary/idiopathic angioedema, or angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

- Pregnant women or those planning to become pregnant, nursing women.
- Patients with hereditary problems of galactose intolerance, glucose-galactose malabsorption, or the Lapp lactase deficiency.
- Patients with pre-existing anti-hypertension treatment with an ACE inhibitor or angiotensin receptor blocker (ARB) are to be excluded. Co-administration of ACE inhibitors, including COVERSYL®, with other agents blocking the Renin-Angiotensin System (RAS), such as ARBs or aliskiren-containing drugs, will not be allowed, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

5.1.3 Justification of selection criteria

The exclusion of certain concomitant conditions and medications as outlined above and in Section 6.9 was necessitated by the known toxicity profile of the agents under investigation and its interaction with other classes of medications, and also based on the understanding of the concomitant conditions in colorectal cancer. This is to assure, to the best of our ability, the safety of the patients who would participate in this study.

5.2 Withdrawal of subjects from study

Patients will remain on trial and will receive regorafenib and perindopril until clinical radiological disease progression, based on RECIST v1.1 criteria. If patients progress on regorafenib, both drugs will be stopped. However, after the patient progresses (i.e. is no longer on trial) the medication can be continued if the investigator feels that there is a clinical benefit.

A subject may discontinue participation in this study at any time at the investigator's discretion or at the request of the subject.

If a subject discontinues before treatment starts (Cycle 1, day 1) she/he is not required to complete end of study assessments.

If a subject discontinues after receiving treatment for any reason, the investigator should make every effort to complete end of study assessment and the one month follow-up assessments of concomitant medications and adverse events.

Any occurrence of death, and any excluded medications taken after study withdrawal should be documented in the CRF and source documents.

Subjects withdrawn from the study retain their subject number, if already given. New subjects will be allocated a new subject number.

5.2.1 Withdrawal of subjects from study treatment

Subjects *must* be withdrawn from study treatment for the following reasons:

- At their own request or at the request of their legally acceptable representative.
- At any time during study treatment and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- If, in the investigator's opinion, continuation of study treatment would be harmful to the subject's well-being.
- Severe allergic reactions, such as exfoliate erythroderma, anaphylaxis, or vascular collapse.
- Any other potential adverse reaction deemed sufficiently serious to warrant discontinuation of treatment by the Investigator.
- Substantial non-compliance with study procedures.
- Patients with a b-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event (see Section 7.5.2).
- Use of illicit drugs or other substances that may, in the opinion of the Investigator or a designated associate(s), have a reasonable chance of contributing to toxicity or otherwise confound the results.
- Any hemorrhage or bleeding event > CTCAE Grade 3 within 4 weeks of start of study medication.

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- Development of any intercurrent illness or situation which would, in the judgment of the Investigator, may affect assessments of clinical status and study endpoints to a relevant degree.
- Patients should come off study treatment for disease progression. If the treating physician feels that the patient will receive clinical benefit from continued study treatment despite progression, the patient may remain on study drug. However, the patient will be considered as having progressive disease, as per the RECIST criteria, version 1.1.
- The development of a second malignancy.
- Patient lost to follow up.
- Interruption of study drug is longer than 28 consecutive days (including the 1 week break in each cycle).
- More than two dose reductions of the study drug are necessary.
- Death.

A subject who is terminated from the study after signing the informed consent but before starting the drug is regarded as a “screening failure”.

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

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

Details for the premature termination of the study are provided in Section 10 (Premature termination of the study).

For all subjects who discontinue study treatment, relevant visit data will be entered into the case report form and any unused study drug will be accounted for and returned. Adverse events or clinical laboratory abnormalities that cause a patient to discontinue from study treatment should be followed until they recover or stabilized.

All subjects will enter the follow-up period upon discontinuation of the treatment drugs. Regardless of the reason for discontinuation all subjects will be followed for survival until death is documented, except for those who specifically withdraw consent to follow-up. Subjects who withdraw consent from study drug treatment may enter the Follow-up Period.

Assessment of survival status will be performed approximately every month. In addition, for subjects, who discontinue study treatment and have not experienced PD, available tumor assessments will be recorded in the CRF until PD is documented.

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Death due to mCRC is not a serious adverse event. If any patient should die during the study treatment or within 30 days of their last dose of study drug, of causes NOT related to the disease itself (mCRC), the Investigator or a designated associate(s) will inform the Bayer HealthCare Medical hotline. If the cause of death is not related to the disease itself (mCRC), the cause of death should be recorded in detail within 24 hours of notification to the investigator on a Serious Adverse Event Form and transmitted to Health Canada.

5.2.2 Withdrawal of subjects from the follow-up period

Subjects *must* be withdrawn from the study follow-up period for the following reasons:

- Patient lost to follow up.
- At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- At the discretion of the investigator.

5.2.3 Replacement

A subject withdrawn from study treatment will not be replaced.

5.3 Subject identification

Subject will be identified by a 3 digit number beginning with 001, sequenced consecutively.

6. Treatments

6.1 Treatments to be administered

The following investigational products will be used in this study:

- Regorafenib, 40 mg tablets
- COVERSYL® (perindopril erbumine) 4 mg.

Stivarga® will be used as per the marketed indication (“on label”), Coversyl® will be used off-label and as such a Clinical Trial Application will be filed with Health Canada.

COVERSYL® (perindopril erbumine) 4 mg will be administered daily for 21 days of a 28-day cycle. Perindopril will be administered orally, first thing in the morning on an empty stomach.

Regorafenib will be administered 160 mg daily for 21 days of a 28-day cycle. Regorafenib will be administered with low fat breakfast, one hour after perindopril. A low fat breakfast as defined by the Stivarga® (regorafenib) Product Monograph is one that is <30% fat, ~300-550 calories. See Appendix 14.4.

Table 1: Treatment Plan

Phase II Study of Perindopril and Regorafenib in mCRC (PARICCA)

Drug	Dose	Administration Guidelines
Perindopril	4 mg daily*	Administered orally on an empty stomach first thing in the morning.
Regorafenib	160 mg daily	Administered orally, one hour after waking with a low fat breakfast.

Caution with use of potassium sparing diuretics.

Caution for development of hypotension with diuretics.

BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemotherapy.

Patients will continue study treatment until disease progression or they meet the criteria in Section 5.2. The dose modifications will follow the pre-defined dose levels outlined in Section 6.4.

6.2 Identity of study treatment

The regorafenib 40 mg tablet contains regorafenib and the inactive excipients microcrystalline cellulose, croscarmellose sodium, magnesium stearate, povidone, colloidal anhydrous silica, Polyvinyl alcohol-part hydrolyzed, Talc, Titanium dioxide - E 171 (color index 77891), Macrogol/PEG 3350, Lecithin (Soy), Iron oxide yellow - E172 (color index 77491), Iron oxide red - E 172.

The perindopril 4 mg tablets contains perindopril erbumine 4g, as well as Chlorophyllin (E141ii) Aluminium Lake, hydrophobic colloidal silica, lactose monohydrate, magnesium stearate, microcrystalline cellulose. Each light green, rod shaped breakable tablet engraved with  on one face and scored on both edges contains: perindopril erbumine 4 mg. pills are available in blister packs of 30 tablets and in bottles of 100 tablets.

6.3 Treatment assignment

N/A – all patients in this single-arm trial will receive treatment with regorafenib and perindopril.

6.4 Dosage and administration

6.4.1 Perindopril

COVERSYL® (perindopril erbumine) 4 mg will be administered daily for 21 days of a 28-day cycle. Perindopril will be administered orally, first thing in the morning on an empty stomach. If a dose is missed, a double dose should not be taken, but just carry on with the next dose at the normal time.

The Investigator or designated study personnel is responsible for dispensing the study drug to patients.

6.4.2 Regorafenib

Regorafenib will be administered 160 mg daily for 21 days of a 28-day cycle. Regorafenib will be administered with low fat breakfast, one hour after perindopril. A low fat breakfast as defined by the monograph¹⁰ is one that is <30% fat, ~300-550 calories (see appendix 14.4).

The rationale for the dose in this study is based upon the phase I data from Study 11650 (in which escalating doses from 10 mg to 220 mg of regorafenib were administered on a discontinuous schedule [3 weeks out of every 4]) and same dose and schedule have been used in Study 14387 (including Asian subjects).

Signs of anti-tumor activity were observed in subjects receiving doses from 60 mg up to 220 mg per day on a discontinuous schedule (3 weeks out of every 4). However, of the 220 mg/day cohort, 8 out of 12 subjects required a dose reduction for toxicity, whereas only 1 subject of 12 on the 160 mg/day cohort required such a dose reduction. Thus, based upon the efficacy and toxicity data, 160 mg was chosen as the dose for this study.

Dose administration

Regorafenib will be orally administered. The Investigator or designated study personnel is responsible for dispensing the study drug to patients.

Regorafenib should be taken in the morning with approximately 8 fluid ounces (240 mL) of water. The study drug should be administered after a light (<30% fat) breakfast. Some examples of low-fat breakfasts are provided in Appendix 14.4.

If a dose of regorafenib is missed, the subsequent dose of regorafenib should not be doubled. The investigator should be informed if the dose of regorafenib taken exceeded the scheduled dose.

Dose modification and delays

(Note that this confidential information comes from Bayer's CONCUR study protocol (integrated protocol v2.0, dated 28Dec2012).

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Doses of study drug may be delayed or reduced in case of clinically significant hematologic and other toxicities that are possibly, probably or definitely related to protocol therapy.

Toxicities will be graded using the NCI Common Terminology Criteria Version 4.2.

The modifications of regorafenib will follow the following pre-defined dose levels:

Table 2: dose modifications for regorafenib

Dose level 0 (standard dose)	160 mg po od	4 tablets of regorafenib, 40 mg-tablet,
Dose level -1	120 mg po od	3 tablets of regorafenib, 40 mg-tablet,
Dose level -2	80 mg po od	2 tablets of regorafenib, 40 mg-tablet,

If a subject experiences several toxicities and there are conflicting recommendations, the recommended dose adjustment which reduces the dose to the lowest level should be used.

Table 3 outlines dose adjustments for toxicities related to study drug except hand-foot skin reaction, hypertension and liver function test (ALT and AST) abnormalities. **Table 4** outlines the suggested dose reductions for HFSR while **Table 5** outlines suggested dose reductions for treatment-emergent hypertension. **Table 6** outlines the suggested dose reductions for ALT and/or AST increases related to study drug.

If reduction by more than two dose levels is required, treatment will be discontinued.

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.

Table 3: Dose Modification/Delay for Toxicities Related to Study Drug (Except Hand Foot Skin Reaction, Hypertension, AST and ALT)^a

Grade of Event (CTCAE version 4.03)	Dose Interruption	Dose Modification	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	No change

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Grade 3	Delay until \leq Grade 2 ^b	Reduce 1 dose level	If toxicity remains \leq Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (\geq Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until \leq Grade 2 ^b	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

a Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity, non clinical significant and asymptomatic laboratory abnormalities.

b If no recovery after a 4-week delay, treatment will be permanently discontinued.

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.

Skin Toxicity Grade (according to CTCAE version 4.03 "Palmar-plantar erythrodysesthesia syndrome")	Occurrence c	Suggested Dose Modification c
Grade 1: Numbness, dysesthesia, paraesthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subjects normal activities	Any	Maintain dose level and institute immediately supportive measures for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort which affects the subject's normal	1st occurrence	Consider decreasing dose by one dose level and institute immediately supportive measures. If no improvement, interrupt therapy for a minimum

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Table 4 Dose Modifications for Hand-Foot Skin Reaction		
Skin Toxicity Grade (according to CTCAE version 4.03 "Palmar-plantar erythrodysesthesia syndrome")	Occurrence ^c	Suggested Dose Modification ^c
activities		of 7 days, until toxicity resolves to Grade 0-1. ^b
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, treat at reduced dose level. ^b
	3rd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level. ^{a,b}
	4th occurrence	Discontinue therapy
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the subject to be unable to work or perform activities of daily living.	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one dose level. ^b
	2nd occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. When resuming treatment, decrease dose by one additional dose level. ^{a,b}
	3rd occurrence	Discontinue treatment permanently.
^a Subjects requiring > 2 dose reductions (< 80mg) should go off protocol therapy ^b If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator ^c A more conservative dose modification approach, if medically indicated, is acceptable, but please contact the sponsor prior to making any changes.		

If no recovery after a 4-week delay, treatment will be discontinued permanently.

For subjects who require a dose reduction for Grade 2 or 3 rash or hand-foot skin reaction (HFSR), the dose of study drug may be increased to the starting dose after one full cycle of therapy has been administered with the reduced dose without the appearance of rash or HFSR > Grade 1.

The following measurements should be considered for prevention and treatment of HFSR:

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

Apply non-urea based creams liberally.e.g.:

Keratolytic Creams: Use sparingly and only to affected (hyperkeratotic) areas

- Urea-based creams
- Salicylic acid 6%

Alpha Hydroxy Acids (AHA) based creams

- Approximately 5-8% provide gentle chemical exfoliation
- Apply liberally two times each day

Topical analgesics like lidocaine 2% to be considered for pain control

Topical corticosteroids like clobetasol 0.05% should be considered for subjects with Grade 2 or 3 hand-foot skin reaction. Avoid systemic steroids.

Cushions

Protect tender areas

- 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

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Table 5: Dose modification for Treatment-Emergent Hypertension			
Grade of Event (CTCAE version 4.03)	Definition	Anti-hypertensive therapy	Regorafenib dosing
Grade 1	Pre-hypertension (systolic BP 120-139 mmHg or diastolic BP 80-89 mmHg)	None	Continue regorafenib. Consider increased blood pressure monitoring.
Grade 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 mmHg -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 mmHg ^a . When regorafenib is restarted, continue at the same dose level.
Grade 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 mmHg -Start anti-hypertensive medication AND/OR -Increase current anti-hypertensive medication AND/OR -Add additional anti-hypertensive medications.	Hold regorafenib until diastolic BP ≤ 90 mmHg, and if symptomatic, until symptoms resolved. 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 .
Grade 4	Life-threatening consequences (e.g. malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)		Discontinue therapy
<p>Abbreviations: BP = blood pressure; CTCAE = Common Terminology Criteria for Adverse Events, version 4.03</p> <p>a Subjects requiring a delay of > 4 weeks should discontinue protocol therapy.</p> <p>b If blood pressure remains controlled for at least one full cycle, dose re-escalation is permitted at the investigator's discretion.</p> <p>c Subjects requiring > 2 dose reductions (a dose lower than 80 mg po od) should discontinue protocol therapy.</p>			

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Blood pressure (BP) should be monitored weekly for the first 6 weeks of treatment. Blood pressure is to be recorded by qualified staff, e.g. a study nurse, treating physician, or nurse practitioner and entered onto the CRF.

The dose modification schedule for treatment emergent hypertension during regorafenib dosing should be followed (see Table 5). Subjects' BP measurements will be monitored and appropriate treatment to effectively control hypertension under regorafenib treatment is strongly recommended.

The selection of anti-hypertensive medication used in this setting should be performed at the investigator's discretion, considering possible site-specific treatment guidelines. All medication should be recorded in the subject's CRF.

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Table 6: Dose modifications/interruption for ALT and/or AST increases related to study drug			
Grade of Event (CTCAE version 4.03)	1 st occurrence	Restart	Reoccurrence
AST and/or ALT baseline G0 → G1 or baseline G1 → G2	Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.		Treat on time and check AST, ALT and bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks.
AST and/or ALT baseline G0 → G2	Delay until ≤ G1 and check AST, ALT, bilirubin 2x/week.	Reduce 1 dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks. ^a	Discontinue ^b
AST and/or ALT baseline any grade → G3	Delay until ≤ G1 if baseline was G0 or G1 OR until G2 if baseline was G2. Check AST, ALT, bilirubin 2x/week. If ALT or AST > 8 x ULN with a concomitant rise in bilirubin (of any degree) compared to previous bilirubin values, consider permanent discontinuation at the first occurrence ^b .	Reduce 1 dose level and check AST, ALT, bilirubin 2x/week for 2 weeks followed by weekly assessments for at least 4 weeks. ^a	Discontinue ^b
AST and/or ALT baseline any grade → G4	Discontinue ^b		
<p>Abbreviations: AST = aspartate aminotransferase, ALT = alanine aminotransferase</p> <p>^a If all values remain stable for 2 full cycles, dose re-escalation may be considered at the discretion of the investigator. After re-escalation AST, ALT, bilirubin should be checked 2x/week for 2 weeks, followed by weekly assessments for at least 4 weeks.</p> <p>^b In case of discontinuation, check AST, ALT, bilirubin should be checked twice a week for 2 weeks, followed by weekly assessments until recovery to baseline.</p>			

During the first 2 cycles of treatment, ALT, AST and bilirubin must be monitored weekly.

6.5 Blinding

N/A All patients in the study will receive both regorafenib and perindopril.

6.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements. Study supply of regorafenib, along with storage and handling instructions will be provided by Bayer HealthCare. Perindopril, including its storage and handling instructions will be obtained by the sponsors from the market. Both study drugs will be inaccessible to unauthorized personnel.

Special storage conditions and a complete record of batch numbers and expiry dates can be found in the study file; the site-relevant elements of this information will be available in the investigator site file. The responsible site personnel will confirm receipt of study drug and will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to BCCA specified procedures. Written instructions on medication destruction will be made available to affected parties as applicable.

To have complete control over the distribution and use of the study drug, the drug accountability must be performed on Day 1 of each cycle starting on Cycle 2. Bottles must be returned to the Investigator with all unused medication. Throughout the study, all unused study medication will be accounted for. The information will be recorded in the drug dispensing log, as per BCCA protocol.

6.7 Treatment compliance

An adequate record of the receipt, distribution and return of all study medication supplies must be recorded on the Drug Accountability Form. The number of tablets dispensed and returned by the patients will be recorded in the drug accountability logs in the CRF.

Drug accountability must be done at every cycle, starting on Day 1 of Cycle 2.

The dose and schedule of regorafenib and perindopril administered to each subject will be recorded in the CRF. The reason(s) for dose delay, reduction or interruption also will be recorded in the CRF.

6.8 Post-study therapy

All subjects will enter the follow-up period upon discontinuation of study treatment. Regardless of the reason for discontinuation all subjects will be followed for survival until death is

documented, except for those who specifically withdraw consent to follow-up. Subjects who withdraw consent from study drug treatment may enter the Follow-up Period.

6.9 Prior and concomitant therapy

All medication which is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator (except strong CYP3A4 inhibitors/inducers [see Appendix 14.7 and 14.8]).

All concomitant medications (including start/stop dates, dose frequency, route of administration and indication) must be recorded in the patient's source documentation, as well as in the appropriate pages of the CRF. Specific caution should be employed when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9 or the Phase II glucuronosyl transferases UGT1A1 and 1A9. Such concomitant medications should be avoided, if possible.

Concomitant administration of ketoconazole, a strong CYP3A4 inhibitor, with regorafenib resulted in an increase in mean exposure (AUC) of regorafenib of approximately 33%, and a decrease in mean exposure of the active metabolites, M-2 (N-oxide) and M-5 (N-oxide and N-desmethyl), of approximately 90%. It is recommended to **avoid concomitant use of strong inhibitors of CYP3A4 activity** (e.g. clarithromycin, grapefruit juice, itraconazole, ketoconazole) as their influence on the steady-state exposure of regorafenib and its metabolites has not been studied. (See Appendix 14.7)

Concomitant administration of rifampin, a potent inducer of CYP3A4, resulted in a mean decrease in regorafenib AUC of approximately 50%. There are no clinical data evaluating the effect of chronically co-administered CYP3A4 inducers on regorafenib's efficacy. Since there is a possibility of decreased regorafenib efficacy upon chronic co-administration of CYP3A4 inducers with regorafenib, due to the lower plasma concentrations, **chronic co-administration of strong CYP3A4 inducers with regorafenib should be avoided to the extent possible**. (See Appendix 14.8)

In vitro data indicate that regorafenib, as well as its active metabolites M-2, inhibits glucuronidation mediated by uridine diphosphate glucuronosyl transferases UGT1A1 and UGT1A9, whereas M-5 only inhibits UGT1A1 at concentrations that are achieved in vivo at steady state. Administration of regorafenib with a 5 day break prior to administration of irinotecan resulted in humans in an increase of approximately 44% in mean exposure (AUC) of SN 38, a substrate of UGT1A1 and an active metabolite of irinotecan. An increase in mean exposure (AUC) of irinotecan of approximately 28% was also observed. This indicates that co administration of regorafenib may increase systemic exposure to UGT1A1 and UGT1A9 substrates.

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Administration of regorafenib (160 mg for 14 days) prior to administration of a single dose of rosuvastatin (5 mg), a BCRP substrate, resulted in a 3.9-fold increase in mean exposure (AUC) of rosuvastatin and a 4.6-fold increase in C_{max} . This indicates that co-administration of regorafenib may increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, fluvastatin, atorvastatin). **Therefore, it is recommended to monitor patients closely for signs and symptoms of increased exposure to BCRP substrates.**

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation. Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure. There was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5. Effects of other antibiotics have not been studied. The clinical significance of the neomycin effect and potential interactions with other antibiotics is unknown, but may result in a decreased efficacy of regorafenib.

The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation. Bile salt-sequestering agents may interact with regorafenib by forming insoluble complexes which may impact absorption (or reabsorption), thus resulting in potentially decreased exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.

Co-administration of ACE inhibitors, including COVERSYL[®], with other agents blocking the RAS, such as ARBs or aliskiren-containing drugs, will not be allowed, since such treatment has been associated with an increased incidence of severe hypotension, renal failure, and hyperkalemia.

Caution with use of potassium sparing diuretics

Caution for development of hypotension with diuretics

BSC includes any concomitant medications or treatments: antibiotics, analgesics, radiation therapy for pain control (limited to bone metastases), corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumor agents or anti-neoplastic chemotherapy.

Permitted concomitant medications:

- Standard therapies for concurrent medical conditions. Prophylactic anti-emetics may be administered according to standard practice.

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- Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator. St John's wort is not permitted.
- Bisphosphonates
- Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that no prior evidence of underlying abnormality in coagulation parameters exists. Close monitoring of at least weekly evaluations will be performed until INR/PTT is stable based on a measurement that is pre-dose as defined by the local standard of care.
- Clinical data indicate that regorafenib has no effect on digoxin pharmacokinetics, therefore can be given concomitantly with p-glycoprotein substrates, such as digoxin, without a clinically meaningful drug interaction.

Non-permissible concomitant medications:

- Systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy, hormonal therapy and experimental or approved therapies during this trial or within 14 days before starting to receive study medication.
- TKIs
- Bone marrow transplant or stem cell rescue.
- Prior radiation and concomitant palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Use of biologic response modifiers, such as granulocyte colony stimulating factor (G-CSF), within 3 weeks of study entry. G-CSF and other hematopoietic growth factors may be used during the study in the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however they may not be substituted for a required dose reduction. Patients taking chronic erythropoietin are permitted.
- Patients taking narrow therapeutic index medications (e.g., warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital and cyclosporine) should be monitored proactively. Warfarin is metabolized by the cytochrome enzyme CYP2C9 and its levels may be especially affected by regorafenib.

Therapeutic monitoring should be performed consistent with the local clinical standard of care following dose modification of the agent. In general, patients should be closely monitored for side effects of all concomitant medications regardless of path of elimination.

7. Procedures and variables

7.1 Schedule of procedures

Please see study schedule, Table 7.

- Patients will be seen by physician every week for the first cycle, every two weeks for the second cycle, at the start of each cycle after this, and at end of treatment.
- Assessment of concomitant medications at the start and during each visit.
- ECOG testing at start of treatment, at the start of physician visit and at the end of treatment.
- Blood pressure will be measured every week for the first cycle, on day 1, 7, and 14 in the second cycle, at the start of each cycle after this, and at follow up visit.
- Liver function tests [albumin, bilirubin (total), bilirubin (direct), alkaline phosphatase, GGT, AST, LDH] will be administered every week for the first cycle, every two weeks for the second cycle, at the start of each cycle after this, and at follow up visit.
- Lipase testing, electrolytes, TSH, chemistry, CEA testing, CBC, and creatinine will be done at D1 of each cycle and at end of treatment.
- A twelve-point ECG will be administered on D1 of each cycle and at the end of treatment.
- Other tests will be administered as per standard of care for regorafenib and perindopril.

The study protocol will include a patient education module. This will consist of a patient education brochure regarding the management of HFSR and will include the preventative measures patients can take to manage this side effect.

Patients will have photos of hands and feet taken at BCCA media services for illustrative purposes only, on Day 1, Day 7, Day 14 and Day 21 of the first cycle only. A total of about eight photographs per visit will be taken to capture the dorsal and plantar sides of the patient's hands and feet. The digital photographs will be labeled with your participant study number and the date. A digital copy of each photograph will be stored in the Cancer Agency Information System and a hardcopy stored in the subject study file. All photographs for the subject's study folder are to be printed with images approximately 6.25 x 9 inches on 8.5 x 11 photo paper. All photos need to be identified with study ID number and date taken.

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7.1.1 Tabulated overview

Table 7

Procedure	Day -28 to Day -1	Day -14 to Day -1	Day -7 to Day -1	Cycle 1				Cycle 2				Cycle 3+	End of treatment	Follow up (+1 month)
				Day1	Day7	Day14	Day21	Day1	Day7	Day14	Day21			
Medical History	x												x	
Physician Visit		x		x	x	x	x	x		x		x	x	
Concomitant Meds.		x		x	x	x	x	x	x	x		x	x	x
ECOG		x		x	x	x	x	x		x		x	x	
Blood Pressure		x		x	x	x	x	x	x	x		x	x	
Liver Function Tests			x	x	x	x	x	x		x		x	x	
12-lead ECG	x			x				x				x	x	
Cardiac Function Test*				x ¹				x ¹				x ¹		
Lipase Testing			x	x [#]				x				x	x	
PT or PT-INR and PTT			x	x [#]				x				x	x	
Full urinalysis, measure of proteinuria and GFR			x	x [#]				x				x	x	
AE				x	x	x	x	x	x	x		x	x	x
CEA			x	x [#]				x				x	x	
CBC			x	x [#]				x				x	x	
Creatinine			x	x [#]				x				x	x	
Electrolytes			x	x [#]				x				x	x	
TSH			x	x [#]				x				x	x	
Chemistry			x	x [#]				x				x	x	
hCG			x											
CT - every eight weeks	x			x								x		
Photos				x	x	x	x							

Lipase, Creatinine, Electrolytes are generally inclusive with chemistry.

34 patients, Study expected to last 2 -4 cycles

Tests will be administered as per standard of care for Regorafenib

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Weekly monitoring by physician in first cycle

* Echocardiogram or MUGA scan

¹ Echocardiogram or MUGA scan only if clinically indicated. Echocardiograms or MUGA scans should be performed by the same operator to minimize inter-observer variability.

7.1.2 Timing of assessments

7.1.2.1 Screening

The assessments required as part of Screening can be completed in one or more visits, as long as the assessments are completed within the time frames listed below.

The following procedures and assessments will be performed **within 28 days of starting study drug**:

- Obtainment of written informed consent. No screening procedures may be performed unless written informed consent has been obtained (see Section 11.2)
- Allocation of unique Study Identification Number
- Confirm pathologic documentation of a primary diagnosis of CRC.
- Radiological tumor assessment using the RECIST criteria, version 1.1 (see Appendix 14.1) must be performed. The radiological evaluation must include a CT or MRI of the chest, abdomen and pelvis and should meet the standard of care for the imaging of lesions in the respective organ system(s). A PET scan is not acceptable for radiological evaluation.
- All additional suspected sites of disease should be imaged. A CT or MRI scan of the head must be performed with appropriate contrast media if a patient is suspected of having brain metastases, or is symptomatic.
- Appropriate radiological evaluation should be obtained if bone metastases are suspected (e.g., bone scan).
- Complete medical history including demographics, allergies, prior surgery and prior chemo/radiation therapy with documentation of treatment response. See section 7.5.1.1 for detailed instructions on the differentiation between medical history and adverse events.
- Previous HFSR (or HFS) of any grade with other chemotherapy (yes/no response only, no chart review).
- 12-lead ECG

The following procedures and assessments will be performed **within 14 days of starting study drug**:

- ECOG performance status (Appendix 14.6).
- Physical examination including review of all organ systems, examination of pertinent organ systems, vital signs (heart rate, blood pressure, and temperature) weight and height.
- The blood pressure measurements must be performed in a consistent manner using a manual cuff on the same arm. Have the patient sit comfortably for 5 minutes with feet on the floor and arm supported at heart level prior to taking the evaluation. The assessment must be made with the patients in the sitting position using the same arm for all evaluations. Two additional measurements, taken 5 minutes apart, should be conducted if the first blood pressure is abnormal.

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- Record of all concomitant prescribed and over-the-counter medications. All medications and significant non-drug therapies taken within 14 days before study treatment must be recorded in the CRF.

The following procedures and assessments will be performed **within 7 days of starting study drug**:

- A CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts.
- Electrolyte panel: sodium, potassium, chloride and Chemistry panel: Aspartate Amino-Transferase (AST), bilirubin (total and direct), Gamma GT, alkaline phosphatase, total protein, albumin, calcium, lipase, amylase, phosphate, Lactic Dehydrogenase (LDH), glucose, creatinine and Blood Urea Nitrogen (BUN).
- Thyroid function test (TSH, free T3, free T4).
- Coagulation panel: Prothrombin time (PT) or the International Ratio of PT (PT-INR) and Partial Thromboplastin Time (PTT).
- Urinalysis: appearance, pH, glucose, ketones, erythrocytes, leukocyte esterase, nitrite, bilirubin, urobilinogen, protein, creatinine, and protein/creatinine ratio. A microscopic analysis should be performed if the appearance is turbid, or if protein, leukocytes, erythrocytes or nitrite are out of normal range.
- Quantification of proteinuria by urinary protein/creatinine ratio (UPCR) on a random urine sample preferably taken at mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dl) to urine creatinine (in g/dl). If UPCR is outside of Normal Range (>30 g/mol Creat), then a 24-hour urine protein test should be performed to confirm Grade 3 or higher proteinuria (>3.5 g/24 hours).
- Measurement of GFR according to the MDRD (Modified diet in renal disease) abbreviated formula.
- Carcinoembryonic antigen (CEA) testing.
- A negative urine or serum pregnancy test for women of childbearing potential.
- The inclusion and exclusion criteria should be checked during the screening period to ensure appropriate patients are enrolled.

7.1.2.2 Treatment

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

- The inclusion and exclusion criteria should be checked to ensure appropriate patients are treated at Day 1 of Cycle 1 only.
- Physical examination including vital signs (pulse and blood pressure), weight, temperature and examination of pertinent organ systems ECOG performance status

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- Toxicity and adverse events documentation (including Start/Stop dates, seriousness, CTC notation and grading, relationship to study drug, outcome and action taken) using CTCAE v4.03
- Concomitant medications (including start/stop dates, dose, indication)
- Echocardiogram or MUGA scan only if clinically indicated. Echocardiograms or MUGA scans should be performed by the same operator to minimize inter-observer variability.

The following laboratory evaluations are not required at Day 1 of Cycle 1 if these were completed within 7 days of starting study drug treatment. Otherwise, these laboratory evaluations are required on Day 1 of each cycle:

- CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts. (note: BCCA lab does 5 part differentials).
- Electrolyte panel: sodium, potassium, chloride and Chemistry panel: Aspartate Amino-Transferase (AST), bilirubin (total and direct), alkaline phosphatase, triglyceride levels, uric acid, total protein, albumin, calcium, lipase, amylase, phosphate, Lactic Dehydrogenase (LDH), glucose, creatinine and Blood Urea Nitrogen (BUN)
- Thyroid function test (TSH, free T3, free T4)
- Coagulation panel: Prothrombin time (PT) or the International Ratio of PT (PT-INR) and Partial Thromboplastin Time (PTT). If a patient is on warfarin with stable PT/INR at baseline, the PT/INR should be assessed on Day 5 of Cycle 1. If either of these values is above the acceptable range, the doses should be modified and the assessments should be repeated weekly until it is stable.
- Urinalysis: appearance, pH, glucose, ketones, erythrocytes, leukocyte esterase, nitrite, bilirubin, urobilinogen, protein, creatinine, and protein/creatinine ratio. A microscopic analysis should be performed if the appearance is turbid, or if protein, leukocytes, erythrocytes or nitrite are out of normal range.
- Quantification of proteinuria by urinary protein/creatinine ratio on a random urine sample preferably taken at mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dl) to urine creatinine (in g/dl).
- Measurement of GFR according to the MDRD (Modified diet in renal disease) abbreviated formula.

The following items are not required at Day 1 of Cycle 1 if these were completed within 7 days of starting study drug treatment. Otherwise, these items are to be complete on Day 1 of each cycle:

- 12-lead ECG
- Assessment of AEs
- Concomitant medications
- Provide blood pressure diary to the patient

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- Provide rash diary to the patient
- Provide patient education brochure to patient

The blood pressure must be monitored weekly for the first six weeks of study treatment. Either the blood pressure can be recorded by the treating physician and entered onto the CRF or by the patient and entered onto a patient diary. In the latter case, the patient should be instructed to contact the physician in the event of systolic ≥ 150 mm Hg and / or diastolic ≥ 100 mm Hg. The physician should confirm the reading before recording it into the CRF. Blood pressure measurements will be performed in patients sitting for 5 minutes prior to the evaluation. The patient should be instructed to take their blood pressure in the morning and repeat two more times for accuracy.

- Dispense study drug and perform drug accountability after Cycle 1.
- Photos will be taken of hands and feet for illustrative purposes.

The following assessments should be performed on **day 7 of the first cycle** (+/- 3 days):

- Physician visit
- ECOG Status
- Liver functions tests
- Blood pressure
- Assessment of AEs
- Concomitant medications
- Patient will have photos taken of hands and feet

The following assessments should be performed on **day 14 of the first cycle** (+/- 3 days):

- Physician visit
- ECOG Status
- Liver functions tests
- Blood pressure
- Assessment of AEs
- Concomitant medications
- Patient will have photos taken of hands and feet

The following assessments should be performed on **day 21 of the first cycle** (+/- 3 days):

- Physician visit
- ECOG status
- Liver Function Tests
- Blood pressure
- Assessment of AEs
- Concomitant medications

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- Patient will have photos taken of hands and feet

The following assessments should be performed on **day 7 of the second cycle** (+/- 3 days):

- Blood pressure
- Assessment of AEs
- Concomitant medications

The following assessments should be performed on **day 14 of the second cycle** (+/- 3 days):

- Physician visit
- ECOG status
- Liver function tests
- Assessment of AEs
- Concomitant medications
- Blood pressure

Tumor measurements (CT/MRI scans) will be conducted every 8 weeks. A PET scan is not acceptable for radiological evaluation. Throughout the study, the identical lesions to those identified and measured at baseline must be evaluated using the same technique, and preferably by the same investigator/radiologist. MRI/CT scans must meet the standard of care for the imaging of lesions in the respective organ system(s). Copies of all imaging (CT scans, MRI, X-rays, ultrasound, photographs of cutaneous lesions, etc.) performed for tumor assessment in all enrolled patients will be stored electronically at the site.

7.1.2.3 End of Treatment Visit

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

- Brief medical history and complete physical examination including review of all organ systems, examination of pertinent organ systems, vital signs (heart rate, blood pressure and temperature) and weight
- ECOG performance status
- A CBC with differential should be performed: RBC, hemoglobin, hematocrit, platelet count and WBC. WBC must include differential neutrophil, lymphocyte, monocyte, basophil and eosinophil counts.
- Liver function tests
- CEA testing
- Creatinine
- Urinalysis: appearance, pH, glucose, ketones, erythrocytes, leukocyte esterase, nitrite, bilirubin, urobilinogen, protein, creatinine, and protein/creatinine ratio. A microscopic analysis should be performed if the appearance is turbid, or if protein, leukocytes, erythrocytes or nitrite are out of normal range.

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- Quantification of proteinuria by urinary protein/creatinine ratio on a random urine sample preferably taken at mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dl) to urine creatinine (in g/dl).
- Measurement of GFR according to the MDRD (Modified diet in renal disease) abbreviated formula.
- 12-lead ECG
- Concomitant medications
- Toxicity and adverse events documentation
- For patients who discontinue for reasons other than disease progression, tumor measurements and evaluation of tumor response of all measurable lesions should be performed according to RECIST criteria, version 1.1.

7.1.2.4 Safety Follow-Up Visit

Patients have to be evaluated for symptoms and adverse events in a visit **30 days (+/- 7 days)** after permanently stopping study treatment. All AEs starting within 30 days after the last dose of study medication should be recorded. This contact may be completed via telephone. The following assessments should be performed:

- Concomitant medications (including anti-cancer medication)
- Toxicity and adverse events documentation

7.1.2.5 Follow-up Period

Physician visits: during follow up period, patients will be seen by physician every four weeks until disease progression, then every two months as per standard of care.

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. After the 30-day follow up period, no additional AE will be reported.

- After the last contact of the Safety Follow-Up Visit (or after the EOT visit if the Safety Follow-Up Visit is not available), subjects will be off study.
- Status of disease and date of progression (If tumor assessments are available for subjects who have not yet experienced PD, enter the follow-up tumor evaluations in the CRF until PD is diagnosed).
- Date and cause of death while on study will be captured.
- Documentation of all new cancer therapies.

Telephone follow-up is acceptable. Site staff must use caution when contacting the subject's family for this information, especially if they are no longer under the care of the investigator, so as to not inadvertently cause any distress to the family of a subject who is no longer alive.

Subjects who withdraw consent from study drug treatment should enter the Follow-up Period (unless consent to follow-up is specifically withdrawn).

7.2 Population characteristics

7.2.1 Demographic

Baseline subject data pertaining to demographic information should be documented accordingly in the CRFs include the following:

- Date of Birth (Age)
- Sex
- Race/ethnicity
- Weight
- Height

7.2.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.5.1.1.

7.2.3 Other baseline characteristics

Baseline patient data relating to disease factors include:

- Date of diagnosis and stage of CRC
- ECOG performance status
- Prior antineoplastic therapies
- Laboratory results
- ECG findings
- Incidence of previous HFSR will be recorded as “yes/no”; no chart review is required.

All medications and significant non-drug therapies taken within 14 days before study entry must be recorded in the CRF, including:

- Medication trade name and dose
- Reason for medication
- Start Date and End date or if continuing at time of study entry.

7.3 Efficacy

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The primary endpoint of this trial is a safety endpoint. Efficacy measurement in this study will be assessed as a secondary endpoint, and will be measured by assessing progression-free survival (PFS). PFS will be evaluated based on RECIST v1.1 criteria, 20% progression or any new lesion.

Measurements will be made at baseline and then every 8 weeks during the treatment period until progressive disease is documented, and also at the end of treatment visit if applicable. At baseline, information on all potential sites of tumor lesions should be obtained, at a minimum patients must have a radiologic examination of chest, abdomen and pelvis. Throughout the study period, the same lesions to those identified and measured at baseline must be evaluated using the same technique, the identical contrast agent and the same slice thickness. If additional lesions are suspected, the relevant anatomical regions should be evaluated by appropriate radiologic examinations.

If a patient discontinues treatment prematurely before progression (e.g., due to toxicity), the investigator should perform a complete physical, laboratory and radiological assessment as soon as possible after study drug discontinuation. After treatment discontinuation, tumor assessments should be continued until progression, even if the patient receives other treatments.

For the purposes of defining progressive disease, every effort should be made to obtain radiographical imaging at the defined timepoints.

In cases where radiographic imaging is not possible, clinical progression may be used. Clinical progression is based on the judgment of the investigator.

The complete list of variables to be analyzed for this study will be provided in the statistical analysis plan.

7.5 Safety

Although we are assuming that the co-administration of perindopril with regorafenib will mitigate HFSR symptoms, this may not be the case. Grade 3 HFSR rate will be evaluated after the first 10 patients have completed at least one cycle of regorafenib. If a significantly higher rate of grade 3 HFSR is seen in these first 10 patients i.e. Grade 3 is seen in more than 5 out of the 10 patients, the study will be discontinued.

Safety variables for **regorafenib** are as follows: adverse events, laboratory changes (hematology, clinical chemistry and clinical urinalysis), changes in vital signs (blood pressure, heart rate, respiratory rate, temperature) and electrocardiogram (ECG). These will be measured as per standard of care for regorafenib, as per study schedule (Table 7). See more details from product monograph below.

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Safety variables for **perindopril** can be obtained from the COVERSYL® Product Monograph. The most frequent adverse reactions observed with perindopril are: cough, dizziness, headache, asthenia, gastro-intestinal disorders (abdominal pain, nausea, dyspepsia). The most serious adverse reactions are: hypersensitivity reaction (angioedema), renal dysfunction (in high risk patients), pancreatitis, blood disorders (pancytopenia, agranulocytosis, and thrombocytopenia). During the long-term safety assessment in heart failure patients, the severe adverse events occurring with the highest frequency were angina pectoris and orthostatic hypotension. The most severe drug reactions from post-marketing experience were pancreatitis and blood disorders (pancytopenia, agranulocytosis, and thrombocytopenia).

More detailed safety variables from the regorafenib monograph include:

Regorafenib has been associated with an increased incidence of electrolyte abnormalities (including hypophosphatemia, hypocalcemia, hyponatremia and hypokalemia) and metabolic abnormalities (including increases in thyroid stimulating hormone, lipase and amylase). The abnormalities are generally of mild to moderate severity, not associated with clinical manifestations, and do not usually require dose interruptions or reductions. It is recommended to monitor biochemical and metabolic parameters during regorafenib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Dose interruption or reduction, or permanent discontinuation of regorafenib should be considered in case of persistent or recurrent significant abnormalities.

Since drugs with anti-angiogenic properties may suppress wound healing, treatment with regorafenib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume regorafenib after surgery should be based on clinical judgment of adequate wound healing. Regorafenib should be discontinued in patients with wound dehiscence.

Regorafenib may decrease heart rate. Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure.

Patients with a history of ischemic heart disease should be monitored for clinical signs and symptoms of myocardial ischemia. In patients who develop new or acute onset cardiac ischemia and/or infarction regorafenib should be withheld until resolution. The decision to re-initiate regorafenib therapy should be based on careful consideration of the potential benefits and risks of the individual patient. Regorafenib should be permanently discontinued if there is no resolution.

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Regorafenib should be permanently discontinued in patients who develop gastrointestinal perforation or fistula.

Treatment with regorafenib should be stopped in patients with severe or life threatening hemorrhage. Patients receiving warfarin should be closely monitored.

For patients with observed worsening of liver function tests, dose modification (interruption, reduction) or discontinuation of regorafenib is recommended.

In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, regorafenib should be discontinued until further pulmonary investigation excludes interstitial lung disease and pneumonitis.

Patients with severe hepatic impairment will be excluded. Closely monitor patients with any hepatic impairment for adverse reactions, discontinuation of regorafenib, along with control of hypertension and supportive medical management of other symptoms is recommended.

7.5.1 Adverse events

7.5.1.1 Definitions

Definition of adverse event (AE)

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

Surgeries and/or procedures are not Adverse Events – they are therapeutic measures for conditions that require such intervention. However, the condition requiring surgery may be an Adverse Event. Therefore, if surgical procedure is reported, the basic condition leading to surgery is entered as event respectively.

Disease progression in itself should not be reported as an AE. However, if disease progression results in events that fit AE definition, these should be reported as such.

In the following differentiation between medical history and AEs, the term “condition” may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).

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- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

In this study, investigators should also report signs and symptoms that are associated with progressive disease or the worsening of the existing cancer, and avoid using the AE term progressive disease.

Definition of serious adverse event (SAE)

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

- The admission results in a hospital stay of less than 12 hours
- The admission is pre-planned (i.e. elective or scheduled surgery arranged prior to the start of the study)
- The admission is not associated with an AE (e.g. social hospitalization for purposes of respite care).

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

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

e. Is a congenital anomaly / birth defect

f. Is a medically important event as judged by the investigator

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Investigators should also report any sign and symptom of progressive disease or worsening of the existing cancer as a separate SAE if the "serious" criteria are met. Investigators should avoid reporting progressive disease as the AE term.

All of the following events are to be reported to the sponsor as SAEs following the reporting instructions:

- Acute myeloid leukemia (AML)
- myelodysplastic syndrome (MDS) occurring after chemotherapy for cancer
- Additional primary cancers (including skin cancers) regardless of relationship to study treatment

A Serious Adverse Event should be described as "Death" when the cause of death is unknown; otherwise "Fatal" must be entered as the outcome of the Adverse Event and/or reason for seriousness.

All adverse events must be assessed by the investigator for severity and seriousness.

7.5.1.2 Classifications for adverse event assessment

CTCAE v4.03 criteria will be used for evaluation during the trial.

The incidence of HFSR will be expressed as the number of patients out of study (N=34) who are experiencing HFSR of all grades. Severity will be evaluated using CTCAE v4.03 criteria.

The incidence of hypertension will be expressed as the number of patients on study (N=34) who are experiencing hypertension of all grades. Severity will be evaluated using CTCAE v4.03 criteria.

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

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 Intensity

The severity (or intensity) of adverse events should be graded according to NCI-CTCAE v4.03. If no exact matching code is available in CTCAE v4.03 then use the following guide:

- CTC 1 = Mild AE, transient in nature and generally not interfering with normal activities
- CTC 2 = Moderate AE, sufficiently discomforting to interfere with normal activities
- CTC 3 = Severe AE, prevents normal activities
- CTC 4 = Life-threatening and/or disabling AE
- CTC 5 = Results in death (fatal)

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7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF. The causality assessment should be done separately for each study treatment as detailed in the CRF.

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

Possible answers are “yes” or “no”

An assessment of “no” would include:

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

or

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

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

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

7.5.1.2.4 Action taken with study treatment

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

The study treatment action should be recorded separately for each study treatment as detailed in the CRF.

- Drug withdrawn
- Drug interrupted

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- Dose reduced
- Dose not changed
- Dose increased
- Not applicable
- Unknown

Treatments administered specifically because of the adverse event should be recorded using the categories below:

- None
- Remedial drug therapy
- Other

7.5.1.2.6 Outcome

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

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

7.5.1.3 Assessments and documentation of adverse events

All adverse events occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

7.5.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 7.5.1.1.

Study investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed. All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to Health Canada using the SAE

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form, as well as to the Bayer Pharmacovigilance Department. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

SAEs occurring after the protocol-defined observation period will be processed by the investigator according to all applicable regulations.

In each case of a fatal or life-threatening reaction, the investigator must seek relevant follow-up information and must complete a follow-up report without delay to Bayer and Health Canada as described below.

For all SAEs, the investigator is required to document in full, the course of the SAE and any therapy given, including any relevant findings/records in the report.

It is not mandatory to report SAEs occurring after the protocol-defined observation period, however, at the investigator's discretion these may be reported if considered potentially relevant.

7.5.1.5 Responsibility for Reporting Serious Adverse Events to Bayer

Each Investigator will report to Bayer Inc. Pharmacovigilance department any SAE or AE of Special Interest within 24 hours of becoming aware of such event, in order to allow Bayer to process and/or submit such safety information according to the mandated timelines to health authorities worldwide.

Report event by email or fax to Bayer Inc. Pharmacovigilance:

BAYER SAE REPORTING NUMBER

Fax: 1-866-232-0565

Email: DSI_Canada@bayer.com

7.5.1.6 Prompt Reporting of SAEs to Health Canada

It is responsibility of the Sponsor of the study to report to Health Canada within 24 hours all serious adverse events (SAEs), as defined by applicable law or regulation regardless of attribution to the study drug and expectedness that are experienced by any Study subject receiving a study drug.

The Health Canada number for SAE reporting at the Marketed Health Products Directorate (MHPD):

Telephone: 1-866-234-2345

Fax: 1-866-678-6789

E-mail: cadrmpp@hc-sc.gc.ca

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions (SUSARs)) will be performed by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the investigator according to all applicable regulations.

7.5.1.5 Expected adverse events

The most frequently observed adverse drug reactions ($\geq 30\%$) in patients receiving regorafenib are described in the Stivarga[®] (regorafenib) Product Monograph and include asthenia/fatigue, hand-foot skin reaction, diarrhea, decreased appetite and food intake, hypertension, dysphonia and infection.

The most serious adverse drug reactions in patients receiving regorafenib are severe liver injury, hemorrhage, cardiac ischemia/infarction, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), Stevens-Johnson syndrome/toxic epidermal necrolysis, and gastrointestinal perforation or fistula). Of these, hypertension and hemorrhage have been observed most frequently.

The most frequent adverse reactions observed with perindopril are described in the COVERSYL[®] Product Monograph and include: cough, dizziness, headache, asthenia, gastro-intestinal disorders (abdominal pain, nausea, dyspepsia).

The most serious adverse reactions from perindopril are: hypersensitivity reaction (angioedema), renal dysfunction (in high risk patients), pancreatitis, blood disorders (pancytopenia, agranulocytosis, and thrombocytopenia).

During the long-term safety assessment in heart failure patients, the severe adverse events occurring with the highest frequency were angina pectoris and orthostatic hypotension.

The most severe drug reactions from post-marketing experience were pancreatitis and blood disorders (pancytopenia, agranulocytosis, and thrombocytopenia).

7.5.1.6 Adverse events of special safety interest

Regorafenib is an investigational drug and current knowledge of the adverse events associated with this compound is limited.

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

Based on data from Phase I/II studies with regorafenib and from current knowledge of the pharmacological properties of other small molecule TKIs in this drug class, as soon as there is reasonable suspicion of any of the following AEs, the investigator should immediately notify Bayer as outlined in section 7.5.1.4. These events are:

- Acute renal failure (CTC AE Grade 3) or severe proteinuria (CTC AE Grade 3)
- Interstitial lung disease
- Acute cardiac failure
- Clinically significant bleeding (CTCAE Grade 3)
- Stevens Johnson Syndrome
- Erythema multiforme

7.5.2 Pregnancies

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

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

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

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

7.5.3 Further safety

An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as an SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. CTC grade 4 baseline laboratory abnormalities that are part of the disease profile should not be reported as an SAE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he/she should consult with the study monitor for the Sponsor. CTC grade 4 lab abnormalities will be documented in the lab data and will be reviewed on a regular basis.

8. Statistical methods and determination of sample size

8.1 General considerations

Statistical analyses will be performed using SAS 9.3. Demographic and other baseline characteristics will be listed and summarized. Qualitative data will be summarized using frequencies and percentages and quantitative data will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum and maximum). Secondary safety variables will be summarized using descriptive statistics and exploratory graphical presentations of the data.

Duration of study treatment exposure, cumulative dose and dose intensity will be summarized. The number of patients with dose changes/interruptions and withdrawals will be presented along with reasons for the dose change.

Variables related to tumor response and disease progression will be evaluated based on investigator assessed RECIST criteria, version 1.1. In cases where radiographic imaging is not possible, clinical progression may be used. Clinical progression is based on the judgment of the investigator.

Toxicity related variables will be evaluated using the CTCAE v4.03 criteria.

Biomarker and pharmacokinetics will not be performed in this study and no subgroup analysis will be performed.

8.2 Analysis sets

The primary analysis set will consist of all evaluable patients. An evaluable patient is defined as a patient who meets all inclusion/exclusion and who has received at least one dose of study medication. The safety set will consist of all patients who receive at least one dose of study medication.

8.3 Primary Objective

The primary objective is to determine the proportion of patients that have any grade HFSR toxicity when treated with a combination of regorafenib and perindopril.

8.3.1 Primary Endpoint

The primary endpoint of this study is proportion of patients with any grade HFSR toxicity. Toxicities will be evaluated used CTCAE v4.03 criteria.

8.3.2 Statistical hypothesis and method of analysis

The primary analysis will be a comparison of the proportion of patients with any grade HFSR toxicity to 47% using the normal approximation z-test statistic and 2-sided 5% significance level. The statistical hypotheses are

H0: $P = 0.47$ versus H1: $P \neq 0.47$

where P is the proportion of any grade HFSR toxicity.

The study includes a single interim safety analysis after 10 patients have completed the study medication.

The proportion of patients having worst grade 3 HFSR toxicity will be determined along with the 95% confidence interval.

8.4 Secondary Objectives

The secondary objectives are to evaluate the time to development of worst grade 3 HFSR toxicity, proportion of all grades of hypertension, proportion of all grade toxicities and progression-free survival. All toxicities will be evaluated using CTCAE v4.03.

8.4.1 Time to worst grade 3 HFSR toxicity

Time to worst grade 3 HFSR toxicity is defined as the time (days) from start date of study drug to date of first documented grade 3 HFSR toxicity and will be calculated only for patients who had a HFSR toxicity grade 3.

8.4.2 Progression-free survival

Progression-free survival is defined as the time (days) from start date of study drugs to date of first documented disease progression (radiological or clinical) or death due to any cause, if death occurs before progression is documented. The actual date that the tumor scan was performed will be used for this calculation. Progression-free survival for patients without disease progression or death at the time of the final analysis will be censored at the last date of tumor evaluation. Progression-free survival for patients who have no tumor assessments after baseline will be censored at 1 day. Missing or non-evaluable tumor assessments will not be taken into account in the calculation of PFS. Every effort will be made to obtain radiologic imaging for documentation of progression. In those cases where patients are unable to obtain radiologic examinations due to deterioration of medical condition, the date of clinical progression will be used for the determination of the date of progression. The PFS distribution will be presented descriptively using Kaplan-Meier curves. The median PFS from the Kaplan-Meier distribution will be determined along with the associated 95% confidence interval.

8.5 Safety

Safety variables are as follows: adverse events, the number of laboratory values that fall outside of pre-determined ranges (hematology, clinical chemistry and clinical urinalysis), changes in vital signs (blood pressure, heart rate, respiratory rate, temperature) and electrocardiogram (ECG).

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All adverse events whether considered drug-related or not, will be reported with start/stop dates, action taken, whether treatment was discontinued, any corrective measures taken, and outcome. For all events, the relationship to treatment and the severity of the event will be determined by the Investigator, using the terms and definitions given in Section 5.1.

A Treatment-emergent adverse event is defined as any event arising or worsening after the start of study drug administration until 30 days after the last study medication

8.6 Planned interim analyses

A single interim analysis is planned to be performed at the point that 10 patients have completed their first cycle of study treatment. This will be to determine if the study should continue. The study will be discontinued if 5 out of the first 10 patients exhibit a Grade 3 HFSR. The lower bound limit of the 95% confidence interval would be 18.7% which is higher than the 17% of patients who experienced HFSR grade 3 severity in the CORRECT trial.

8.7 Determination of sample size

A sample size of 34 patients achieves 80% power to detect a 50% reduction in all grades of HFSR toxicity (from 47% as seen in the CORRECT trial to 24%) using the normal approximation to the binomial distribution and a 2-sided 5% significance level.

9. Data handling and quality assurance

9.1 Data recording

Designated investigator staff will enter the data required by the protocol in a specific study data collection tool. Designated investigator staff will not be given access until they have been trained. The data entered will be reviewed by investigational staff for completeness and accuracy and will provide instruction for any required corrections or additions to the data. Obvious errors will be corrected by the designated investigator data entry staff. Validation program checks for data discrepancies will allow the data to be confirmed and corrected before analysis.

9.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements.

When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

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The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

9.3 Data processing

Clinical data management will be performed in accordance with investigator's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IVRS, laboratory, ECG).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

9.4 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection. The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

9.5 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

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The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership). The investigator site file is not to be destroyed without the sponsor's approval.

The investigator's contract will contain all regulations relevant for the study center.

10. Premature termination of the study

The study will be discontinued if 5 of the first 10 patients exhibit a Grade 3 or higher HFSR. Note that in the CORRECT trial, 47% of patients experienced HFSR of all grades with 17% experiencing HFSR with grade 3 severity.

(Note: Given the small patient numbers (n=10) for the interim analysis and using the expected number from CORRECT, there would be ~2 expected with HFRS at Grade 3. If you have n≥3 to discontinue the study, that may be problematic given a single patient can have a significant impact at such low numbers. Increasing it to 5 would indicate there is a signal suggesting a ≥2 fold increase in grade 3 HFSR events and study should be discontinued.)

The sponsor/Investigator has the right to close this study at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
 - Safety findings from this study (e.g. SAEs)
 - Results of any interim analysis
 - Results of parallel clinical studies
 - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority (ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be retained as per BCCA regulations.

In case of study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

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Details for individual subject's withdrawal can be found in Section 5.2.1.

11. Ethical and legal aspects

11.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for the center before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained. The Sponsor/Investigator will ensure a list of the EC/IRB members involved in the vote, and a statement to confirm that the EC/IRB is organized and operates according to GCP and applicable laws and regulations, is filed with the study documents.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol. However, the Sponsor/Investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB.

Any deviations from the protocol must be explained and documented by the investigator. Details on discontinuation of the study can be found in Section 10.

11.2 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor/investigator.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject / legal representative or proxy consentor (if the subject is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

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Each subject / legal representative or proxy consentor will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject / legal representative or proxy consentor voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject / legal representative or proxy consentor will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject's clinical record must clearly show that informed consent was obtained prior to these procedures.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consentors will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject / legal representative or proxy consentor of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

11.3 Publication policy

BAYER acknowledges the interest of the study sponsors to publish the findings of the STUDY and is supportive towards such activity.

To ensure against inadvertent disclosure of unprotected INVENTIONS and CONFIDENTIAL INFORMATION, the study sponsors agree to comply to the following terms on publication:

Study Sponsors shall provide to BAYER any proposed publication or oral presentation relating to the STUDY or STUDY DRUG or the RESULTS (hereinafter called "PUBLICATION") at least sixty

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(60) days prior to the intended submission or presentation of the PUBLICATION in order to allow BAYER to review it.

If BAYER does not notify Study Sponsors within sixty (60) days of BAYER's receipt of the intended PUBLICATION, Study Sponsors shall be free to publish.

BAYER may recommend any changes to the PUBLICATION it reasonably believes are necessary for scientific purposes. Study Sponsors agree that the implementation of such recommended changes shall not be unreasonably refused.

If BAYER informs Study Sponsors that such PUBLICATION could be expected to have an adverse effect on the confidentiality of any of BAYER'S CONFIDENTIAL INFORMATION, Study Sponsors shall prevent the PUBLICATION, unless the CONFIDENTIAL INFORMATION can be deleted from the PUBLICATION without detriment effect on the scientific correctness of the PUBLICATION.

If the PUBLICATION could in BAYER'S view have an adverse effect on the ability to obtain patent protection for any INVENTION, BAYER may request a delay of the PUBLICATION for a reasonable period of time in order to permit the preparation and filing of any desired patent application by or on behalf of BAYER, such period, however, not to exceed ninety (90) days.

Study Sponsors shall include a statement in any PUBLICATION that creation of the data was supported in part by BAYER.

The Study Sponsors will make the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

11.4 Compensation for health damage of subjects / insurance

BCCA maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the province and country in which the study is performed.

11.5 Confidentiality

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.

Subject names will be kept confidential. Only the subject number and initials will be recorded in the CRF.

Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities 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.

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

The investigator will maintain a list to enable subjects to be identified.

12. Reference list

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Li J, Qin S, Yau T et al. CONCUR: a randomized double-blind placebo controlled phase 3 study of regorafenib monotherapy in Asian patients with previously treated metastatic colorectal cancer (mCRC). *Ann Oncol* 2014; 25 (Suppl 2): ii114–ii115.

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Robert C et al. Cutaneous side effects of kinase inhibitors and blocking antibodies. *Lancet Oncol* 2005; 6: 491.

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13. Protocol amendments

Any amendments will be inserted into this section.

Summary of Changes:

Protocol Version 1.2 dated 03 June 2016

- Correction of minor typographical errors and formatting errors in the document.
- Clarifications to the protocol by reconciling protocol text with tabulated overview.
- Removal of the inclusion criteria $CEA \leq 3$ times the ULN to reflect clinical practice.
- Removal of required Screening cardiac function test (i.e. echocardiogram or MUGA scan) since there is no Exclusion/Inclusion criteria pertaining to results of a cardiac function test. Furthermore, as regorafenib has no cardiac toxicity, a cardiac function test is not required for this study.
- Removal of ECOG assessment and liver function tests at C2D7 Visit since no Physician Visit is scheduled.
- Clarification that blood pressure measurement is required at C2D14.
- Clarification that 12-lead ECG is required at D1 of each cycle and at EOT visit.
- Clarification that urinalysis is required at EOT visit.
- Removal of ECOG assessment and blood pressure measurement at Safety Follow-up Visit since this visit may be conducted via telephone.

Protocol Version 2.0 dated 20 September 2016

- Correction of minor typographical errors and formatting errors in the document.
- Update of Exclusion Criteria pertaining to previous or concurrent cancers. As this study is meant to be quite pragmatic, it is overly restrictive to require participants to have no other cancer within 5 years prior to study enrollment. Instead, only patients with a concurrent cancer requiring treatment that is distinct in primary site or histology from colorectal cancer may not be enrolled.
- Addition of Exclusion Criteria: Patients receiving systemic anticancer therapy including cytotoxic therapy, signal transduction inhibitors, immunotherapy, hormonal therapy and experimental or approved therapies during this trial or within 14 days before starting to receive study medication. Chemotherapy/radiation is cleared by 14 days and most patients need treatment quickly when they progress. The 30 days was from a global strict randomized trial CORRECT.
- Clarification of Exclusion Criteria pertaining to proteinuria. 24-hour urine protein test is only required if protein/creatinine ratio on a random urine sample preferably taken at

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mid-morning results in a ratio greater than 30g/mol Creat. The 24-hour urine protein test should be performed to confirm Grade 3 or higher proteinuria (>3.5g/24 hours). Proteinuria is usually from bevacizumab which is given in first line. In PARICCA, participants receive regorafenib for third- or fourth-line treatment. Proteinuria is screened with urinalysis and the 24-hour urine protein test needs only to be done if >30g/mol.

- Clarification of Screening procedures in Section 7.1.2.1 Screening relating to quantification of proteinuria. If UPCR is found to be greater than ULN, then a 24-hour urine protein test should be performed to confirm Grade 3 or higher proteinuria (>3.5g/24 hours).
Proteinuria is usually from bevacizumab which is given in first line. In PARICCA, participants receive regorafenib for third- or fourth-line treatment. Proteinuria is screened with urinalysis and the 24-hour urine protein test needs only to be done if >30g/mol.
- Clarification of photography procedures in Section 7.1 Schedule of procedures. In previous version of protocol, it was not detailed that a total of approximately 8 photographs will be taken of the dorsal and plantar/palmer surfaces of each of the participant's hands and feet at each specified interval. The labeling procedures are also clarified in this amendment.
- On Day 1 of each cycle, the participant is to receive a Rash Diary to complete (Section 7.1.2.2 Treatment). In order to more adequately document the onset of rash during treatment, participants will be asked to complete a Rash Diary during each treatment cycle. Information collected through this Rash Diary will assist in assessing time to development of HFSR toxicity. The Rash Diary will be collected by the designated study personnel upon completion of the diary, following each treatment cycle.

Protocol Version 2.1 dated 07 December 2016

- Correction of minor typographical errors and formatting errors in the document.
- Change of Inclusion Criteria relating to alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). Patients with liver involvement of their cancer may be included if ALT, AST, and ALP are ≤ 5 times ULN. The rationale is to align with the eligibility in the CORRECT phase III trial of regorafenib.
- 7.1 Schedule of procedures (Page 43) – Clarification of the liver function tests required every week for the first cycle, every two weeks for the second cycle, at the start of each cycle after this, and at follow up visit.

Protocol Version 2.2 dated 08 February 2017

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- List of abbreviations: Addition of ACE (angiotensin converting enzyme) and ARB (angiotensin receptor blocker).
- Clarification of exclusion criterion relating to pre-existing anti-hypertensive treatment. The exclusion criterion was: “Patient selection to exclude patients with pre-existing anti-hypertension treatment, in particular other ACE inhibitors....” The exclusion criterion is now: “Patients with pre-existing anti-hypertensive treatment with an ACE inhibitor or angiotensin receptor blocker (ARB) are to be excluded....” This update makes it clearer that patients may still be eligible for participation if they have controlled hypertension using an anti-hypertensive that is not an ACE inhibitor or ARB.

14. Appendices

14.1 RECIST

Response and progression will be evaluated in this study using the RECIST criteria version 1.1. (*Eisenhauer EA et al. 2009*) Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used.

Measurable Disease:

Tumor lesions: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm) or MRI. If scans with slice thicknesses greater than 5mm are used, the minimum size should be twice the slice thickness.
- 20 mm by chest x-ray
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

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.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components that can be evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component meets the definition of measurability.

All tumor measurements must be recorded in millimetres (or decimal fractions of centimetres). Tumor lesions situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15mm short axis) are considered non-measurable disease. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitic involvement of skin or lung, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques and blastic bone lesions are all non-measurable.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as *target lesions* and be recorded and measured at baseline. These 5 lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs and should be suitable for reproducible repeated measurements. 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. The baseline sum diameters will be used as reference to further characterize any objective tumor regression of the measurable dimension of the disease. If there are >5 measurable lesions, those not selected as *target lesions* will be considered together with non-measurable disease as *non-target lesions*.

Non-target Lesions: All non-measurable lesions (or sites of disease) plus any measurable lesions over and above the 5 listed as *target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present”, “absent” or in rare cases “unequivocal progression”.

Best Response

All subjects will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR): Disappearance of all clinical and radiological evidence of tumor (both *target* and *non-target*). Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Stable Disease (SD): Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no unequivocal progression of existing non-target lesions and no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate

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an absolute increase of at least 5mm. Unequivocal progression of existing non-target lesions or the appearance of one or more new lesions will also constitute progressive disease.

Table 1: Response for patients with Target and Non-Target Lesions

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
CR	CR	No	CR	
CR	Non-CR/Non-PD	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD or not all evaluated	No	PR	
SD	Non-PD or not all evaluated	No	SD	documented at least 6 wk. from enrollment
Not all evaluated	Non-PD	No	NE	
PD	Any	Yes or No	PD	
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

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

Table 2: Response for patients with Non-Target Lesions only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD*
Not evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* Non-CR/non-PD is preferred over “stable disease” for non-target disease.

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

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

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

CT / MRI - CT is the best currently available and reproducible methods to measure target lesions selected for response assessment. CT scans should be performed with cuts of 5 mm or less in slice thickness. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound - Ultrasound is not useful in assessment of lesion size and should not be used as method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy / Laparoscopy - The utilization of these techniques for objective tumor evaluation is not advised.

Cytology / Histology - These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

14.2 NCI Common Terminology Criteria for Adverse Events

This study will utilize NCI Common Terminology Criteria for Adverse Events for toxicity and serious adverse event reporting. Version 4.03¹ will be used. Version 3.0 was used in the CORRECT trial, however Version 4.03 will be used for comparison to future studies.

¹ http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

14.3 New York Heart Association Functional Classification

Class	NYHA Functional Classification
I	Subjects have cardiac disease but <i>without</i> the resulting <i>limitations</i> of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects have cardiac disease resulting in <i>slight limitation</i> of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects have cardiac disease resulting in <i>marked limitation</i> of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects have cardiac disease resulting in <i>inability</i> to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

14.4 Examples of a low fat breakfast

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

One cup of cereal (i.e., Special K), 8 ounces of skimmed 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).

14.5 Glomerular Filtration Rate (GFR)

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated Glomerular Filtration Rate (GFR), calculated using the abbreviated Modification of Diet in Renal Disease (MDRD) study formula.

This equation of 4 variables (serum creatinine level, age, sex, and ethnicity) is recommended by the National Kidney Foundation (NKF) for use in individuals 18 years or older.²

The formula is as follows:

aMDRD formula

$$\text{GFR (mL/min /1.73m}^2\text{)} = k \times 186 \times [\text{SCR}]^{-1.154} \times [\text{age}]^{-0.203}$$

Where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and SCR is measured in mg/dL.

Patients with a baseline GFR < 30 ml/min calculated by this method will not be allowed to participate in the study.

². References: Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med.* 2006 Aug 15;145(4):247-54.

A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med.* 1999 March 16;130 (6)(Modification of Diet in Renal Disease Study Group):461-70.

Definition and classification of stages of chronic kidney disease. *American Journal of Kidney Diseases.* 2002 February;39(2 Supply 1):S46-S75.

14.6 ECOG

Grade	Description
0	Fully active, able to carry on all pre-disease performances without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Death.

14.7 Overview of STRONG CYP3A4 inducers

Ajmaline

Avasimibe

Carbamazepine

Enzalutamide

Fosphenytoin

Hypericum perforatum, St. John's wort

Methylphenobarbital

Mitotane

Phenobarbital

Phenytoin

Primidone

Phenobarbital

Rifampicin

Rifamycin

Rifapentin

14.8 Overview of STRONG CYP3A4 inhibitors

Boceprevir

Clarithromycin

Cobicistat

Conivaptan

Delavirdine

Indinavir

Itraconazole

Ketoconazole

Lopinavir

Mibefradil

Miconazole

Nefazodone

Nelfinavir

Posaconazole

Ritonavir

Saquinavir

Telaprevir

Telithromycin

Tipranavir

Troleandomycin

Voriconazole