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Protocol Title: A Phase I/II Study of Regorafenib and Pembrolizumab in Metastatic Colorectal Cancer Patients in 3rd and 4th line setting
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A Phase I/II Study of Regorafenib and Pembrolizumab in Metastatic Colorectal Cancer Patients in 3rd and 4th line setting

Test drug(s):	Regorafenib and Pembrolizumab		
[Study purpose:]	MTD, safety and preliminary efficacy		
Clinical study phase:	I/II		
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Synopsis

A Phase I/II Study of Regorafenib and Pembrolizumab in Metastatic Colorectal Cancer Patients in 3rd and 4th line setting.

Clinical study phase	I/II
Study objective(s)	The objective of the study is to assess recommended combination dose, safety and preliminary efficacy, and predictive biomarkers for combination of regorafenib and pembrolizumab. The objective of the phase one is safety of the combination and identification of the recommended dose (RD) for combination therapy. We will employ a 3+ 3 design with expected accrual of 3-18 patients. The objective of phase II is preliminary efficacy and tolerability of the combination RD of regorafenib and pembrolizumab.
Background treatment	Colorectal cancer (CRC) remains a major cause of cancer mortality in US and across the world.[1] Despite significant improvement in the survival of the patients with colorectal cancer over the past decade, almost all patients with metastatic disease will succumb to the disease, resulting is a significant number of deaths every year.
Indication	Third and fourth line metastatic colorectal cancer
Diagnosis and main criteria for inclusion	**Inclusion (partial list):** • Patients who provided written informed consent to be subjects in this trial • Patients at least 18 years of age on the day of providing consent • Patients with histologically or cytologically confirmed advanced or metastatic colorectal cancer who had failed or are intolerant of oxaliplatin, irinotecan, and 5-FU. Patients with MSI colorectal cancer are not candidate for treatment on this trial. • Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1within 7 days of start of treatment • Patients capable of taking oral medication • Patients with evaluable or measurable lesions as per RECIST version 1.1 • Patients with adequate organ function at the time of enrollment as defined below: o Neutrophil count ≥1200/mm^3 o Platelet count ≥7.5 × 10^4/mm^3 o Hgb > 9 (transfusion >2 weeks before testing permitted) o Aspartate transaminase (AST), alanine transaminase (ALT) ≤2.5-times the upper limit of normal (≤5-times in patients with liver metastasis) Total bilirubin ≤1.5-times the upper limit of normal o Creatinine ≤1.5-times the upper limit of normal o Lipase ≤ 1.5 x the ULN o International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless receiving treatment with therapeutic anticoagulation. Patients being treated with anticoagulant, e.g. heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care. • In women with the potential for pregnancy (including patients with amenorrhea due to medical reasons, such as chemical menopause), after consenting to the study, the patient must agree to take contraception from enrollment and for at least 23 weeks after taking the final dose of the investigational drug (a period of 30 days [ovulation cycle] is added to five times the elimination half-time of I/O agent). Women with the potential for

pregnancy include those who have begun menstruation, who have not undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy, and who have not gone through menopause. Menopause is defined as the consecutive absence of menstrual periods for ≥12 months. Total abstinence is an acceptable mode of contraception.

- In the case of men, the patient must agree after consenting to the study to take contraception from enrollment and for at least 31 weeks after taking the final dose of the investigational drug (a period of 90 days [the spermatogenesis cycle] is added to five times the elimination half-time of I/O agent. Total abstinence is an acceptable mode of contraception.

Exclusion criteria

- Patients who have undergone systemic chemotherapy, radiotherapy, surgery, or hormone therapy <2 weeks before enrollment, also see exclusion #8.

  Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
  Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
- Patients with a history of taking regorafenib or immune check point inhibitors.
- Patients with hypertension that is difficult to control (systolic blood pressure ≥150 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with several hypotensive agents
- Patients with acute coronary syndrome (including myocardial infarction and unstable angina), and with a history of coronary angioplasty or stent placement performed within 6 months before enrollment
- Patients with a large amount of pleural effusion or ascites requiring more than weekly drainage.
- Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- Patients with a ≥grade 3 active infection according to NCI-CTCAE version 5.0
- Patients with symptomatic brain metastasis (1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease).

- Patients with partial or complete gastrointestinal obstruction
- Patients with interstitial lung disease with symptoms or signs of activity
- Patients who test positive for either anti-HIV-1 antibodies, anti-HIV-2 antibodies, anti-HTLV-1 antibodies, hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibodies*. (please use prior history for reference, testing is not required unless deemed necessary by the investigator)

  *Patients who test positive for either anti-HBs or anti-HBc antibodies, and those who have HBV-DNA measurements greater than the detection sensitivity will also be excluded.
- Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease
- Patients who require systemic corticosteroids (excluding temporary usage for tests, prophylactic administration for allergic reactions, or to alleviate swelling associated with radiotherapy) or immunosuppressants, or who have received such a therapy <14 days before enrollment in the present study
- Patients with a history or findings of ≥grade III congestive heart failure according to the New York Heart Association functional classification
- Patients with a seizure disorder who require pharmacotherapy
- Persistent proteinuria > 3.5 g/24 hours measured by urine protein-creatinine

	ratio from a random urine sample (≥Grade 3, NCI-CTCAE v 5.0). • Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation. • Major surgical procedure or significant traumatic injury within 28 days before start of study medication. • Non-healing wound, non-healing ulcer, or non-healing bone fracture • Patients with evidence or history of any bleeding diathesis, irrespective of severity • Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study medication • Women who are pregnant or breastfeeding, or with the potential for pregnancy unwilling to undergo contraception. • Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. • Has an active infection requiring systemic therapy. • MSI colorectal cancers are not candidate for enrollment on this trial.
Study design	Phase I is a standard 3+3 design evaluating escalating doses of regorafenib in combination with fixed dose pembrolizumab. The primary endpoint is to identify the recommended dose (RD) of the combination. The phase II is an open label single arm study to assess the preliminary efficacy and tolerability of the combination therapy at RD in colorectal cancer patients who had failed standard therapy. The primary endpoint is PFS, we assume that combination therapy will result in prolongation of progression free survival by 50% compared to historical PFS with single agent regorafenib. Given that PFS in CORRECT trial was 1.9 mos with type one error of 10%, power of 80% we will need a sample size of 63 pts. The expected PFS in the treatment group will be 2.85 months. The accrual is expected to happen over 24 months. Tolerability will be assessed by median duration of treatment; combination is defined to be tolerable if the median duration of treatment is at least 20% better than CORRECT data (1.7 months).
Type of control	This study has no control
Number of subjects	A total of 3-18 patients will be enrolled and treated on the phase I. A total of 69 patients will be enrolled on the phase II portions of this trial. Six patients who are treated at MTD/RP2D of the phase I portion of the study will be counted for the phase II portion of the study too.
Plan for statistical analysis	A standard 3+3 dose escalation rule will be used during the phase I portion of the study to determine MTD/RP2D of combination of regorafenib and pembrolizumab. Progression-free survival will be the primary endpoint. PFS is defined from the start of treatment (day 1 of cycle 1) to the first observation of disease progression or death whichever comes first. The patients are alive and disease progression is not observed, PFS is censored at the date of the latest disease assessment or clinical visit. 63 patients are planned to enroll to have 80% power to detect improvement of median PFS from 1.9 months (CORRECT trial, the historical control, the null hypothesis) to 2.85 months (the alternative hypothesis). The type I error rate using this design will be 0.1. The planned accrual time is 2 years and the additional follow-up time from the end of accrual is 6 months.

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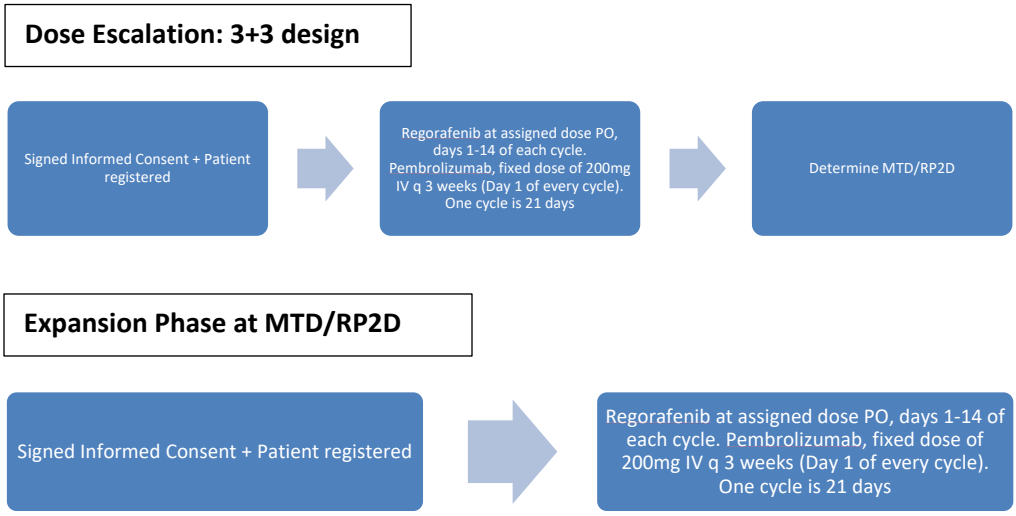
List of abbreviations

ADL	Activities of Daily Living
ALT	Alanine aminotransferase
Ang	Angiopoietin
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	*bis in die*, twice daily
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BUN	Blood Urea Nitrogen
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CR	Complete Response
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CTCAE	Common Terminology Criteria for Adverse Events
DCE	Dynamic Contrast Enhanced
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERK	Extracellular Signal-regulated Kinases
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FLT3	FMS-like Tyrosine Kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular Carcinoma
HFSR	Hand-foot-skin reaction
IB	Investigator's Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate Release
IRB	Institutional Review Board

MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
NM	Nano molar
NYHA	New York Heart Association
PD	Progressive Disease
PDGFR-β	Platelet Derived Growth Factor Receptor-beta
PFS	Progression free survival
PO	*per oris*, oral
PR	Partial Response
PS	Performance Status
PTT	Partial thromboplastin time
QD	*quaque die*, once daily
QOD	*quaque altere die,* every other day
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria for Solid Tumors
RET	Rearranged during transfection
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SD	Stable Disease
SUSARs	Suspected Unexpected Serious Adverse Reactions
TIE2	Tyrosine kinase with Immunoglobulin and Epidermal Growth Factor (EGF) homology domain 2
TK	Tyrosine Kinase
TTP	Time to Progression
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

Study Schema



1. Introduction

Despite significant improvement in the survival of the patients with colorectal cancer (CRC) over the past decade, almost all patients with metastatic disease will succumb to the disease, resulting is a significant number of deaths every year. While the dynamic nature of the tumor and evolution of resistant clones make tumor cell directed therapy in the late stages of the disease more difficult, treatments focusing on microenvironment such as immune therapy and antiangiogenic therapy have substantial chance of success. Despite the success of immune checkpoint blockade in many tumor types, monoclonal antibodies against PD1 and PD-L1 are mostly efficacious in MSI high colorectal cancers with very little efficacy in MSS tumors. Therefore development of treatment strategies for MSS colorectal cancers and improving efficacy in MSI high tumors is an unmet need.

We propose to combine regorafenib (an established agent in advanced setting) and a PD1 inhibitor (pembrolizumab) in colorectal cancer patients in 3rd and 4th line setting. Using a phase I/II design, we will first enroll 3-18 patient on phase I to find the recommended dose for phase II. We will then accrue patients to the phase II portion of the trial with the primary efficacy endpoint of PFS. An extensive biomarker analysis, liquid biopsies and tumor tissue, is planned to identify the population who would most benefit from this combination.

1.1 Background

Colorectal cancer (CRC) remains a major cause of cancer mortality in US and across the world.[1] Despite significant improvement in the survival of the patients with colorectal cancer over the past decade, almost all patients with metastatic disease will succumb to the disease, resulting is a significant number of deaths every year. Regorafenib and TAS-102 are currently approved for treatment of refractory disease and ongoing clinical trials evaluating many different strategies with the goal of improving outcome in this patient population.[2,3]

While the dynamic nature of the tumor and evolution of resistant clones make tumor cell directed therapy in the late stages of the disease more difficult, treatments focusing on microenvironment such as immune therapy and antiangiogenic therapy have substantial chance of success. Despite the success of immune checkpoint blockade in many tumor types, monoclonal antibodies against PD1 and PD-L1 are mostly efficacious in MSI (Micro Satellite Instable) colorectal cancers with very little efficacy in MSS (Micro Satellite Stable) tumors. Therefore, development of treatment strategies for MSS colorectal cancers in parallel to MSI tumors is an unmet need.

Immune check point inhibition is now FDA approved for MSI tumors in advanced setting, while MSS tumors have not shown to be susceptible to immune check point inhibition. Combination therapy may alter the tumor microenvironment and render MSS tumors vulnerable to immune check point inhibition. Hypoxia is a characteristic feature of solid tumors including colorectal cancers and antiangiogenic therapy is effective in advanced patient population. Existing data suggests several mechanisms for immune escape under hypoxia. These include, impaired lymphocyte migration to the tumors and antigen recognition, as well as resistance of tumor cells to lysis in the hypoxic media. The abnormal nature of tumor vasculature and high levels of HIF-1α interferes with lymphocyte trafficking within the tumor mass through down regulation of ICAM-1/2, VCAM-1, and CD34 on endothelial cells.[4] Antiangiogenic therapy has been shown to increase the leukocyte infiltration in the tumor.[5,6] Furthermore HIF-1α can regulate Tcell function through reducing the levels of cytokines[7] and VEGF and PlGF can also regulate the function of dendritic cells.[8-10] Additionally, preclinical models show synergistic activity between PD1 and VEGFR2 blockade in colorectal cancer.[11] Additionally MAPK is an active pathway in colorectal cancer tumorigenesis and progression and reversal of immune evasion by MPRK pathway inhibitor can result in PDL1 induction. Regorafenib is a multi-kinase inhibitor with significant effect on angiogenesis and MAPK pathways.

MSI high tumors are immunogenic and addition of regorafenib to PD1 may enhance the efficacy of PD1 alone. MSS tumors are dependent on angiogenesis, have higher rates of changed copy numbers, and are non-immunogenic. Analysis of a subset of CORRECT trial population suggests that high risk patients, as defined by Marisa classification, have a higher degree of benefit from regorafenib, suggesting that regorafenib may affect other oncogenic pathways in these patients.[12] We are optimistic that this combination may provide a unique treatment option for patients with MSS.

We propose to combine regorafenib and PD1 (pembrolizumab) in colorectal cancer patients in 3rd and 4th line setting. Using a phase I/II design, we will first enroll 3-18 patient on phase I to find the recommended dose for phase II. We will then accrue patients to the phase II portion of the trial with the primary efficacy endpoint of PFS. An extensive biomarker analysis, liquid biopsies and tumor tissue, is planned to identify the population who would most benefit from this combination.

Four patients on dose level 1: 80mg were reviewed by the Phase I DLT Committee. One patient was deemed inevaluable for DLT and was replaced. Three patients were evaluable with no DLT. The trial was recommended to proceed to accrue three patients to dose level 2: 120mg. All three patients at this dose level had either grade 2 or grade 3 rash which required a dose reduction at either cycle 2 or 3. It was determined that the dose level 2: 120mg would

be challenging due to its overall tolerability; therefore, dose level 1: 80mg was recommended to expand and enroll additional three patients for a total of 6 patients to be reviewed.

1.2 Rationale of the study

Although preclinical models for combination kinase inhibitors and immune check point inhibitors are lacking in colorectal cancer, functionality of the pathway is similar in different tumor types. We hypothesize that the hypoxic nature of colorectal tumors and dependence on MAPK pathway results in immune evasion and promotes immune tolerance making immune therapy unsuccessful and that inhibition of angiogenesis and MAPK inhibition will induce intra-tumoral changes and alters these cancers to be more susceptible to immune therapy. Priming these tumors with anti-angiogenic therapy modifies tumor microenvironment and improves trafficking of lymphocytes to the tumor site rendering tumors susceptible to checkpoint blockade. Regorafenib has single agent activity in colorectal cancer and its multikinase inhibitory effect will potentially affect other activated pathways in these patients. Additionally, TKIs can affect the tumor microenvironment through their interactions with MDSC and Tregs[13] and may also alter the expression of MHC class I and II and enhance the immunogenic properties of the tumors.[14]

1.3 Correlative Studies

1.3.1 Immune effector cells in peripheral blood

Although tumor infiltrating immune cells are identified as a major determinant of benefit from immunotherapy, circulating immune cells are probably affected by the immune therapy and have the ability to predict response to treatment.

1.3.2 Cell free RNA/DNA analysis

Circulating tumor DNA will be used to assess mutational spectrum of the tumor. Circulating tumor RNA (ctRNA) contains the functionality of the genes that are actually expressed. In addition, ctRNA also provides information about the quantitative expression levels of genes (i.e., the amount of transcription into mRNA). We intend to use RNA expression as a way of assessing MHC expression as well as PD-L1 expression cell free RNA.

1.3.3 SNP analysis

The impact of germ-line variability on drugs efficacy is a promising tool to provide potential predictive markers for drug benefit. VEGF-A rs2010963 is shown to predict benefit from regorafenib.

1.3.4 Tissue correlatives

We will bank tissue for a comprehensive analysis inclusive of archival tissue for NGS for CMS and immune scoring to be done after completion of the study.

1.4 Regorafenib

Regorafenib has potent preclinical antitumor activity and long-lasting anti-angiogenic activity as measured by dynamic contrast enhanced (DCE) – magnetic resonance imaging (MRI) Regorafenib is a small molecule inhibitor of multiple membrane-bound and intracellular kinases involved in normal cellular functions and in pathologic processes such as oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.[15] In *in vitro* biochemical or cellular assays, regorafenib or its major human active metabolites M-2 and M-5 inhibited the activity of RET, VEGFR1, VEGFR2, VEGFR3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, BRAFV600E, SAPK2, PTK5, and Ab1 at concentrations of regorafenib that have been achieved clinically. In *in vivo* models, regorafenib demonstrated anti-angiogenic activity in a rat tumor model, and inhibition of tumor growth as well as anti-metastatic activity in several mouse xenograft models including some for human colorectal carcinoma.

1.4.1 Preclinical

In vivo, regorafenib exhibited anti-angiogenic and anti-proliferative effects in human colon and breast xenografts as demonstrated by a reduction in microvessel area, reduced Ki-67 staining, and reduced pERK1/2 staining in tissue sections from tumor xenografts, and dose-dependent inhibition of growth in multiple xenograft models (breast, colon, renal, NSCLC, melanoma, pancreatic, thyroid, ovarian).[15,16] Immunohistochemical ex-vivo studies with a phospho –specific monoclonocal anti-ERK 1 / 2 antibody demonstrated inhibition of the MAPK pathway five days after treatment with regorafenib in 2 of 3 tumor models examined (MDA-MB 231 and BxPC-3), but not in NSCLC (H460).

In addition, all tested human tumor xenografts (MDA-MB-231, H460, BxPC-3 and Colo-205) demonstrated a significant reduction in new blood vessels by histomorphometry as detected in tumor samples using a murine CD31 antibody.[15] These data suggest that regorafenib can target the tumor cell MAPK pathway (tumor cell survival) and tumor vasculature in some but not all tumors.

1.4.2 Clinical experience

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

At a preplanned second interim analysis, there was a statistically significant survival benefit for regorafenib. The estimated hazard ratio for overall survival was 0.77 (95% confidence interval [CI], 0.64 to 0.94; 1-sided p = .0052). Patients treated with regorafenib had a median

overall survival of 6.4 months, compared with 5.0 months for placebo — a 29% increase in survival. In addition to improved overall survival, progression-free survival was superior; median progression-free survival was 1.9 months (95% CI, 1.88 to 2.14) for regorafenib and 1.7 months (95% CI, 1.68 to 1.74) for placebo. The estimated hazard ratio for progression-free survival was 0.494 (95% CI, 0.419 to 0.582; 1-sided $p< .000001$). There was a substantial difference in disease control rate in the regorafenib and placebo groups (41% vs. 15%; $p= 0.000001$). Regorafenib demonstrated comparable efficacy benefits across patient subgroups analyzed including age, number of mets, number of lines of prior therapy, and kras status.

The most frequent grade 3+ adverse events in the regorafenib group were hand–foot skin reaction (17%), fatigue (15%), diarrhea (8%), hyperbilirubinemia (8%), and hypertension (7%). The efficacy and safety from the CORRECT study supported FDA approval in September 2012.[2]

A second randomized international, double-blind, placebo-controlled study enrolled patients with mCRC whose disease progressed after approved standard therapies was conducted in Asia Pacific (China, Hong Kong, Taiwan, Republic of Korea, and Vietnam). This multicenter phase III study randomly (CONCUR - A placebo Controlled, randomized, double blind Clinical study Using Regorafenib in Asian CRC patients after failure of standard therapies) assigned 136 Asian patients to regorafenib at 160 mg daily and 68 to placebo. The primary endpoint of the study was overall survival. Sixty percent of patients enrolled received previous targeted therapy.

The study met its primary endpoint, with regorafenib demonstrating a median overall survival of 6.3 months for placebo compared to 8.8 months for regorafenib treated patients - 45% reduction in the risk of death compared with placebo ((hazard ratio 0.55, 95% CI 0.40–0.77, one-sided p=0.00016). Adverse events in CONCUR were consistent with the known safety profile of regorafenib in metastatic colorectal cancer.[17]

The efficacy and safety of regorafenib were examined in the Phase III GRID trial in patients with gastrointestinal stromal tumors (GISTs) who had exhausted all other treatment options. The study involved 199 patients with metastatic and/or unresectable GIST that had become resistant to imatinib and sunitinib. Patients were randomized 2:1 to regorafenib (160 mg orally once daily on a 3 weeks on/1 week off cycle) or placebo, plus best supportive care.

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

events associated with regorafenib were hand-foot skin reaction (56.1%), hypertension (48.5%), and diarrhea (40.9%). The efficacy and safety of the GRID study data supported FDA approval February 2013.

1.5 Pembrolizumab

The programmed cell death 1 (PD-1) pathway represents a major immune control switch which may be engaged by tumor cells to overcome active T-cell immune surveillance. Pembrolizumab (MK-3475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and ultimately immune rejection.

1.5.1 Preclinical

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been ~0.1 to 0.3 nM. In addition to interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFNγ), and levels of other cytokines were found to be modulated by Pembrolizumab. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells. Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo.

1.5.2 Clinical experience

The importance of intact functions of immune surveillance in controlling outgrowth of neoplastic transformations has been known for decades.[18] Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells / FoxP3+ regulatory T cells (T regs) correlates with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, and pancreatic cancer, hepatocellular carcinoma (HCC), malignant melanoma (MEL), and renal cell carcinoma (RCC). Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as MEL.[19,20]

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 which has been

shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).[21,22] The structure of murine PD-1 has been resolved.[23]

PD-1 and family members are type I transmembrane glycoproteins containing an IgVariable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains two tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T cell signaling cascade.[22,24-26] The mechanism by which PD-1 down modulates T cell responses is similar to, but distinct from, that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T cells, B cells, T regs, and natural killer cells.[27,28] Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells, as well as subsets of macrophages and dendritic cells.[29] The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types including non-hematopoietic tissues and in various tumors.[18,30,31] Both ligands are type 1 transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 is only detectably-expressed on antigen presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PDL1 serves to dampen unwarranted T cell function in peripheral tissues.[31] Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including RCC, pancreatic carcinoma, HCC, and ovarian carcinoma. Furthermore, PD-1 has been suggested to regulate tumor-specific T cell expansion in patients with MEL.

The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.
Therapeutic studies in mouse models show that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 and anti-mouse PD-L1 have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T cell infiltration into the tumor and the presence of IFN-γ, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and

activation of effector T cell function in vivo. In-house experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models.

2. Study objectives

The overall objective of the study is to assess recommended combination dose, safety and preliminary efficacy, and predictive biomarkers for combination of regorafenib and pembrolizumab.

2.1 Primary objectives:

- The objective of the phase I part of the study is to assess safety of the combination and identification of the recommended dose (RD) for combination therapy. We will employ a 3+ 3 design with expected accrual of 3-18 patients.

- The objective of phase II part of the study is to evaluate preliminary efficacy and tolerability of the combination RD of regorafenib and pembrolizumab.

2.2 Exploratory objectives:

2.2.1 Immune effector cells:

We aim to measure the phenotype of lymphocytes and Myeloid Derived Suppressor Cells (MDSC), in pre and post-treatment blood samples and correlate these with PFS in colorectal cancer patients receiving regorafenib and pembrolizumab.

2.2.2 CtDNA and CtRNA

Changes in quantity, mutational spectrum, and functional genes with outcome.

2.2.3 SNP analysis

Predictive modeling for efficacy.

3. Investigator[s] and other study participants

1-2 other institutions will be invited to join the USC for accrual. USC will update Bayer and Merck once the other sites had agreed to be a site.

4. Study design

A standard 3+3 design will be used to escalate doses of regorafenib in combination with fixed dose pembrolizumab during the phase I part of the study. The primary goal is to identify the recommended dose (RD) of the combination.

The phase II part of the study is an open label single arm study to assess the preliminary efficacy and tolerability of the combination therapy at RD in colorectal cancer patients who had progressed or not tolerated to oxaliplatin and irinotecan based therapies. The primary endpoint is PFS, we assume that combination therapy will result in prolongation of progression free survival by 50% compared to historical PFS with single agent regorafenob. Given that PFS in CORRECT trial was 1.9 mos with type one error of 10%, power of 80% we will need a sample size of 63 pts. The expected PFS in the treatment group will be 2.85 months. The accrual is expected to happen over 24 months. Tolerability will be assessed by median duration of treatment; combination is defined to be tolerable if the median duration of treatment is at least 20% better than CORRECT data (from 1.7 months to 2.0 months).

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

1. Patients who provided written informed consent to be subjects in this trial
2. Patients at least 18 years of age on the day of providing consent
3. Patients with histologically or cytologically confirmed advanced or metastatic colorectal cancer who had failed or are intolerant of oxaliplatin, irinotecan, and 5-FU. Patients with MSI colorectal cancer are not candidate for treatment on this trial.
4. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1within 7 days of start of treatment
5. Patients capable of taking oral medication
6. Patients with evaluable or measurable lesions as per RECIST version 1.1
7. Patients with adequate organ function at the time of enrollment as defined below:

    - Neutrophil count ≥1200/mm^3
    - Platelet count ≥7.5 × 10^4/mm^3
    - Hgb > 9.0g/dL (transfusion >2 weeks before testing permitted)
    - Aspartate transaminase (AST), alanine transaminase (ALT) ≤2.5-times the upper limit of normal (≤5-times in patients with liver metastasis)
      Total bilirubin ≤1.5-times the upper limit of normal
    - Creatinine ≤1.5-times the upper limit of normal
    - Lipase ≤ 1.5 x the ULN
    - International normalized ratio (INR) ≤ 1.5 x ULN and partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN unless receiving treatment with therapeutic anticoagulation. Patients being treated with anticoagulant, e.g. heparin, will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be

performed until INR and PTT are stable based on a pre-dose measurement as defined by the local standard of care.

8. In women with the potential for pregnancy (including patients with amenorrhea due to medical reasons, such as chemical menopause), after consenting to the study, the patient must agree to take contraception from enrollment and for at least 23 weeks after taking the final dose of the investigational drug (a period of 30 days [ovulation cycle] is added to five times the elimination half-time of I/O agent). Women with the potential for pregnancy include those who have begun menstruation, who have not undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy, and who have not gone through menopause. Menopause is defined as the consecutive absence of menstrual periods for ≥12 months. Total abstinence is an acceptable mode of contraception.
9. In the case of men, the patient must agree after consenting to the study to take contraception from enrollment and for at least 31 weeks after taking the final dose of the investigational drug (a period of 90 days [the spermatogenesis cycle] is added to five times the elimination half-time of I/O agent. Total abstinence is an acceptable mode of contraception.

5.1.2 Exclusion criteria

1. Patients who have undergone systemic chemotherapy, radiotherapy, surgery, or hormone therapy <2 weeks before enrollment, also see exclusion #8.

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.
   Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.

2. Patients with a history of taking regorafenib or immune check point inhibitors.
3. Patients with hypertension that is difficult to control (systolic blood pressure ≥150 mmHg and diastolic blood pressure ≥90 mmHg) despite treatment with several hypotensive agents
4. Patients with acute coronary syndrome (including myocardial infarction and unstable angina), and with a history of coronary angioplasty or stent placement performed within 6 months before enrollment
5. Patients with a large amount of pleural effusion or ascites requiring more than weekly drainage.
6. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
7. Patients with a ≥grade 3 active infection according to NCI-CTCAE version 5.0
8. Patients with symptomatic brain metastasis (1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease).
9. Patients with partial or complete gastrointestinal obstruction
10. Patients with interstitial lung disease with symptoms or signs of activity

11. Patients who test positive for either anti-HIV-1 antibodies, anti-HIV-2 antibodies, anti-HTLV-1 antibodies, hepatitis B surface antigen (HBsAg), or anti-hepatitis C virus (HCV) antibodies*. (please use prior history for reference, testing is not required unless deemed necessary by the investigator)

    *Patients who test positive for either anti-HBs or anti-HBc antibodies, and those who have HBV-DNA measurements greater than the detection sensitivity will also be excluded.

12. Patients with concurrent autoimmune disease, or a history of chronic or recurrent autoimmune disease
13. Patients who require systemic corticosteroids (excluding temporary usage for tests, prophylactic administration for allergic reactions, or to alleviate swelling associated with radiotherapy) or immunosuppressants, or who have received such a therapy <14 days before enrollment in the present study
14. Patients with a history or findings of ≥grade III congestive heart failure according to the New York Heart Association functional classification
15. Patients with a seizure disorder who require pharmacotherapy
16. Persistent proteinuria > 3.5 g/24 hours measured by urine protein-creatinine ratio from a random urine sample (≥Grade 3, NCI-CTCAE v 5.0).
17. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
18. Major surgical procedure or significant traumatic injury within 28 days before start of study medication.
19. Non-healing wound, non-healing ulcer, or non-healing bone fracture
20. Patients with evidence or history of any bleeding diathesis, irrespective of severity
21. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study medication
22. Women who are pregnant or breastfeeding, or with the potential for pregnancy unwilling to undergo contraception.
23. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
24. Has an active infection requiring systemic therapy.
25. MSI colorectal cancers are not candidate for enrollment on this trial.

5.1.3 Excluded therapies and medications, previous and concomitant

- Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than study treatment (regorafenib and pembrolizumab).
- Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 2 weeks of trial entry (signing of the informed consent form is OK in the washout period).

- Major surgical procedure, open biopsy, or significant traumatic injury within 28 days before start of study medication.
- Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids. However, prophylactic anticoagulation as described below is allowed:
    - Low dose warfarin (1 mg orally, once daily) with PT-INR ≤ 1.5 x ULN is permitted. Infrequent bleeding or elevations in PT-INR have been reported in some subjects taking warfarin while on regorafenib therapy. Therefore, subjects taking concomitant warfarin should be monitored regularly for changes in PT, PT-INR or clinical bleeding episodes.
    - Low dose aspirin (≤ 100 mg daily).
    - Prophylactic doses of heparin.
- During the study, strong CYP3A4 inhibitors (eg, clarithromycin, grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole) or strong CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort) are not permitted.
- Live vaccines administered <30 days before the initiation of treatment with the investigational drug and during the trial period. Examples of live vaccines are as follows (however, the list is not exhaustive): measles, mumps, rubella, chicken pox/herpes zoster, yellow fever, rabies*, BCG for tuberculosis, and typhoid vaccines*. Inoculation with inactive vaccines (e.g., seasonal influenza vaccines) is permitted; however, the intranasal administration of attenuated influenza vaccines (e.g., Flu-Mist®) is prohibited.
- Systemic glucocorticoids for purposes other than treating symptoms caused by notable events with a suspected immunological etiology. Upon deliberation with the PI, the use of corticosteroids may be permitted according to the physiological dose required to alleviate symptoms (e.g., to control symptoms of acute asthma).

5.2 Withdrawal of subjects from study

5.2.1 Withdrawal

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

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Pregnancy. Pregnancy will be reported with the same time lines as SAE. (Note: subjects who have been withdrawn from treatment with study drug because of

pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)

- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Subject is lost to follow-up.

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

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

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

In all cases, the reason for withdrawal (progression vs. toxicity vs. patient’s choice) must be recorded in the CRF and in the subject's medical records.

5.2.2 Screen Failures/Dropouts

A subject who discontinues study participation prematurely for any reason is defined as a “dropout” if the subject has already been administered at least one dose of study drug.

A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of “dropout” (see above) is regarded a “screening failure”.

5.2.3 Replacement

During phase I, for subject who dropout due to reasons other than toxicity, we will replace that subject with another subject. These subjects will be followed for PFS.

6. Treatment[s]

6.1 Treatments to be administered

Drug	Dose/Potency	Dose Frequency	Route of Administration
Pembrolizumab	200mg	Q3weeks	IV
Regorafenib	Per dose schedule (phase I) RD (Phase II)	Daily days 1-14 of 21 day cycles	PO

Regorafenib starting dose, dose level 1	80mg	Days 1-14
Regorafenib dose level 2	120mg	Days 1-14

6.2 Treatment assignment

This is an open label phase I/II trial. Patients will receive regorafenib at escalating doses or RD for 14 days and pembrolizumab q3weeks.

All patients (phase I and II) will be seen on a weekly basis for the first 8 weeks for toxicity checks using CTCAE and will have response assessment with CT scan every 8 weeks.

Rules for dose escalation, dose expansion, and termination of escalation are given below.

Dose Limiting Toxicity (DLT)

As a general rule, DLT includes the observation of any of the side effects listed below during the DLT evaluation period and will ultimately be determined upon deliberation between subsites and the principal investigator of the trial. The principal investigator and the study team will have weekly safety meetings and conference calls during phase I period. Monthly meetings will be held monthly for the first 20 patients on phase II and if no unexpected signal of toxicity is observed the frequency of the meetings will be annual to correspond with the reporting period to Data and Safety Monitoring Committee at USC (DSMC). Furthermore, the opinion of the DSMC at USC can be sought as required on an ad hoc basis.

• Hematotoxicity:

–Persistent grade 4 neutropenia lasting ≥7 days;

–neutrophil count of <1000/mm3 with a single temperature of >38.3°C or a sustained temperature of ≥38.0°C for more than one hour.

–Grade 4 thrombopenia or thrombopenia associated with a hemorrhage requiring platelet transfusion.

- Grade 3 thrombocytopenia with bleeding.
- Grade 4 anemia.

• Non-hematotoxicity, please see separate liver and non-liver related information below.

- Liver related toxicities
  - ALT/AST increases 5-8 X ULN with concomitant bilirubin increase < 2 X

ULN not resolving to < 5 X ULN within 7 days
- ALT/AST increases 5-8 X ULN with concomitant bilirubin increase > 2 X ULN
- ALT/AST increases > 8 X ULN regardless of concomitant bilirubin increase
- Bilirubin increase > 3 X ULN not resolving to baseline within 7 days

- Grade ≥ 3 non-liver related with the following specifications:
  - ≥Grade 3 diarrhea, nausea, vomiting, and loss of appetite for ≥5 consecutive days (despite supportive therapy);
  - ≥Grade 3 fatigue for ≥7 consecutive days;
  - ≥Grade 3 electrolyte imbalance for ≥7 consecutive days (despite supportive therapy);
  - Grade 3 dermatologic toxicity (HFSR and non-life threatening events) for ≥7 consecutive days;
  - Grade 4 dermatologic toxicity of any duration;
  - ≥Grade 3 immune-related adverse events lasting for ≥8 consecutive days despite steroid therapy.

• Combination therapy:
When 70% of the planned regorafenib dose cannot be administered because of toxicity other than DLT during the DLT evaluation period it will be considered DLT. This criteria is in place to ensure the combination can be delivered safely.

Maximum Tolerated Dose (MTD)

During the Phase I portion, the maximum tolerated dose (MTD) is defined as the highest dose tested in which none or only one patient experienced DLT, when at least 6 patients were treated at that dose and are evaluable for toxicity. The MTD is one dose level below the lowest dose tested in which 2 or more patients experienced DLT, unless dose level 3 is established as the MTD. At least 6 patients will be treated at the MTD.

Numbers of Patients and Rules for Dose Escalation

Rules for dose escalation and expansion in cohorts of patients are based on DLT occurring in each patient's first cycle of treatment (21 days without delay or interruption). The standard 3+3 rules will be used. Three patients will be treated at each new dose level. If 0/3 patients experience DLT, 3 patients will be treated at the next dose level. If DLT is experienced in exactly 1/3 patients, 3 more patients (for a total of 6) will be treated at that dose level. If no additional DLT is observed at the expanded dose level (i.e. 1/6 with DLT), the dose will be escalated. Escalation will terminate as soon as two or more patients experience any DLT at a given dose level. The Phase I trial will be closed when 6 patients have been treated at the next lower

dose level, and at most 1/6 patients experience DLT. If more than 1/6 patients experience DLT, the next lower dose will be expanded.

All patients who have not experienced any DLT must be observed for a minimum of 3 weeks after the start of the first cycle, before the dose level is escalated.

There will be no dose escalation within a patient.

Toxicities of interest for Pembrolizumab

- Pneumonitis
- Hepatitis
- Colitis
- Hypothyroidism
- Hypophysitis

Miscellaneous

For toxicities of interest for pembrolizumab and unexpected drug-related toxicity (even at lower grade) is seen more frequently than expected, this toxicity will be declared as unacceptable and a dose modification amendment will be made to the study necessitating dose reduction for that toxicity after thorough consultation between the investigator and the sponsor.

For certain toxicities such as laboratory assessments without a clear clinical correlation (e.g. lipase increase without signs of a clinical pancreatitis), a discussion between the investigator and the sponsor may take place if that adverse event should be considered unacceptable and a dose modification amendment will be made to the study necessitating dose reduction for that toxicity.

6.2.1 Regorafenib

Regorafenib tablets will be packaged in high density polyethylene bottles with a white child resistant closure and induction seal. Each bottle includes 30 tablets (for randomized studies) or 28 tablets (for open-label studies) and a 3-gram desiccant. The bottles will have a label affixed containing study identification, product identification, and quantity of tablets. Once the drug has been received it must be kept in a secure, dry location. Study drug must be stored in its original bottle at a temperature not above 25°C (77°F).

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

6.2.2 Pembrolizumab

Pembrolizumab is provided as a white to off white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only. Pembrolizumab powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. Pembrolizumab is formulated with L-histidine as buffering agent, polysorbate 80 as surfactant, sucrose as stabilizer/tonicity modifier, and hydrochloric acid (HCl) and/or sodium hydroxide (NaOH) for pH adjustment (if necessary). The drug

product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2°C - 8°C).
The product after reconstitution with sterile water for injection and the liquid drug product is a clear to opalescent solution which may contain extraneous and proteinaceous particulates. The reconstituted product and liquid product is intended for IV administration. The reconstituted drug product solution and liquid drug product can be further diluted with normal saline in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered. If not used immediately, vials and/or IV bags may be stored at 2-8 °C for up to a cumulative time of 20 hours. If refrigerated, the vials and/or IV bags should be allowed to equilibrate to room temperature prior to subsequent use. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of reconstituted drug product solution and liquid drug product in vials, room temperature storage of infusion solution in the IV bag and the duration of infusion.
For each individual trial, clinical supplies are to be stored in accordance with specific instructions on the label.
Information on dosage and administration for any particular study appears in the protocol for that study, including information on compatibility of pembrolizumab and IV infusion bags and components, and the investigator should refer to the protocol for exact details.

Important Safety Considerations

Pembrolizumab is a humanized monoclonal Ab. Thus far, no serious infusion reactions have been reported however, patients should be closely monitored for potential AEs during antibody infusion and potential AEs throughout the study. In the event that a subject experiences an allergic reaction to pembrolizumab, treatment (i.e., vasopressors, H2-blockers, antihistamines, H1-blockers, steroids) should be administered, as appropriate, and prophylaxis should be considered (please see the IB).[32]

6.3 Study Treatment

Please see details on section 6.1.

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

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

6.3.1 Dose Modification Levels

The starting dose of regorafenib is the RD. Study medication will be administered on a 2 weeks on/1week off schedule [2 weeks out of every 3].

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

The modifications of regorafenib will follow the following predefined dose levels:		
Dose level 2	120 mg po qd	Three 40-mg tablets of regorafenib
Dose level 1	80 mg po qd	Two 40-mg tablets of regorafenib

q.d. = quaque die (once daily); q.o.d. = quaque altere die (every other day)

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

In the case of two or more toxicities of the same grade, the investigator may dose reduce according to that deemed most causally related to study treatment.For Grade 3 toxicity it is acceptable to re-challenge with same dose level at discretion of investigator if toxicity resolved to baseline or lesser grade with medical management within 7 days.

For second occurrence of the same Grade 3 toxicity dose can be reduced to 80mg q.o.d or permanently discontinue at discretion of treating investigator and the rest of the study treatment may be continued. If a dose reduction has been performed, intra-subject dose re-escalation can be considered at the discretion of the treating physician provided that the toxicity(ies) has resolved to baseline.

Tables 6-1, 6-3, and 6-4 outline dose adjustments for toxicities related to regorafenib. Dose adjustment for liver function abnormalities is discussed in table 6-5.

Table 6-1: Recommended dose modification for toxicities except hand-foot-skin reaction, hypertension and ALT/AST/bilirubin

NCI-CTCAE v5.0[a]	Dose Interruption	Dose Modification[b]	Dose for Subsequent Cycles
Grade 0-2	Treat on time	No change	No change
Grade 3	Delay until ≤ Grade 2[c]	Reduce by 1 dose level	If toxicity remains < Grade 2, dose re-escalation can be considered at the discretion of the treating investigator. If dose is re-escalated and toxicity (≥ Grade 3) recurs, institute permanent dose reduction.
Grade 4	Delay until ≤ Grade 2[c]	Reduce by 1 dose level. Permanent discontinuation can be considered at treating investigator's discretion.	

a. NCI-CTCAE = National Cancer Institute - Common Terminology Criteria for Adverse Events, version 5.0
b. Excludes alopecia, non-refractory nausea/vomiting, non-refractory hypersensitivity and nonclinical and asymptomatic laboratory abnormalities.
c. If no recovery after a 4 week delay*, treatment should be permanently discontinued unless subject is deriving clinical benefit.

The table above outlines dose adjustments for hematologic and non-hematologic toxicities related to regorafenib except HFSR and hypertension.

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

Table 6-2: Grading for Hand-Foot-Skin-Reaction

	Grade 1	Grade 2	Grade 3
NCI-CTCAE v5.0 Palmar-plantar erythrodysesthesia syndromea	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters bleeding, edema, or hyperkeratosis) with pain	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain
Further description / examples of skin changes	Numbness, dysesthesia / paresthesia tingling, painless swelling, or erythema of the hands and/or feet	Painful erythema and swelling of the hands and/or feet	Moist desquamation, ulceration, blistering, or severe pain of the hands and/or feet
Effect on activities	Does not disrupt normal activities	Limiting instrumental activities of daily life (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money)	Limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications) and not bedridden
a. Palmer-planter erythrodysesthesia syndrome is a disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of hands or the soles of the feet.			

Table 6.3 Recommended dose modification for hand-foot-skin reaction (HFSR)		
Grade of event (NCI-CTCAE v5.0)	**Occurrence**	**Suggested Dose Modification**
Grade 1	Any	Maintain dose level and immediately institute supportive measures for symptomatic relief
Grade 2	1st occurrence	Consider decreasing dose by one dose level and immediately institute supportive measures. If no improvement, interrupt therapy for a minimum of 7 days, until toxicity resolves to Grade 0-1 [b, c]
	No improvement within 7 days or 2nd occurrence	Interrupt therapy until toxicity resolves to Grade 0-1.[c] When resuming treatment, treat at reduced dose level [b] If dose reduced from the 1st occurrence then discontinue therapy.
	3rd occurrence	Discontinue therapy
	4th occurrence	Discontinue therapy
Grade 3	1st occurrence	Institute supportive measures immediately. Interrupt therapy for a minimum of 7 days until toxicity resolves to Grade 0-1. [c] When resuming treatment, decrease dose by one dose level. [b, d]
	2nd occurrence	Discontinue therapy
	3rd occurrence	Discontinue treatment permanently.

a. More conservative management is allowed if judged medically appropriate by the investigator.
b. If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.
c. If there is no recovery after a 4-week delay, treatment with regorafenib will be discontinued permanently.
d. Subjects requiring > 1 dose reductions should go off protocol therapy.
e. The maximum daily dose is 80 mg. If reduction required resulting in a dose of less than 80mg qod of regorafenib, then regorafenib will be permanently discontinued.

Specific guidance for skin and subcutaneous disorders other than HFSR (includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, exfoliative rash, pruritus, eczema, dermatitis)		
Event	**Regorafenib**	**Pembrolizumab**
G2	• No modifications	• Consider withholding for persistent symptoms • Restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion • Consider discontinuation if NO resolution ≤ 12 weeks of last infusion [1]

G3	• Hold until recovery to ≤ G2 and restart at same dose level or reduce 1 dose level [a] (at the investigator's discretion) • 1st + 2nd re-appearance: Hold until recovery to ≤ G2 and reduce 1 dose level [a] (at the investigator's discretion) • 3rd re-appearance: Discontinue	• Hold and restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion • Hold and discontinue if NO resolution ≤ 12 weeks of last infusion [b]
G4 (when applicable)	• Hold until recovery to ≤ G2 and reduce 1 dose level [a] • 1st re-appearance: Discontinue	• Discontinue [b]

[1] If toxicity returns to Grade 0-1 after dose reduction, dose re-escalation is permitted at the discretion of the investigator if subject has completed one cycle at reduced dose without recurrence of event.

a: If reductions are required resulting in a dose of less than 80 mg q.o.d. of regorafenib, then regorafenib will be permanently discontinued. For grade 3, patient could stay on regorafenib for the first appearance, or hold until resolved to grade 2 or less, restart at the same dose level or lower after discussion between investigator and study chair.

b: after consultation with study chair, if toxicity considered at least possibly related to pembrolizumab.

If reduction required resulting in a dose of less than 80mg qod of regorafenib, then regorafenib will be permanently discontinued.

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

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

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

Control of calluses

Before initiating treatment with regorafenib:

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

During regorafenib treatment:

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

Use of creams

- Non-urea based creams may be applied liberally.

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

Tender areas should be protected as follows:

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

Hypertension

Hypertension is a known AE associated with regorafenib treatment. Subject will have their blood pressure measured at least weekly at the study site during the first 6 weeks of treatment. If additional blood pressure measurements are done outside the study site, and the blood pressure is > 140 mm Hg systolic or > 90 mm Hg diastolic (NCI CTCAE v5.0), then the subject must contact study personnel. The management of hypertension, including the choice of antihypertensive medication, will be performed according to local standards and to the usual practice of the investigator. Every effort should be made to control blood pressure by medical means other than study drug dose modification. If necessary, Table 6-4 outlines suggested dose reductions.

Table 6-4: Management of Treatment-Emergent Hypertension

Grade (CTCAE v5.0)	Antihypertensive Therapy	Regorafenib Dosing
1 Prehypertension (systolic BP 120 - 139 mmHg or diastolic BP 80 - 89 mmHg)	None	• Continue regorafenib • Consider increasing blood pressure (BP) monitoring
2 Systolic BP 140 - 159 mmHg or diastolic BP 90 - 99 mmHg, OR Symptomatic increase by > 20 mmHg (diastolic) if previously within normal limits	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: If BP previously within normal limits, start anti-hypertensive monotherapy If patient already on anti-hypertensive medication, titrate up the dose.	• Continue regorafenib • If symptomatic, hold regorafenib until symptoms resolve AND diastolic BP ≤ 90 mm Hg[a]. When regorafenib is restarted, continue at the same dose level.
3 Systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg OR More than one drug or more intensive therapy than previously used indicated	Treat with the aim to achieve diastolic BP ≤ 90 mm Hg: Start anti-hypertensive medication **AND/OR** Increase current anti-hypertensive medication **AND/OR** Add additional anti-hypertensive medications.	• Hold regorafenib until diastolic BP ≤ 90 mm Hg, and if symptomatic, until symptoms resolve.[a] • When regorafenib is restarted, continue at the same dose level. • If BP is not controlled with the addition of new or more intensive therapy, reduce by 1 dose level.[b] • If Grade 3 hypertension recurs despite dose reduction and antihypertensive therapy, discontinue therapy
4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis)	Per institutional guidelines	Discontinue therapy

a. Patients requiring a delay of >4 weeks should go off protocol therapy
b. If BP remains controlled for at least one cycle, dose re-escalation permitted per investigator's discretion.
c. Patients requiring >1 dose reductions should go off protocol therapy. If reduction required resulting in a dose of less than 80mg q.o.d of regorafenib, then regorafenib will be permanently discontinued.

Liver Function Abnormalities

For patients with observed worsening of serum liver tests considered related to regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in Table 6-5 should be followed.

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

Table 6.5: Dose Modification/interruption for LIVER toxicity

General instructions:

If any of below outlined events will occur: Monitor liver function tests weekly or more frequently until recovery to baseline or stabilization.

If reduction required resulting in a dose of less than 80mg qod of regorafenib, then regorafenib will be permanently discontinued.

For any G3/4 increases in ALT/AST or bilirubin:

If the increases are primarily seen under ongoing regorafenib treatment (e.g. last pembrolizumab infusion was given one week before):

Closely monitor for potential de-challenge, i.e. whether a decrease in ALT/AST and/or bilirubin values is seen within 3 days of regorafenib interruption.

In case no such decrease is seen and/or a further deterioration in liver function is seen: Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper

If immune-related hepatitis is suspected: Directly follow guidance provided in Table 6-6

EVENT	Regorafenib	Pembrolizumab
If ALT/AST≤ 2 x ULN at baseline AND > 5 x ULN OR ALT/AST > 2 x ULN at baseline and 3 fold increase from Baseline BUT NOT EXCEEDING 8 X ULN	Assess according to guidance given in Table 6–6 • Hold until recovery to ≤ G2 or baseline, then reduce 1 dose level • 1st re-appearance: discontinue	Hold and assess + decide on potential restart according to guidance given in Table 6–6
ALT or AST > 5 x ULN accompanied by a thyperbilirubinemia ≥ 2 x ULN or >50% increase from total bilirubin level from baseline	Discontinue and assess according to guidance given in Table 6-6 A patient with Gilbert's syndrome should be managed according to observed elevation of ALT and/or AST if the observed bilirubin increase is below actual increased baseline bilirubin value	Hold and assess + decide on potential restart according to guidance given in Table 6–6
t-bilirubin >2 mg/dL and ALT/AST ≤5 x ULN	No modifications	Hold and assess + decide on potential restart according to guidance given in Table 6–6
Any t-bilirubin > 3.0 mg/dL irrespective of ALT/AST values	Assess according to guidance given in Table 6–6	Hold and assess + decide on potential restart according to guidance given in Table 6–6

	• Hold until recovery to ≤ G1 or baseline, then reduce 1 dose level • 1st re-appearance: Discontinue	
AST and / or ALT > 20 x ULN	Discontinue and assess according to guidance given in Table 6–6	Discontinue and assess according to guidance given in Table 6–6

Table 6.6: Guidance on assessment and further dosing following occurrence of hepatic events of clinical interest

Assessment procedure to be applied

- Notification of Bayer and Merck within 24 hours via SAE report
- Obtain a work-up for hepatitis, including hepatitis A, B,C, D, E, EBV (Epstein-Barr virus), CMV (cytomegalovirus)
- Assess for ingestion of drugs/supplements with hepatotoxic potential and alcohol ingestion
- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy
- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as
- chest X-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be
- started
- If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional
- radiologist should be obtained to see if the obstruction may be relieved
- A careful review of drugs, including herbal and alternative medications should be obtained

Immune-related hepatitis due to study treatment should be suspected if any of the following is seen (Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out):

- AST or ALT baseline values are less than 2×ULN, and AST or ALT laboratory values increase to ≥5×ULN
- Among patients with baseline ALT or AST ≥2×ULN, levels increase to >3× the baseline level
- AST/ALT >500 U/L regardless of baseline level
- Among patients with baseline Tbil levels <1.5 mg/dL: a value of >2.0 mg/dL
- Total bilirubin >3.0 mg/dL regardless of baseline level management
- Interrupt study treatment and alert Bayer and Merck
- Start i.v. corticosteroid (methylprednisolone 125 mg or equivalent) followed by oral corticosteroid
- Monitor with weekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR.

If symptoms and laboratory tests resolve to Grade ≤1 or baseline (if abnormal at baseline), taper steroids over 28 days. Study treatment may be restarted after steroid treatment has been tapered to prednisone ≤10 mg/day (or equivalent dose of another agent).

If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks, or patients show evidence of decompensation treatment must be permanently discontinued.

For toxicity management guidelines for pembrolizumab please refer to appendix 2, section 16.2.

Prevention/management strategies for diarrhea

Diarrhea can be a common side effect of regorafenib. The preventive/management strategies for diarrhea should be consistent with local standards (e.g., anti-diarrheals and optimized hydration status).

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

Table 6.7: General instructions for management of lower gastrointestinal toxicity:

- Monitor all patients for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and bowel perforation (i.e. peritoneal signs and ileus)
- For diarrhea G1 and G2:
  - oral fluids, loperamide, avoid high fibre/lactose diet
- For diarrhea G2 (> 7 days) or higher, please consider per local institutional guidelines:
  - Blood tests (e.g. hematology and general chemistry including liver function tests (AST, ALT, Bilirubin))
  - Stool (e.g. culture, Clostridium difficile, cytomegalovirus (CMV) or other viral etiology, ova and parasite)
  - GI consultation and Imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy)
  - Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper upon AE improving to ≤ G1 and continue to taper over at least 4 weeks
- For severe and life-threatening diarrhea and/or immune-related colitis:
  - Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance
  - Fluid and electrolytes should be administered via i.v. infusion.
  - Urgent GI consultation and Imaging (e.g., CT scan of abdomen and pelvis and GI endoscopy with biopsy)
  - i.v. corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids

Event	Regorafenib	Pembrolizumab
Diarrhea G1; <4 stools/day over baseline	No modifications	No modifications
Diarrhea G2; 4-6 stools/day over baseline	No modifications, BUT if diarrhea G2 persistent (not back to ≤ G1 in 7 days), hold regorafenib until back to ≤ G1. Restart at same dose level or reduce 1 dose level[a] (at the investigator's discretion).	No modifications, BUT if diarrhea G2 persistent (not back to ≤ G1 in 7 days), withhold until back to ≤ G1; Restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion and corticosteroid has been tapered,

Diarrhea G3; ≥7 stools/day over baseline	G3: Hold regorafenib until back to ≤ G1. Restart at same dose level or reduce 1 dose level[a] (at the investigator's discretion)	G3: Withhold; restart at same dose if resolution to ≤ G1 or baseline ≤ 12 weeks of last infusion and corticosteroid has been tapered Recurrent G3: permanently discontinue
Diarrhea G4; Life-threatening consequences	G4: Interrupt until ≤ G1. Restart at one dose level below[a]	G4: Permanently discontinue

AE= adverse event; ALT= alanine aminotransferase; AST= aspartate aminotransferase; CMV= cytomegalovirus; CT= computed tomography; G1/2/3/4= grade 1/2/3/4; GI= gastrointestinal; i.v.= intravenous(ly); irAE= immune-related adverse event.

a: If reduction required resulting in a dose of less than 80mg q.o.d of regorafenib, then regorafenib will be permanently discontinued.

Prevention/management strategies for rash

All patients should be instructed to use moisturizing lotions. Use of topical steroids for management of rash is recommended. The steroid of choice is triamcinolone, except for head and neck rash which should be managed with hydrocortisone.

6.4 Drug logistics and accountability

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

6.4.1 Accountability

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

6.4.2 Destruction and Return

At the end of the study, unused supplies of regorafenib and pembrolizumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. The certificate of destruction should be sent to Bayer and Merck.

6.5 Treatment compliance

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

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

6.6 Prior and concomitant therapy

All medication that is considered necessary for the subject's welfare, and which is not expected to interfere with the evaluation of the study treatment, may be given at the discretion of the investigator. All medications (including contrast media) taken within 2 weeks prior to the start of the study medication and during the study must be recorded in the subject's source documentation and in the CRF (including start/stop dates, dose frequency, route of administration, and indication). Specific caution should be taken when considering or administering a concomitant medication that is metabolized by the cytochrome enzymes CYP2C8, CYP2B6 and CYP2C9. Such concomitant medication should be avoided, if possible.

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

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

Permitted concomitant therapy includes:

- Standard therapies for concurrent medical conditions.
- Supportive care for any underlying illness.
- Palliative radiation therapy is allowed if the target lesion(s) are not included within the radiation field and no more than 10% of the bone marrow is irradiated.
- Granulocyte colony-stimulating factor (G-CSF) and other hematopoietic growth factors may be used in the management of acute toxicity, such as febrile neutropenia, when clinically indicated or at the investigator's discretion. However, they may not be substituted for a required dose reduction. Subjects are permitted to take chronic erythropoietin.
- Treatment with nonconventional therapies (such as acupuncture), and vitamin/mineral supplements are permitted provided that they do not interfere with the study endpoints, in the opinion of the investigator.
- Bisphosphonates

- Subjects who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT are stable. Close monitoring (day5 of cycle 1 and day 1 of each cycle) is mandatory. If either of these values are above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until they are stable.

The following are not permitted:

- Other investigational treatment during or within 2 weeks before starting study treatment
- Systemic antitumor therapy, including cytotoxic therapy, signal transduction inhibitors, immunotherapy, and hormonal therapy
- Bone marrow transplant or stem cell rescue
- Subjects taking narrow therapeutic index medications should be monitored proactively (e.g. warfarin, phenytoin, quinidine, carbamazepine, Phenobarbital, cycloosporin, and digoxin). Warfarin is metabolized by the cytocrome enzyme CYP2C9 and its levels may be especially affected by regorafenib
- Use of any herbal remedy (e.g. St. John's wort [Hypericum perforatum])
- Please note: Patients should be seen frequently / early during treatment as per Prescribing Information
- Liver function tests should be obtained before initiation of regorafenib and monitored at least every 2 weeks during first 2 months of treatment. Thereafter liver function should be monitored monthly or more frequently as clinically indicated
- Monitor blood pressure weekly for the first 6 weeks of treatment and every cycle or more frequently as clinically indicated.

7. Timing of assessments

Potential candidates will undergo screening as outlined in calendar, **study treatment has to be started within 7 days of screening**.

All subjects will be seen weekly for the first two cycles and every 3 weeks afterwards (coordinated with days of pembrolizumab administration). Tumor measurement should be done every 8 weeks.

Each cycle can be started within 5 days of expected dates to accommodate for scheduling issues.

	Screening	Cycle 1 and 2			Cycle 3 on			Follow-up	
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	End of TX 30 days (+/- 7 days) of last tx date	FU phone call every 6 months (+/- 7 days) for 24 months
Informed consent, Review of Eligibility Criteria	X[2]								
Medical History & Demographics	X[2]								
Physical Exam (including vital signs), Weight, Performance Status	X[2]	X	X	X	X			X	
Tumor biopsy (optional and encouraged)				X*					
PT/INR, PTT, aPTT	X[2]		X	X*					
Serum pregnancy test[3]	X[1]	X			X				
CBC, CMP (Safety and follow up)	X[1]	X	X	X	X				
Lipase	X[2]								
Urinalysis (Safety)	X[1]								
ECG (Safety)	X[2]								
TSH, Free T4 (Safety and f/u)	X[2]	X			X			X	
Radiology scans for tumor measurement	X[2]						X**	X**,[6]	
Blood sample for SNP			X[4]						
Blood sample for DNA/RNA and PBMC***	X[5]				X[5]			X[5]	
Archival Tumor Tissue (paraffin embedded) Minimum 10 slides @ 5 micron thickness unstained/unprocessed	X								

Pill diary and compliance		X			X			X	
Toxicity Assessment/AE (CTCAE V5)		X	X	X	X			X	
Regorafenib		X	X		X	X			
Pembrolizumab		X			X				
Concomitant meds		X			X				
End of study/start of new treatment								X	X

* biopsy can be done between day # 11 and day # 19 of cycle 1 only, PT/INR, PTT to be done within one week of biopsy
** Seven day window, CT scan is preferred to other modalities unless there are contraindications to the scan and contrast
*** Collection only at baseline, C3D1 and EOT
1 within 7 days of Cycle 1 Day 1
2 within 28 days of Cycle 1 Day 1
3 for women of child bearing potential only
4 purple top. Send specimen to Lenz lab.
5 Two speckled top, one gold top as well as four yellow top tubes. The yellow tubes will go to USC Norris Cancer Center IMC Lab (Dr. Da Silva) and speckled top and gold top to Pathology lab, Pamela Ward
6 If last imaging within 3 weeks of this date, no need to repeat scans.

All screening procedures done within 72 hours of C1D1 do not need to be repeated

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly. A +/- 3 day window is allowed for scheduling of study visits that must be moved for other reasons

Contact information:

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Room 5410
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323-865-0572
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7.1 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.

7.2 Efficacy

PFS is measured in subjects who start treatment and is defined as the time from start of treatment to clinical/radiographic progression (RECIST 1.1 criteria) or death.

Tolerability is defined as the median duration of combination therapy.

7.3 Safety

All subjects who receive at least one dose of study treatment will be valid for the safety analysis.

All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

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

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

This trial will use the NCI-CTCAE v5.0 criteria for assessment of toxicity and SAE reporting with regard to toxicity grade.

7.3.1 Adverse events

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

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

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

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

7.3.1.1 Definition of adverse event (AE)

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

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

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

7.3.1.2Definition of serious adverse event (SAE)

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

a. Results in death.

b. Is life-threatening.

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization.

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

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

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

d. Results in persistent or significant disability / incapacity.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect.

f. Is another medically important serious event as judged by the investigator.

SAEs will be recorded from the time point of the study treatment to 30 days after the last dose.

Adverse Drug Reaction (ADR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means in view of the investigator and/or company that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility and that the adverse event is associated with the use of the drug.

Serious Adverse Drug Reaction (SADR):

A Serious Adverse Drug Reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drug.

7.3.1.3Classifications for adverse event assessment

The following classifications should be used:

- Seriousness

- Intensity

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

- Causal relationships to study drug:
  To be assessed separately for concomitant agents

Example 1 Doxorubicin (open regorafenib (blinded) Versus Doxorubicin (open label) + matching placebo (blinded)	The relationship to study drug will assume that both active entities (regorafenib or doxorubicin) are suspect drugs if both drugs are given in combination. Due to regorafenib, regorafenib and placebo being blinded, the assumption is that both compounds could be in causal relationship as long as doxorubicin and regorafenib /placebo (blinded) are given in combination. In

	exceptional cases, the investigator can state in the comment field that he/she believes that the event is more likely to be caused by doxorubicin.
Example 2 Dose-escalation trial, open-label study regorafenib + bevacizumab	The assessment of the relationship of an AE to the administration of study drug is the investigator's clinical decision based on all available information at the time of the completion of the CRF. Study drug refers to regorafenib and/or bevacizumab and the assessment of relationship to study drug will be done for each drug separately. If the investigator feels such a distinction cannot be made (e.g. due to a suspected underlying interaction) the same assessment will be documented for both drugs

- Study treatment action
- Other specific treatment of AE
- Causal relationship to protocol-required procedures(s)
- Outcome

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

7.3.1.1.1 Seriousness

For each AE, the seriousness must be determined according to the CTCAE criteria.

7.3.1.1.2 Intensity

The intensity of the AE is classified according to the CTCAEv5.0. Grade refers to the severity (intensity) of the AE:

CTCAEv5 Grade 1: mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention is not indicated.

CTCAEv5 Grade 2: moderate; minimal, local, or noninvasive intervention is indicated; limiting to age-appropriate instrumental activities of daily living (ADL; instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).

CTCAEv5 Grade 3: Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization is indicated; disabling; limiting to self care ADL (self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

CTCAEv5 Grade 4: life-threatening consequences; urgent intervention is indicated.

CTCAEv5 Grade 5: death due to an AE.

7.3.1.1.3 Immune-mediated adverse reactions

Immune-mediated adverse reactions occurred in patients receiving pembrolizumab. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of pembrolizumab, administration of corticosteroids and/or supportive care.
For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids (see below). Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Restart pembrolizumab if the adverse reaction remains at Grade 1 or less. If another episode of a severe adverse reaction occurs, permanently discontinue pembrolizumab.

Immune-mediated pneumonitis
Pneumonitis has been reported in patients receiving pembrolizumab. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging. Exclude other causes of pneumonitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, with hold pembrolizumab for moderate (Grade 2) pneumonitis, and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) pneumonitis (see Immune-mediated adverse reactions above). If Grade 2 pneumonitis is repeated pembrolizumab will be discontinued permanently.

Immune-mediated colitis
Colitis has been reported in patients receiving PEMBROLIZUMAB. Monitor patients for signs and symptoms of colitis. Exclude other causes of colitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold pembrolizumab for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue pembrolizumab for life-threatening (Grade 4) colitis (see Immune-mediated adverse reactions above).

Immune-mediated hepatitis
Hepatitis has been reported in patients receiving pembrolizumab. Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis. Exclude other causes of hepatitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids and, based on severity of liver enzyme elevations, withhold or discontinue pembrolizumab (see Immune-mediated adverse reactions above).

Immune-mediated nephritis
Nephritis has been reported in patients receiving pembrolizumab. Monitor patients for changes in renal function. Exclude other causes of nephritis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold pembrolizumab

for moderate (Grade 2), and permanently discontinue pembrolizumab for severe (Grade 3) or life-threatening (Grade 4) nephrits (see Immune-mediated adverse reactions above).

Immune-mediated endocrinopathies
Hypophysitis has been reported in patients receiving pembrolizumab. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency). Exclude other causes of hypophysitis, and manage treatment in accordance with the guidelines above. Administer corticosteroids, withhold pembrolizumab for moderate (Grade 2), withhold or discontinue pembrolizumab for severe (Grade 3) and for life-threatening (Grade 4) hypophysitis (see Immune-mediated adverse reactions above).

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Exclude other causes of diabetes. Administer insulin for type 1 diabetes, and withhold pembrolizumab in cases of severe hyperglycemia until metabolic control is achieved.
Thyroid disorders have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Administer corticosteroids, withhold pembrolizumab for severe (Grade 3) hyperthyroidism, and permanently discontinue pembrolizumab for life-threatening (Grade 4) hyperthyroidism.
Treat symptoms of hyperthyroidism as appropriate (see Adverse Reactions: Section 7.1.3, and Immune-mediated adverse reactions above). Isolated hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids.
For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that resolved and is controlled with hormone replacement, continuation of pembrolizumab may be considered.

Other immune-mediated adverse events
Across clinical studies with pembrolizumab in approximately 5000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: uveitis and severe skin reactions.

Infusion-related reactions
Across clinical studies with pembrolizumab in approximately 5000 patients, severe infusion-related reactions have been reported in less than 0.1% of patients. For severe infusion reactions, stop infusion and permanently discontinue pembrolizumab. Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

General Approach to Handling irAEs

irAE grade	Withhold/discontinue	Supportive care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold pembrolizumab	Consider systemic corticosteroids in

(With repeated hepatitis and pneumonitis, pembrolizumab should be stopped)		addition to appropriate symptomatic treatment
Grade 3 and 4	Withhold pembrolizumab Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1-2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks.

7.3.1.1.4 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.

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

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

Possible answers are “yes” or “no”.

An assessment of “no” would include:

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

or

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

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

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

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge):

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

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

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

Possible answers are "yes" or "no".

7.3.1.1.5 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.

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

7.3.1.1.6 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy

7.3.1.1.7 Outcome

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

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

Assessments and documentation of adverse events

The definition of adverse events (AEs) is given on Section 7.3.1.1.

All AEs, SAEs and other reportable safety events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator.
● All AEs from the time of treatment allocation/randomization through 30 days following cessation of study treatment must be reported by the investigator.
● All AEs meeting serious criteria, from the time of treatment allocation/randomization through 30 days following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier must be reported by the investigator.
● All pregnancies and exposure during breastfeeding, from the time of treatment allocation/randomization through 120 days following cessation of study treatment, or 30 days following cessation of study treatment if the participant initiates new anticancer therapy must be reported by the investigator.
● Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately by the investigator if the event is considered to be drug-related.
Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify Merck.

Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given on Page Section 7.3.1.2.

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

Throughout the course of the STUDY, the Principal Investigator and study personnel agree to comply with the obligations of adverse event reporting as set forth below, 'Safety Reporting Requirements' and with FDA regulations.

SPONSOR/ INSTITUTION is responsible for all the pharmacovigilance obligations and safety reporting pursuant to the applicable law and regulations in the country where the STUDY is performed.

Additionally, the SPONSOR/INSTITUTION shall immediately, within 24 hours at the latest, report to BAYER by fax or and/or email and to Merck. Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

(1) any other relevant safety information including but not limited to:

a. reports of drug exposure via mother / father with and without adverse events (exposure during conception, pregnancy, childbirth and breastfeeding) including their outcome;

b. if linked to a serious adverse event, reports of misuse, abuse, overdose , medication error and other uses outside what is foreseen in the protocol, drug dependency, occupational exposure, suspected transmission of an infectious agent, withdrawal syndrome, drug interactions with respect to the STUDY DRUG;

and

(2) any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:

- Development Safety Update Reports / relevant parts of IND reports for the STUDY;
- Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees (e.g. reportable non-serious cases);

CONTRACT PARTNERS commit to promptly respond to any query from BAYER and Merck regarding adverse event documentation. This will include queries related to specific treatment assignment for reported Serious Unexpected Adverse Drug Reactions.

Safety Reporting Requirements

The PRINCIPAL INVESTIGATOR must accept full responsibility for the trial and the safety of the subjects participating in the trial. The PRINCIPAL INVESTIGATOR is responsible for the ongoing safety evaluation of the study and shall provide to USC, BAYER and MERCK all Serious Adverse Events (SAEs) within 24 hours of the PRINCIPAL INVESTIGATOR'S awareness.

Adverse Drug Reaction (ADR):
All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means in view of the investigator and/or company that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility and that the adverse event is associated with the use of the drug.

Serious Adverse Drug Reaction (SADR):
A Serious Adverse Drug Reaction is an event that meets any of the criteria for seriousness as previously defined and has a possible causal relationship to the study drug.

Requirements for Reporting of Serious Adverse Events:

All SAEs must be reported to USC, Bayer and Merck within 24 hours of the Principal Investigator's awareness and must include the following minimum information:

1. **The name and contact information of the reporter**
2. **The name of the study drug(s)**
3. **A description of the reported SAE**
4. **A patient identified by one or more of the following:**
   a. **Patient initials**
   b. **Patient number**
   c. **Knowledge that a patient who experienced the adverse event exists**
   d. **Age**
   e. **Sex**
5. **An investigator assessment of study drug causality. For studies with combination therapy, a separate causality assessment should be provided for each study drug.**

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

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

Action(s) taken, if any

For blinded studies, the Principal Investigator will provide the treatment assignment upon request for patients who experience SAEs. The Principal Investigator will provide the final treatment assignment immediately after the end of the study.

Expedited Reporting of Other Safety Information:
The Investigator/ Sponsor shall report to USC, Bayer and Merck within 24 hours of the investigator's awareness of other events such as:

An adverse event related to study specific procedures
Any new and important event related to treatment with the study drug(s).
Any pregnancy during which a female patient was exposed to the study drug(s)
Any pregnancy in the partner of a male patient, where the male patient was exposed to study drug at the time of conception or conception occurred within two weeks of the last dose of study drug(s).
Any other relevant safety information including but not limited to reports on drug interaction, overdose, drug abuse or misuse, drug dependency, withdrawal syndrome, medication error, occupational exposure and lack of drug effect (LODE) occurring at any time during the treatment phase;

Any communication concerning safety related information to regulatory authorities or ethics committees including but not limited to:

- Development Safety Update Reports (DSUR) / relevant parts of IND reports for the STUDY;
- Any other safety related reports, issues and queries that are either raised by or communicated to regulatory authorities or ethics committees;

The Investigator/Sponsor may report SAEs using:
A MedWatch 3500A form available at http://www.fda.gov/medwatch/

All reports shall be sent to:

LENZ@med.usc.edu; DrugSafety.GPV.US@bayer.com and Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).

Facsimile: Bayer:(973) 709-2185 and Merck 215-661-6229

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

Address: 100 Bayer Blvd., Whippany, NJ 07981
FDX or UPS only 67 Whippany Road, Whippany NJ 07981 for UPS

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

Phone: 1-888-842-2937

The Principal Investigator commits to respond promptly to any query from Bayer regarding SAE reports.

Expected adverse events

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

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

Adverse events of special safety interest

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

Based on data studies with regorafenib and from current knowledge of the pharmacological properties of other small molecule tyrosine kinase inhibitors in this drug class, as soon as there is reasonable suspicion of any of the following AEs, the investigator should immediately notify the sponsor as outlined in Section 7.4.1.4.

Reportable adverse events include:

- Acute renal failure (NCI-CTCAE version 5.0 ≥ grade 3) or severe proteinuria (NCI-CTCAE version 5.0 ≥ grade 3)
- Interstitial lung disease
- Acute cardiac failure
- Clinically significant bleeding (NCI-CTCAE version 5.0 ≥ grade 3)
- Stevens-Johnson Syndrome and erythema multiforme
- Hepatic failure
- Reversible posterior leukoencephalopathy syndrome
- Gastrointestinal perforation or fistula

Merck:

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215-661-6229).
For the time period beginning when the consent form is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any participant must be reported within 2 working days to Merck Global Safety if it causes the participant to be excluded from the trial, or is the

result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the participant initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 2 working days to Merck Global Safety.

Events of clinical interest for this trial include:
1. an overdose of Merck product that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.3.2 Pregnancies

The investigator must report to Bayer and Merck 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.

Progressive disease

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

Death

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

7.4 Appropriateness of procedures / measurements

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

disease.

8. Treatment Evaluation Using RECIST Guideline

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) (Eisenhauer, et al, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

8.1 Definitions of Measurable and Non-Measurable Disease

8.1.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.
A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

8.1.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

8.1.3 Measurement Methods

All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers. The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
Imaging-based evaluation is preferred to evaluation by clinical examination when both

methods have been used at the same evaluation to assess the antitumor effect of a treatment.

8.1.3.1Target Lesions

All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions.

8.1.3.2Non-Target Lesions

All non-measurable lesions and measurable lesions that have not been selected as target lesions should be included as non-target lesions.
The primary lesion should always be classified as a non-target lesion irrespective of its size and whether or not it can be accurately measured.
Lymph nodes that have a short axis <10 mm are considered non-pathological and should not be recorded.
Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.
It is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

8.1.4 Response Definition

A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

On follow up imaging a sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.

Response categories	Definition	Comment
Complete Response (CR)	The disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.	Requires normalization of tumor markers. All lymph-nodes must be non-pathological in size (<10mm short axis).

		Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits is considered PR or SD depending on the baseline.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters.	
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as a reference the smallest sum diameters while on study.	
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.	Unequivocal progression of existing non-target lesions with below definition is considered PD. There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare progressive disease (PD) for measurable disease; ie, an increase in tumor burden representing an additional 73% increase in ‘volume’ (which is equivalent to a 20% increase diameter in a measurable lesion).

8.2 Treatment Beyond Progression

Subjects will be permitted to continue with treatment beyond initial RECIST 1.1 defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Subject is tolerating treatment
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. If the decision is taken to continue treatment beyond progression, the subject will remain on the trial and continue to be treated and monitored according to the study calendar.

Subjects should discontinue treatment upon further evidence of further progression (second progression), defined as an additional 20% or greater increase in tumor burden (SPD: sum of product of diameters) from time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm). Treatment should be discontinued permanently upon documentation of further progression.

9. Correlative Studies

We propose a series of assays to help us identify the predictive biomarkers for future clinical trials. Efforts should be made for all patients with biopsiable lesion to undergo biopsy on day #11-19. The archival tissue and biopsied tissue will be banked for future analysis. Biopsy is planned to assess changes in the immune microenvironment due to regorafenib.

Additionally, all subjects will have liquid biopsies at baseline and with the first restaging and then at progression (if different than the first restaging).

The discovery of biomarkers relevant to the field is expanding rapidly and thus the list of biomarkers will be assessed at the time of analysis. A panel of biomarkers of interest are listed below.

Tissue:

- Expression of PDL1. PD-1 expression in tumor tissue.[33] MHC class I and II expression at baseline (archival tissue) and in collaboration with Merck.
- Additionally, archival tumor tissue will be obtained for NGS and correlation between CMS classification, mutational load, and immune scoring and treatment benefit.

Blood:

- A panel of proprietary biomarkers (SNPs in angiogenic and immune pathways) developed at Dr. Lenz's lab will be used for assessment of toxicity and efficacy.
- We intend to look at the global markers of immune activation by screening PBMC for: CD3, CD4, CD8, CD25, FoxP3, HLA-DR, ICOS1, CTLA-4, CD45RO, CD45RA, CD27, PD-1, CCR7, CD 62L, CD 69, ICOS, CD 95, CD127 and CD137 for analysis

by multi-color flow cytometry to phenotype and quantify the changes in immune markers following treatment on both $CD4^+$ helper T cells, regulatory T cells and $CD8^+$ cytotoxic T cells. Specifically the following sets of antibodies will be informative to the function of the T cells: CD45RA/CCR7/CD62L (naïve vs memory), FoxP3/CD25/CD127/CTLA-4 (nTreg),CD69/ICOS/PD-1/CD95 (activation vs exhaustion).

- Additionally, will collect CTC, cell free RNA and DNA at baseline and at progression for analysis of expression of MHC class I and II expression, and mutational load.

10.Statistical methods and determination of sample size

This is an open label single institution phase I/II with combination of regorafenib and pembrolizumab in patients with advanced colorectal cancer who have progressed or not tolerated standard therapies.

End points:

- Phase I: Dose limiting toxicity during the first course of therapy.
- Phase II: Progression-free survival (PFS), defined from the start of treatment (day 1 of cycle 1) to the time of disease progression or death from any cause whichever is sooner. Patients will be considered evaluable for PFS if they have received at least one dose of treatment and have at least one post baseline tumor assessment.
- Phase II: Overall survival, defined as the time from the start of treatment (day 1 of cycle 1) to death from any cause.

10.1 Study design/sample size calculation

A standard 3+3 dose escalation rule will be used during the phase I portion of the study to determine MTD/RP2D of combination of regorafenib and pembrolizumab. 3 dose levels of regorafenib will be assessed. The dose level of pembrolizumab will be fixed. The definitions of DLTs, MTDs, and DLT observation period as well as rules for dose escalation, expansion, and de-escalation are clearly defined in section 6. The study could be stopped when ≥ 2 out of the first 3 patients treated at starting dose experienced DLTs. Or all dose levels are expanded with additional 3 patients. Thus 3 to 18 patients could be enrolled and treated during phase I part of the study.

As soon as MTD/RP2D is determined, the phase II portion of the study will start. We use SWOG's one arm non-parametric survival design to determine the sample size. Progression-free survival will be the primary endpoint. PFS is defined from the start of treatment (day 1 of cycle 1) to the first observation of disease progression or death whichever comes first. The patients are alive and disease progression is not observed, PFS is censored at the date of the latest disease assessment. 63 patients are planned to enroll to have 80% power to detect improvement of median PFS from 1.9 months (CORRECT trial, the historical control, the null hypothesis) to 2.85 months (the alternative hypothesis). The type I error rate using this design will be 0.1 (one sided). The planned accrual time is 2 years and the additional follow-

up time from the end of accrual is 6 months. An expected 20 events are expected to occur during the follow up period.

The approximate upper critical PFS value is 2.44 months.

The total sample size of this phase I/II study is between 3 and 75 patients. Six patients who are treated at MTD/RP2D of the phase I portion of the study will be counted for the phase II portion of the study too.

10.2 Analysis sets

During the phase I portion of the study. All patients who are evaluable for DLTs will be counted and used in the decision of dose escalation, expansion, de-escalation, and stopping. Patients who are inevaluable for DLTs will be replaced. However, all eligible patients who start treatment with study drugs will be counted in patient description. During the phase II portion of the study, all patients who start treatment with study drugs will be included. All patients need scan at the end of their study period to be counted for endpoints.

10.3 Statistical and analytical plans

Description analysis will be performed for both phase I and phase II parts of the study in terms of baseline demographic and disease characteristics and prior treatment. All DLTs will be listed by dose level. Toxicities that are not qualified as DLTs will be summarized by dose level, cycle, type, grade, and attribution to study drugs. Treatment cycles will be summarized by dose level.

Kaplan Meier curves will be used to show PFS and OS. Medians and probabilities of PFS and OS at 3 and 6 months and their 95%CI confidence intervals will be given. Response rate (CR or PR) will be calculated among patients during the phase II portion of the study for calculation of disease control rate (CR+PR+SD). All patients who are counted during that portion will be included in the denominator.

10.4 Planned interim analyses

There is no planned interim analysis for efficacy during the phase II portion of the study. A safety monitoring plan is laid out to further assess tolerability of the combination of regorafenib and pembrolizumab at MTD/RP2D among the first 20 patients during the phase II portion of the study. Our statistician will monitor the data for toxicity monthly and provide reports to PI and DSMC for update.

10.5 Endpoints

PFS: PFS is defined from the start of treatment (day 1 of cycle 1) to the first observation of disease progression (initial RECIST 1.1 progression) or death whichever comes first. The patients who are alive and disease progression is not observed, PFS is censored at the date of the latest disease assessment.

OS: OS is defined from the start of treatment (day 1 of cycle 1) to death. The patients who are alive and OS is censored at the last date known to be alive.

11.Data handling and quality assurance

11.1 Data recording

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

11.2 Monitoring

11.2.1 **Adherence to Protocol/Per Patient:** It is the responsibility of the USC Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at USC are all performed as specified in the protocol. When a study is opened at two or more institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

11.2.2 **Day-to-Day Monitoring – Eligibility:** At USC, the Study Coordinator will assist the Investigator in reviewing eligibility and will assemble the required source documents, and do a final review by completing an Eligibility Registration Worksheet. When a study is opened at two or more institutions, the PI at each institution will review the patient eligibility in accordance with that institution's policy. For all institutions, the Eligibility Registration Worksheet with a copy of Informed Consent and supporting source documents will be submitted to CISO QA via email or Fax for verification prior to registering the patient on study.

Multi-Site Registration:
All participants in the multi-site trial are subject to central registration, which is used for tracking study accrual, checking eligibility, and monitoring adequate participation of women and minorities. Subject registration will be conducted through the coordinating center at the NCCC-CISO. External sites will identify eligible subjects and verify enrollment availability with the MCC prior to consenting patients. The external site is required to notify the MCC of a new signed informed consent within 48 business hours and note the basic consent information on the screening log. A copy of the consent will accompany the complete eligibility packet for verification. The MCC will enter the patient, demographic, and consent information in the applicable USC database. The MCC will assign a study patient sequence ID and communicate this to the external site.
The Coordinating Center Program Hours are 8 am to 4 pm, Monday through Friday, based on the PST zone. The MCC will be closed on official government holidays unless otherwise indicated. The contact number for the MCC is 323-865-3122.
External sites will verify eligibility prior to submitting documents to the MCC for central registration. External sites must submit registration requests to the MCC at least one full business day prior to the planned treatment start date. Registration will require the external site to submit to the MCC all of the following:

- A completed registration form with patient demographics:
- Zip code
- Payor Source

- Age
- Sex
- Race
- Ethnicity
- Initials
- Date of Birth (DOB)
- A completed Eligibility Checklist signed by the investigator
- A copy of the most recently IRB-approved, patient signed informed consent form
- All required screening tests, within the time parameters specified by the protocol study calendar
- All other de-identified source documents needed to verify all points of eligibility
- Any On-Study forms for registration specified by protocol

These documents must be securely emailed to the MCC staff. With advance notice documents will also be accepted faxed to 323-865-0457. The MCC will verify completeness of documents and confirm eligibility. The MCC will enter the registration information in the USC OnCore® database. The MCC will then fax or securely email the completed Registration Form with the assigned study sequence ID to the external site as confirmation of patient registration.

An external site must maintain a log of all subjects who sign informed consents. The log must also document an explanation for exclusion due to screen failure. The MCC will provide sites with a Patient Tracking Log at the time of site activation. In the event of screen failure, external sites must submit the Screen Failure form to the MCC within one business day of determining screen failure.

Participating sites are required to retain, in a confidential manner, sufficient information on each subject so that the subject may be contacted should the need arise.

All documents, investigative reports, or information relating to the patient are strictly confidential. Any patient specific reports (i.e. Pathology reports, MRI reports, Operative reports, etc.) submitted to the CISO-MCC must have the patient's full name and social security number redacted (blacked out) and the assigned CISO-MCC patient ID number, protocol number, and site number written in. Patient initials only may be included or retained for cross verification of identification.

A registration verification letter will be emailed (preferred) or faxed to the registering site within one working day for patients registered to CISO-MCC multi-site trials. Treatment may not be initiated until the site receives this faxed or emailed verification.

11.2.3 **Day-to-Day Monitoring – Informed Consent:** Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. A copy of the ICF will also be provided to CISO QA for review. CISO SOP 3.3 will be followed.

11.2.4 **Day-to-Day Monitoring – Treatment:** The PI and co-investigators are responsible for ensuring that treatment is given per protocol. The Study Coordinator will review the treatment orders with the treating investigator. Regardless of who the treating

physician is, there will be only one responsible Study Coordinator for each study at each of the hospitals affiliated with the USC Norris Cancer Center. The treating investigator will review the status of each patient on-study, with the Study Coordinator and treating physicians, on an on-going basis. When a study is opened at two or more institutions, CISO QA will periodically audit medical records for the subjects on study at other institutions to ensure compliance and adherence to the protocol.

11.2.5 **Data Management – Patient Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, all written source documents not associated with the study research are maintained in the patient chart, which is stored in the Department of Medical Records at the appropriate hospital. At the Norris Hospital, the official medical record is the Electronic Patient File (EPF). Radiographical images are stored in the Department of Radiology and in an electronic system called Synapse. At Los Angeles County General Hospital the official medical record is called Affinity. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patients' hospital charts. It is the responsibility of the research staff to ensure that the patient chart contains the required documents and work closely with treating investigators to ensure all protocol-related assessments are carefully documented.

11.2.6 **Data Management – Research Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, to facilitate adherence to the protocol schedule and data management, research charts are created to collect copies of the relevant notes, orders and results that are in the Patient Chart. In Addition, all source documents related to the research, such as original informed consent forms, HIPAA Forms, AE assessment worksheets, disease response worksheets and NTFs are maintained in the Research Charts. Protocol calendars, worksheets, and checklists, are also kept in the research chart. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site. It is the responsibility of the Data Manager to ensure that the research chart contains all the required documents.

11.2.7 **Data Management – Case Report Forms:** It is the responsibility of the Data Manager to complete the required case report forms. For in-house trials, case report forms are developed for each trial; these are used to finalize the data entry screens in the Cancer Center clinical trials database. It is the responsibility of the PI to review

the Off-Study Summary form which summarizes pertinent toxicity, response and adherence information, once the patient has completed treatment.

Principal investigator and the study team at USC will have weekly safety meetings and conference calls during phase I period. These meetings will be held monthly, for the first 20 patients on phase II and if no unexpected signal of toxicity is observed the frequency of the meetings will be annual to correspond with the reporting period to DSMC. Furthermore, the opinion of the Data and Safety Monitoring Committee at USC can be sought as required on an ad hoc basis.

11.3 Audit and inspection

Inspections by regulatory health authority representatives i.e. FDA and IEC(s)/IRB(s) are possible. The investigator should notify Bayer and Merck 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

See section 11.2 for further details.

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

12. Premature termination of the study

- 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.

The investigator has the right to close his/her center at any time.

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

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

13. Ethical and legal aspects

13.1 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 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 all participating centers 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 and also forwarded to Bayer.

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.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Bayer. However, the 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/Bayer 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/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

13.2 Subject information and consent

Each subject / legal representative or proxy consenter 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 consenter 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 consenter 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.

1. 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 Bayer and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.
2. For minors or adults under legal protection, consent shall be given by the legal guardian(s). The consent of a minor or adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.
3. In emergency situations, when prior consent of the patient is not possible, the consent of the patient's legal representative(s) or proxy consenter, if present, should be requested. The patient should be informed about the study as soon as possible and his/her consent to continue the study should be requested.

The informed consent form and any other written information provided to subjects / legal representatives or proxy consenters 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 consenter 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.

13.3 Publication policy

Bayer recognizes the right of the investigator to publish results upon completion of the study. However, the investigator must send a draft manuscript of the publication or abstract to Bayer at least thirty days in advance of submission in order to obtain approval prior to submission of the final version for publication or congress presentation. This will be reviewed promptly and approval will not be withheld unreasonably. In case of a difference of opinion between Bayer and the investigator(s), the contents of the publication will be discussed in order to find

a solution which satisfies both parties. All relevant aspects regarding data reporting and publication will be part of the contract between Bayer and the investigator/institution

The Principal Investigator should ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

13.4 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.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14. Reference list

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians 2017;67:7-30.
2. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.
3. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19.
4. Bellone M, Calcinotto A. Ways to Enhance Lymphocyte Trafficking into Tumors and Fitness of Tumor Infiltrating Lymphocytes. Front Oncol 2013;3:231.
5. Dirkx AE, oude Egbrink MG, Castermans K, et al. Anti-angiogenesis therapy can overcome endothelial cell anergy and promote leukocyte-endothelium interactions and infiltration in tumors. Faseb J 2006;20:621-30.
6. Huang Y, Yuan J, Righi E, et al. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proceedings of the National Academy of Sciences of the United States of America 2012;109:17561-6.
7. Lukashev D, Klebanov B, Kojima H, et al. Cutting edge: hypoxia-inducible factor 1alpha and its activation-inducible short isoform I.1 negatively regulate functions of CD4+ and CD8+ T lymphocytes. Journal of immunology (Baltimore, Md : 1950) 2006;177:4962-5.
8. Gabrilovich DI, Chen HL, Girgis KR, et al. Production of vascular endothelial growth factor by human tumors inhibits the functional maturation of dendritic cells. Nat Med 1996;2:1096-103.
9. Lin YL, Liang YC, Chiang BL. Placental growth factor down-regulates type 1 T helper immune response by modulating the function of dendritic cells. J Leukoc Biol 2007;82:1473-80.
10. Rolny C, Mazzone M, Tugues S, et al. HRG inhibits tumor growth and metastasis by inducing macrophage polarization and vessel normalization through downregulation of PlGF. Cancer Cell 2011;19:31-44.
11. Yasuda S, Sho M, Yamato I, et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. Clin Exp Immunol 2013;172:500-6.
12. Teufel M, Schwenke S, Seidel H, al. e. Molecular subtypes and outcomes in regorafenib-treated patients with metastatic colorectal cancer (mCRC) enrolled in the CORRECT trial. ASCO Annual Meeting; 2015; Chicago.
13. Ozao-Choy J, Ma G, Kao J, et al. The novel role of tyrosine kinase inhibitor in the reversal of immune suppression and modulation of tumor microenvironment for immune-based cancer therapies. Cancer research 2009;69:2514-22.
14. Sers C, Kuner R, Falk CS, et al. Down-regulation of HLA Class I and NKG2D ligands through a concerted action of MAPK and DNA methyltransferases in colorectal cancer cells. International journal of cancer Journal international du cancer 2009;125:1626-39.
15. Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. International journal of cancer Journal international du cancer 2011;129:245-55.

16. Ferrara N. VEGF and the quest for tumour angiogenesis factors. Nat Rev Cancer 2002;2:795-803.
17. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology 2015;16:619-29.
18. Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28:4531-8.
19. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23:2346-57.
20. Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358:2698-703.
21. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.
22. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proceedings of the National Academy of Sciences of the United States of America 2001;98:13866-71.
23. Zhang X, Schwartz JC, Guo X, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.
24. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. Journal of immunology (Baltimore, Md : 1950) 2004;173:945-54.
25. Sheppard KA, Fitz LJ, Lee JM, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett 2004;574:37-41.
26. Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.
27. Agata Y, Kawasaki A, Nishimura H, et al. Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. Int Immunol 1996;8:765-72.
28. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation-induced expression of human programmed death-1 gene in T-lymphocytes. Exp Cell Res 1997;232:25-8.
29. Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med 2000;191:891-8.
30. Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8:793-800.
31. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.
32. Fuchs CS, Doi T, Jang RW, et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol 2018;4:e180013.
33. Thompson RH, Dong H, Lohse CM, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res 2007;13:1757-61.

15. Appendices

15.1 Examples of a low fat meal

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).

15.2 Toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.

	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM). [i]