TITLE:	**A Phase Ib/II Clinical Study of BBI608 in Combination with Standard Chemotherapies in Adult Patients with Advanced Gastrointestinal Cancer**
PROTOCOL NUMBER:	**BBI608-246**
STUDY DRUG:	**BBI608**
SPONSOR:	**Boston Biomedical, Inc.** **640 Memorial Drive** **Cambridge, MA 02139** [redacted]
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DATE OF PROTOCOL:	**September 17th, 2013**
AMENDMENT 1:	**September 26th, 2015**
AMENDMENT 2:	**August 17th, 2016**
AMENDMENT 3:	**December 6th, 2016**
AMENDMENT 4:	**June 23rd, 2017**

Confidentiality Statement

SYNOPSIS

Study Title:	**A Phase Ib/II Clinical Study of BBI608 in Combination with Standard Chemotherapies in Adult Patients with Advanced Gastrointestinal Cancer**
Study Number:	BBI608-246
Study Phase:	Phase Ib/II
Study Drug:	BBI608, a novel investigational small molecule anticancer drug that targets cancer stem cells.
Primary Objectives:	Phase Ib: To determine the safety, tolerability and preliminary anti-tumor activity of BBI608 when administered in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan in adult patients with advanced gastrointestinal (GI) cancer. Phase II: To assess the objective response rate (ORR) of BBI608 administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory metastatic colorectal cancer (mCRC).
Secondary Objectives:	To determine the pharmacokinetic profile of BBI608 administered in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab or regorafenib. To determine the pharmacodynamics (biomarkers) of BBI608 administered in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. To assess the preliminary anti-tumor activity of BBI608 administered in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. To assess the disease control rate (DCR), progression free survival (PFS), and overall survival (OS) of BBI608 administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory mCRC.
Study Design:	This is an open label, multi-center, Phase Ib study of BBI608 administered in combination with either FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. A study cycle will consist of daily and continuous oral administration of BBI608 for four weeks (28 days) in combination with FOLFOX6 with and without bevacizumab, or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. Cycles will be repeated until disease progression, unacceptable toxicity, or another discontinuation criterion is met. Arm A (FOLFOX6) – Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with doses separated by approximately 12 hours. On Cycle 1 Day 1 (C1D1), a standard FOLFOX6 regimen will begin and will be repeated every 14 days thereafter. In the case of toxicity, dose adjustment is permitted.

	Arm B (FOLFOX6 with bevacizumab) – Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with the doses separated by approximately 12 hours in 28 day cycles. On Cycle 1 Day 1 (C1D1), a standard FOLFOX6 with bevacizumab regimen will begin and be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted. Arm C (CAPOX) – Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with doses separated by approximately 12 hours in 28 day cycles. On Cycle 1 Day 1 (C1D1), a standard CAPOX regimen will begin and will be repeated every 21 days thereafter. In the case of toxicity, dose adjustment is permitted. Arm D (FOLFIRI) – Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with doses separated by approximately 12 hours in 28 day cycles. On Cycle 1 Day 1 (C1D1), a standard FOLFIRI regimen will begin and be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted. Arm E (FOLFIRI with bevacizumab) – Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with the doses separated by approximately 12 hours in 28 day cycles. On Cycle 1 Day 1 (C1D1), a standard FOLFIRI with bevacizumab regimen will begin and be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted. Arm F (regorafenib) – Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with doses separated by approximately 12 hours. On Cycle 1 Day 1 (C1D1), patients will receive regorafenib 120 mg once daily, with a low-fat meal, for 21 consecutive days of every 28 days thereafter. In case of toxicity, dose adjustment is permitted. If regorafenib is tolerated in the first cycle, dosage may be increased to 160 mg once daily as tolerated after first cycle. Arm G (irinotecan) - Starting on day (-) 5 of cycle 1, BBI608 will be administered continuously twice daily with the doses separated by approximately 12 hours in 28 day cycles. On Cycle 1 Day 1 (C1D1), irinotecan 180 mg/m^2 will begin and be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted. Initially, 3 patients will be enrolled in each combination arm (except for the irinotecan study arm for which enrollment will begin with the expansion phase skipping DLT period assessment being that RP2D for BBI608 in combination with irinotecan has been established at the time of this amendment*) at a BBI608 dose level of 240 mg twice daily (480 mg total daily dose—Cohort I). If 0 out of 3 patients experience a DLT, then the BBI608 dose will be escalated to 480 mg twice daily (960 mg total daily dose—Cohort II) and 6 patients will be enrolled at this dose level. If 1 out of 3 patients in the 240 mg by mouth twice daily cohort experience a DLT, then an additional 3 patients will be enrolled in that arm. If a DLT occurs in ≥ 2 of the 6 patients in an arm, then the BBI608 dose will be reduced to 160 mg twice daily (320 mg total daily dose—Cohort Ib) and 6 patients will be enrolled at this does level. If ≤1 of 6 patients experience a DLT at the 240 mg by mouth twice daily dose level, then BBI608 dose will be escalated to 480 mg by mouth twice daily (960 mg total daily dose) and 6 patients will be enrolled at this dose level. If ≤ 1 out of 6 patients experiences a DLT at 480 mg by mouth twice daily, this dose level will be considered the Recommended Phase 2 Dose (RP2D) for BBI608 in that combination. If ≥2 out of 6 patients experience a DLT at 480 mg by mouth twice daily, then RP2D will be declared as the next lowest dose level at which ≤1 out of 6

	patients experiences a DLT. Safety of BBI608 at 480 mg by mouth twice daily (960 mg total daily dose) may be evaluated in each combination arm, including if a lower RP2D has previously been established in that combination based on acceptable safety and efficacy profile, for as long as ≤1 of 6 patients experience a DLT at the 240 mg by mouth twice daily dose level (480 mg total daily dose). DLT assessment will be performed as above with 6 patients enrolled at the dose of 480 mg by mouth twice daily (960 mg total daily dose). Up to an additional 15 evaluable patients may be enrolled in each cohort at the dose of 480 mg by mouth twice daily (960 mg total daily dose) as long as ≤1 of 6 patients experience a DLT at the 480 mg by mouth twice daily dose level (960 mg total daily dose). A trial arm of BBI608 in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan will continue to enroll patients only if no more than 1 out of 6 patients for each combination experience a protocol-defined DLT. It is expected that, for each combination arm, approximately 9 to 12 patients will be enrolled in the dose escalation part of the study and up to an additional 15 evaluable patients may be enrolled at RP2D. An additional 20 evaluable subjects will be enrolled on the hepatocellular carcinoma, cholangiocarcinoma, gastric/GEJ, esophageal or pancreatic adenocarcinoma disease cohorts. Up to an additional 50 evaluable FOLFIRI/XELIRI-refractory colorectal (CRC) patients will be enrolled on the FOLFIRI study arm (with bevacizumab if clinically indicated) as an expansion cohort. FOLFIRI/XELIRI-refractory CRC patients will have failed treatment with FOLFIRI/XELIRI with or without bevacizumab regimen with failure defined as progression of disease during or ≤3 months after the last dose of FOLFIRI/XELIRI with or without bevacizumab. For the XELIRI/FOLFIRI-refractory CRC patients enrolled on the expansion cohort for whom bevacizumab is clinically indicated, bevacizumab 5 mg/kg will be administered intravenously following irinotecan/leucovorin infusion. In case of toxicity, dose adjustment is permitted. A study cycle will consist of 28 days of daily administration of BBI608 in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. Pharmacokinetic (PK) and pharmacodynamic assessments will be performed in the first cycle only for each drug combination. If there is an indication of drug accumulation, PK assessment can be performed for more than two cycles. Safety and tolerability of BBI608 in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan will be assessed for the duration of study treatment and for 30 days after the last dose of BBI608. Evaluation of anti-tumor activity of BBI608 in combination with FOLFOX6 with and without bevacizumab or CAPOX or FOLFIRI with and without bevacizumab, regorafenib or irinotecan will be performed at 8 week intervals while patients remain on study according to RECIST 1.1. Patients will have confirmatory radiographic scanning within approximately 4 weeks of initial results of partial or complete response (PR or CR) according to RECIST 1.1.
Study Population:	This study will enroll patients with advanced gastrointestinal cancer for which a protocol chemotherapy regimen is an appropriate treatment option in the judgment of the Physician Investigator. Examples of gastrointestinal cancers potentially eligible for protocol therapy include colorectal cancer (CRC), hepatocellular carcinoma (HCC), pancreatic adenocarcinoma, cholangiocarcinoma, and gastro-esophageal carcinoma. Patients may be

	treatment-naïve or may have received standard chemotherapy; including regimens containing fluoropyrimidine, or oxaliplatin, or irinotecan, or regorafenib, or bevacizumab. Additional key inclusion criteria include: Karnofsky performance status score of $\geq$ 70%, a life expectancy of greater than 3 months, and adequate bone marrow, renal and hepatic function. Patient accrual will occur over a period of time dependent upon the enrollment rate of the study.
Test Product, Dose, and Mode of Administration:	Patients in this trial will receive BBI608 orally twice daily, approximately one hour prior to or two hours after meals with the first dose given in the morning and doses separated by approximately 12 hours. For patients receiving FOLFOX6, a standard FOLFOX6 regimen will begin administration on day 1 cycle 1 and will subsequently be repeated every 14 days thereafter, or twice per 28 day cycle. For patients receiving FOLFOX6 with bevacizumab, a standard FOLFOX6 with bevacizumab regimen will begin administration on day 1 cycle 1 and will subsequently be repeated every 14 days thereafter, or twice per 28 day cycle. For patients receiving CAPOX, a standard CAPOX regimen will begin administration on day 1 of cycle 1 and will subsequently be repeated every 21 days thereafter. For patients receiving FOLFIRI, a standard FOLFIRI regimen will begin administration on day 1 of cycle 1 and will subsequently be repeated every 14 days thereafter, or twice per 28 day cycle. FOLFIRI-refractory patients enrolled as part of the expansion cohort can resume FOLFIRI at the last dose that they received prior to progression on FOLFIRI. For patients receiving FOLFIRI with bevacizumab, a standard FOLFIRI with bevacizumab regimen will begin administration on day 1 cycle 1 and will subsequently be repeated every 14 days thereafter, or twice per 28 day cycle. For patients receiving regorafenib, 120 mg will be taken orally once daily starting on day 1 of cycle 1 for 21 consecutive days of every 28 days thereafter. If regorafenib is tolerated in the first cycle, dosage will be increased to 160 mg once daily as tolerated after the first cycle. For patients receiving irinotecan, irinotecan 180 mg/m^2 will begin administration on day 1 of cycle 1 and will subsequently be repeated every 14 days thereafter, or twice per 28 day cycle. Cycles will be repeated until progression of disease, unacceptable toxicity, or another discontinuation criterion is met.
Duration of Treatment:	For an individual patient, treatment with BBI608 and the combination drug will continue until unacceptable toxicity, disease progression (clinical or radiological) or another discontinuation criterion is met. It is expected that most patients will receive between one and four cycles of BBI608 for a treatment period of 4 to 16 weeks.

Criteria for Determination of Dose-Limiting Toxicity:	A DLT is defined by the occurrence of any of the following toxicities possibly or probably related to BBI608, or BBI608 in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan within the 28 days of Cycle 1: ● CTCAE (Common Terminology Criteria for Adverse Events) Grade 4 hematological toxicity. ● Grade 3 or 4 non-hematological toxicity, except Grade 3 nausea/vomiting/anorexia, diarrhea, or fatigue will be considered a DLT only if it persists more than three (3) days despite optimal medical management; and alopecia will not be considered a DLT. ● Any other toxicity that in the view of the Principal Investigator represents a clinically significant hazard to the patient. Whether a DLT has occurred will be assessed during the first 28 days of BBI608 therapy. Subjects who received fewer than 28 consecutive days of BBI608 dosing due to toxicity will be eligible for DLT assessment. DLT will be determined from adverse events, changes from baseline in physical examination findings and laboratory parameters. The incidence of adverse events and DLTs will be evaluated for each combination arm and for all patients.
Pharmacokinetic and Pharmacodynamic Variables:	Pharmacokinetic variables to be determined include maximum plasma drug concentration (Cmax), volume of distribution, area under the time-concentration curve (AUC), distribution half-life, and terminal half-life. PK draws in FOLFOX6 with and without bevacizumab, and FOLFIRI with and without bevacizumab, and regorafenib arms will be performed beginning on day 1 and day 15 of Cycle 1. PK draws in the CAPOX arm will be performed beginning on day 1 and day 22 of Cycle 1. PK draws will not be collected for the irinotecan arm. Response (increase or decrease) of several biomarkers as well as intratumoral concentration of BBI608 from biopsied tumors following BBI608 administration will be examined in patients with accessible tumors who consent to an optional biopsy. Tumor biopsies will be collected prior to the first dose of BBI608 and on day 1 of cycle 2 for patients with accessible tumors.
Statistical Methods:	<u>Phase Ib:</u> All patients receiving at least one daily dose of BBI608 will be considered evaluable for safety analyses. In addition to the evaluation and categorization of adverse events, listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented. Patients who have received at least one cycle of BBI608 and who have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics. <u>Phase II:</u> The primary endpoint, ORR, will be determined for FOLFIRI-refractory CRC patients as a single stage design. This analysis will test the following: $H_o: \pi \leq 0.05$ Versus $H_a: \pi > 0.05$ If ORR response rate with FOLFIRI treatment alone is estimated at 5% and a

	true ORR response rate with FOLFIRI (with bevacizumab if clinically indicated) in combination with BBI608 is 12%, a sample size of 50 evaluable patients produces a two-sided 95% confidence interval with a width of 0.2, for a 95% exact confidence interval of 4.5%-24.5%.

DOSE ESCALATION SCHEME

BBI608-246: A Phase 1b Clinical Trial

Cohort	No. Subjects[#]	Dose Level	Total Daily Dose of BBI608
I	3	Level 1	480 mg
Ib*	3	Level 1b	320 mg
II**	3	Level 2	960 mg

Groups may be expanded to six subjects, as provided in the protocol.
*This cohort will be created if DLT is observed in ≥2 of 6 patients at dose level 1 (480 mg)
** This cohort may be created if a lower RP2D has been previously established based on acceptable safety and efficacy profile, for as long as ≤1 of 6 patients experience a DLT at the 240 mg by mouth twice daily dose level (480 mg total daily dose).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ALT	Alanine transaminase (SGPT)
ANOVA	Analysis of variance
AP	Alkaline phosphatase
AST	Aspartate transaminase (SGOT)
AUC	Area under the time-concentration curve
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CDER	Center for Drug Evaluation and Research
C_{max}	Maximum plasma drug concentration
C_{min}	Minimum plasma drug concentration
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CRF	Case report form
CT	Computed tomography
CV	Coefficient of variation
CTCAE	Common terminology criteria for adverse events
DLT	Dose limiting toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit

HED	Human equivalent dose
Hgb	Hemoglobin
HGF	Hepatocyte growth factor
HIPAA	Health Information Portability and Accountability Act
IC_{50}	Inhibitory concentration, 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest diameter
LDH	Lactic dehydrogenase
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observable adverse effect level
NOEL	No observable effect level
ORR	Overall response rate
PD	Progressive disease
PK	Pharmacokinetic
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose
RBC	Red blood cell (count)
SAE	Serious adverse event
SD	Stable disease
SE	Standard error

SGOT	Serum glutamic oxaloacetic transaminase (AST)
SGPT	Serum glutamic pyruvic transaminase (ALT)
T_{max}	Time to maximum plasma concentration
TNM Scale	Tumor node metastases scale
ULN	Upper limits of normal
WBC	White blood cell (count)

1 PRECLINICAL SUMMARY AND STUDY RATIONALE

1.1 Scientific Background of BBI608

Recent studies have uncovered the presence of cancer stem cells (CSC, also called tumor initiating cells or cancer stem-like cells) which have self-renewal capability and are considered to be fundamentally responsible for malignant growth, relapse and metastasis. Importantly, CSCs are inherently resistant to conventional therapies. Therefore, a targeted agent with activity against cancer stem cells holds great promise for cancer patients (Boman and Wicha, 2008; Clevers, 2011; Lobo et al., 2007; Magee et al., 2012; Singh and Settleman, 2010).

BBI608 is a small molecule that targets cancer by blocking self-renewal of and inducing apoptosis in cancer stem cells. While not a kinase inhibitor, BBI608 works by inhibiting the STAT3 pathway. With our proprietary target discovery technology TPIV®, scientists at Boston Biomedical, Inc. have discovered that the STAT3 pathway activity is critical for the self-renewal and survival of cancer stem cells in human cancer, including gastrointestinal malignancies such as colorectal, pancreatic, and gastric/GEJ adenocarcinoma.

STAT3 is closely linked to another important downstream oncogene, β-catenin (Kawada et al., 2006). The later contributes to tumorigenesis and metastasis in colorectal cancer (CRC) as a result of APC mutation and is implicated in other gastrointestinal malignancies such as gastroesophageal adenocarcinoma, cholangiocarcinoma, hepatoma and pancreatic adenocarcinoma (White et al., 2012). Additionally, nuclear β-catenin localization has important clinical implications and is associated with CSC-promoting epithelial-to-mesenchymal transition (EMT) (Schmalhofer et al., 2009). STAT3 activation leads to nuclear accumulation of β-catenin in CRC cells leading to increased cancer stem cell abundance and worse prognosis in this subset of CRC patients (Kawada et al., 2006). Similar to STAT3 dysregulation predicting poor prognosis in CRC, increase in nuclear β-catenin predicts poor outcome in CRC (Morikawa et al., 2011). Furthermore, combination of nuclear β-catenin with high p-STAT3 levels is associated with the worst prognosis of all in CRC (Kawada et al., 2006). Blockade of the STAT3 pathway, therefore, offers a novel and potentially highly effective strategy to target cancer stem cells as well as the bulk of the heterogeneous cancer cells, while sparing normal cells and normal adult stem cells.

1.2 Preclinical Efficacy

Cancer stem cells are intrinsically resistant (more than 5 to 10 fold) to chemotherapeutic drugs. BBI608 has potent activity (~100 to 500 nM) against cancer stem cells *in vitro* and *in vivo* while sparing normal hematopoietic stem cells (IC50 not reached at 30 μM), thereby offering a wide therapeutic window. The dependence on STAT3 is conserved in various non-stem cancer cells. BBI608 has demonstrated *in vitro* efficacy in a broad spectrum of human cancer cell lines derived from both solid tumors and hematologic malignancies (IC50 ~100 nM to 500 nM). BBI608 monotherapy has demonstrated potent anti-tumor activity *in vivo* in multiple murine xenograft models of human cancer, including liver, head and neck, breast, prostate, colon, gastric and pancreatic cancers, in the absence of adverse effects. Additionally, BBI608 monotherapy has demonstrated antimetastatic activity using *in vivo* spontaneous metastasis mouse models.

When administered in mouse xenograft model, chemotherapeutic agents, including 5-FU, oxaliplatin, irinotecan, regorafenib increase pSTAT3 levels and enrich cancer stem cells abundance. BBI608 is able to significantly decrease pSTAT3 levels as well as deplete stem cell abundance, and blocks the induction

of pSTAT3 and cancer stem cells by chemotherapeutic agents. Similar encouraging preclinical data is seen when BBI608 is combined with either irinotecan, or oxaliplatin, or regorafenib. *In vitro*, treatment with BBI608 combined with irinotecan or oxaliplatin or regorafenib results in potent and synergistic colony formation inhibition in multiple CRC cell lines. Additionally, combined treatment with BBI608 and irinotecan or oxaliplatin or regorafenib suppresses levels of p-STAT3 and β-catenin, while monotherapy with irinotecan or oxaliplatin or regorafenib leads to upregulation of these proteins. Tumor tissue of combination-treated animals reveals synergy with increase in cancer cell death and decrease in tumor cell proliferation. In *in vivo* mouse CRC xenograft model, combination treatment of BBI608 with regorafenib completely suppresses tumor growth, while being safe and well tolerated by the animals. These data suggest broad potential of BBI608 for a wide variety of human gastrointestinal cancers.

1.3 GLP Toxicology

GLP 28-day repeat dose toxicology studies were performed in both rats and dogs at doses of 10, 30 and 100 mg/kg/day of BBI608 by oral gavage.

In the rat study, 100 mg/kg was not tolerated by the male rats. Toxic observations include significant weight loss, soft feces and diarrhea, and decreased food consumption, which led to early sacrifice. These observations recovered in the remaining male rats within 14 days after termination of dosing. Female rats receiving 100 mg/kg/day showed weight loss during the first week of dosing, however, weight gain recovered during the continued dosing phase without significant abnormal clinical observations.

In the rat study, abnormal laboratory findings (azotemia, hyponatremia, hypochloremia, hyperkalemia, polycythemia, neutrophilia, monocytosis, and lymphopenia) were observed primarily in moribund male rats dosed at 100 mg/kg. These findings are consistent with acute renal failure in the setting of dehydration and diarrhea. In rats dosed at 100 mg/kg for 28 days, there was mild decrease in sodium, chloride and albumin levels and mild elevation of white blood cells, red blood cells, neutrophils, lymphocytes and monocytes. No significant abnormal laboratory findings were seen in recovered rats, suggesting these abnormal laboratory findings are reversible. There were no abnormal laboratory findings in rats dosed at 10 and 30 mg/kg.

In the rat study, histopathological findings were noted in the rats dosed at 100 mg/kg, primarily in moribund male rats, including microscopic changes in the stomach and urinary bladder (focal or multifocal chronic ulceration, epithelial hyperplasia, chronic active inflammation or hemorrhagic changes), in lymphoid tissues (mild to marked lymphoid atrophy with mild to moderate lymphocyte apoptosis in thymus; mild to moderate lymphoid atrophy and mild to moderate mastocytosis in mesenteric lymph nodes; mild to moderate lymphoid atrophy in 2 moribund male rats of the 100 mg/kg group and some elevation of hemosiderosis in the spleen) and in adrenal glands (mild cortical vacuolation). These findings are considered non-specific changes related to the test vehicle in the setting of dehydration and diarrhea. There were no significant histopathological findings in recovered rats, suggesting these histopathological changes are reversible. There was no significant test vehicle related microscopic changes in rats dosed at 30 mg/kg and 10 mg/kg.

In the rat study, toxicokinetics showed that all dose groups in rats achieved BBI608 exposure well above the predicted exposure levels needed for efficacy with exposure lasting beyond 10 hours.

For the dog study, toxicity was observed in dogs receiving 100 mg/kg/day consisting of mild weight loss, as well as clinical observations including emesis, diarrhea, mucoid and soft feces. These adverse effects were reversible within 14 days in the setting of continued dosing. No treatment related clinical pathology, gross pathology or histopathological effects were observed at any dose level. All dose groups achieved plasma levels of BBI608 above the predicted levels needed for efficacy, with exposure lasting beyond 10 hours.

The no observable adverse effect level (NOAEL, based on clinical observation, laboratory tests, gross and histopathological changes) for rats administered BBI608 daily orally over 28 days was 30 mg/kg/day (human equivalent dose: 180 mg/m2) and the NOAEL in dogs administered BBI608 daily orally over 28 days was 30 mg/kg/day (human equivalent dose: 600 mg/m2).

1.4 Safety and Encouraging Signs of Antitumor Activity in Phase I and II Studies

In the Phase I dose escalation study of BBI608 monotherapy, 14 cohorts (N=41) were dosed from 20 mg to 2000 mg/day. All of the patients in this study were in the last line of treatment. Eighteen (44%) of the patients had CRC, representing the most common type of cancer studied in this trial. Other types of cancers varied from 2-7% of the total, including gastric/GEJ, pancreatic, NSCLC, prostate, head and neck, melanoma and others. Vast majority of the patients (78%) in this study progressed on $\geq$3 prior regimens.. Adverse events were generally mild, including grade 1-2 diarrhea, nausea, anorexia and fatigue with a total of 4 grade 3 events (diarrhea and fatigue). MTD was not reached. At 400 mg/day the plasma concentration of BBI608 was sustained at a concentration > 1.5 uM (several fold above the IC_{50} [ave.~0.09 uM]) for >8 hours. RP2D has been determined to be 480 mg bid. Among those evaluable for tumor response (RECIST 1.1), disease control (disease stabilization and regression) was observed in 65% of patients. Prolonged time to progression was observed in 46% of evaluable patients, including patients with CRC, head & neck, gastric, ovarian, melanoma, and breast cancer. In the subset of patients with CRC (N=18), disease control was seen in 67% of those evaluable. Median progression free survival (PFS) and overall survival (OS) of 14 and 47 weeks, respectively, were observed in evaluable CRC patients. Median OS for biomarker-positive (nuclear β-catenin and high p-STAT3) CRC patients was 53 weeks and 54 weeks, respectively. In this study, BBI608 has shown a favorable safety and PK profile, and encouraging signs of activity, particularly in CRC.

In addition, BBI608 has been evaluated in combination therapy in the Phase Ib/II studies. BBI608 has been safely combined at full dose with paclitaxel or capecitabine (BBI608-201 and BBI608-224, respectively), with a similar adverse event profile compared to monotherapy of either of the agents. The RP2D of BBI608 in combination with weekly paclitaxel or capecitabine has been determined to be 480 mg po bid.

Given the clinical data thus far, and the encouraging *in vitro* and *in vivo* results seen with combination of BBI608 with 5-FU or oxaliplatin or irinotecan or regorafenib, further evaluation of BBI608 in combination therapy to treat gastrointestinal malignancies is warranted.

1.5 Safety and Encouraging Signs of Antitumor Activity in the BBI608-246 Study

Since activating the BBI608-246 study, BBI608 combined with bi-weekly standard FOLFIRI with or without bevacizumab has been administered safely to 94 patients. The RP2D of BBI608 combined with FOLFIRI with or without bevacizumab was declared to be 240 mg PO BID (480 mg total daily dose). Combination treatment with BBI-608 and FOLFIRI with or without bevacizumab was well tolerated with no dose-limiting toxicity and safety profile similar to that of each regimen individually with no difference in safety observed with addition of bevacizumab. Most common adverse events included Grade 1 and 2 diarrhea, abdominal cramps, nausea, vomiting and anorexia (please see table below). Of the 65 patients for whom safety data is available at the clinical cut off of this application, Grade 3 AEs observed in 20 patients included diarrhea (12), fatigue (4), dehydration (1), hyponatremia (1), hypokalemia (1), hypophosphatemia (1), weight loss (1) and burning in rectum (1) resolved with dose reduction and/or supportive care. Additional adverse events included sequelae likely secondary to GI events, such as fatigue and dehydration. There were no Grade 4 or 5 adverse events observed.

Subjects with Adverse Events Possibly Related to BBI-608 in Combination with bi-weekly FOLFIRI with or without Bevacizumab

Total number of subjects with AE data: N = 65

		Any Grade		Grade 1		Grade 2		Grade 3	
System	*CTCAE*	#	%	#	%	#	%	#	%
Gastrointestinal Disorders	Diarrhea	55	84.6%	47	72.3%	30	46.2%	16	24.6%
	Nausea	48	73.8%	41	63.1%	20	30.8%	0	0.0%
	Vomiting	38	58.5%	29	44.6%	16	24.6%	0	0.0%
	Abdominal Pain	31	47.7%	24	36.9%	15	23.1%	2	3.1%
	Constipation	16	24.6%	14	21.5%	6	9.2%	0	0.0%
	Mucositis Oral	11	16.9%	10	15.4%	2	3.1%	0	0.0%
	Flatulence	8	12.3%	6	9.2%	2	3.1%	0	0.0%
	Dyspepsia	7	10.8%	5	7.7%	4	6.2%	0	0.0%
Constitutional	Fatigue	42	64.6%	38	58.5%	26	40.0%	5	7.7%
	Weight Loss	12	18.5%	11	16.9%	3	4.6%	1	1.5%
Metabolism And Nutrition Disorders	Anorexia	34	52.3%	28	43.1%	14	21.5%	0	0.0%
	Hypokalemia	8	12.3%	6	9.2%	5	7.7%	3	4.6%
Neuro-Psychiatric	Dysgeusia	9	13.8%	9	13.8%	1	1.5%	0	0.0%
Renal And Urinary Disorders	Urine Discoloration	11	16.9%	11	16.9%	0	0.0%	0	0.0%
Other	Mucositis	11	16.9%	9	13.8%	3	4.6%	0	0.0%

*Events observed in 10% or more study subjects; adverse events graded using CTCAE v 4.1

We recently reported efficacy data on 46 subjects with advanced CRC enrolled in combination with FOLFIRI with or without bevacizumab. Of the heavily pretreated patients with an average of >2 prior lines of therapy, 21 patients (46%) previously progressed on FOLFIRI with or without bevacizumab (O'Neil, ASCO 2016). DCR (PR+SD) was observed in 37 of 40 evaluable patients (93%) with PR in 13 patients (33%) (33 - 67% regression) and SD with tumor regression in 18 patients (45%), which compare favorably with the DCR of 68% and ORR of 5.4% observed with FOLFIRI with bevacizumab and with the DCR of 54% and ORR of 3.9% observed with FOLFIRI alone (Bennouna 2013). Of 20 patients who had progressed on FOLFIRI with or without bevacizumab previously and were evaluable for tumor assessment, disease control (PR+SD) was observed in 18 patients (90%), tumor regression was observed in 15 patients (75%) of which 6 patients achieved PR (30%). Among 14 XELIRI/FOLFIRI-refractory patients who had previously progressed on FOLFIRI with or without bevacizumab during or < 3 months of last dose, disease control (PR+SD) was observed in 12 patients (86%), tumor regression was observed in 9 patients (64%) of which 3 patients achieved PR (25%), confirming encouraging signs of anti-tumor activity in CRC patients, including FOLFIRI-refractory patients. Given the BBI608-246 clinical data seen with combination with BBI608 with FOLFIRI with or without bevacizumab, further evaluation of BBI608 in combination with FOLFIRI (with bevacizumab if clinically indicated) in FOLFIRI/XELIRI-refractory CRC patients is warranted.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of Phase Ib of this study is:

- To determine the safety, tolerability and recommended Phase 2 dose (RP2D) of BBI608 when administered in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan in adult patients with advanced gastrointestinal cancer.

The primary objective of Phase II of this study is:

- To assess the objective response rate (ORR) of BBI608 administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory mCRC.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the pharmacokinetic profile of BBI608 administered in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, or regorafenib.
- To determine the pharmacodynamics (i.e., identify biomarkers) of BBI608 administered in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan.

- To assess the preliminary anti-tumor activity of BBI608 administered in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan.
- To assess the disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) of BBI608 administered in combination with FOLFIRI (with bevacizumab if clinically indicated) in patients with FOLFIRI/XELIRI-refractory mCRC.

3 SELECTION OF STUDY POPULATION

This study will be conducted in patients with advanced solid gastrointestinal malignancies for whom treatment with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan is an appropriate treatment option in the judgment of physician investigators.

The study will be conducted at sites in the United States, Canada, and Europe.

3.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Signed written informed consent must be obtained and documented according to International Conference on Harmonisation (ICH)- Good Clinical Practice (GCP), the local regulatory requirements, and permission to use private health information in accordance with the Health Insurance Portability and Accountability Act (HIPAA) prior to study-specific screening procedures.
2. A histologically confirmed solid tumor of the gastrointestinal tract including
    a. Advanced unresectable, metastatic or recurrent colorectal carcinoma (CRC) for which treatment with FOLFOX6 with or without bevacizumab, FOLFIRI with or without bevacizumab, CAPOX, or regorafenib would be acceptable as determined by the Investigator.
        i. FOLFIRI/XELIRI-refractory patients with CRC enrolling on the FOLFIRI (with bevacizumab if clinically indicated) study arm must have failed treatment with one FOLFIRI or XELIRI with or without bevacizumab regimen for unresectable or metastatic disease. Treatment failure is defined as progression of disease (clinical or radiologic) during treatment with FOLFIRI or XELIRI with or without bevacizumab or $\leq$ 3 months after the last dose of treatment with FOLFIRI or XELIRI with or without bevacizumab.
        ii. Patients with CRC enrolling on the regorafenib arm of this study will have previously received at least two previous lines of therapy for advanced colorectal cancer, and will have previously received treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Patients with K-ras wild type tumors enrolling on the regorafenib arm will also have previously received either cetuximab or panitumumab.
        iii. Advanced unresectable, metastatic or recurrent hepatocellular carcinoma for which treatment with FOLFOX6 or CAPOX would be acceptable as determined by the Investigator.

iv. Advanced unresectable, metastatic or recurrent pancreatic adenocarcinoma for which treatment with FOLFOX6, CAPOX, FOLFIRI or irinotecan would be acceptable as determined by the Investigator.

b. Advanced unresectable, metastatic or recurrent cholangiocarcinoma for which treatment with FOLFOX6 or CAPOX would be acceptable as determined by the Investigator.

i. Advanced unresectable, metastatic, or recurrent gastric, GEJ or esophageal adenocarcinoma for which treatment with FOLFOX6, CAPOX, FOLFIRI or irinotecan would be acceptable as determined by the Investigator.

c. Patients may be treatment-naïve, or may have received standard chemotherapy; including regimens containing a fluoropyrimidine, or oxaliplatin, or irinotecan, or regorafenib, or bevacizumab.

3. ≥18 years of age.
4. Karnofsky performance status score ≥70% (Appendix E).
5. Male or female patients of child-producing potential agree to use contraception or avoidance of pregnancy measures during the study and for 30 days after the last BBI608 dose.
6. Females of childbearing potential have a negative serum pregnancy test.
7. Aspartate transaminase (AST) level ≤2.5 x upper limit of normal (ULN) and alanine transaminase (ALT) ≤2.5 × upper limit of normal (ULN). For patients with liver metastases, AST ≤3.5 ULN, and AST ≤3.5 ULN may be enrolled if agreed upon by the investigator and medical monitor for the sponsor.
8. Hemoglobin (Hgb) ≥10 g/dl.
9. Total bilirubin level ≤1.5 × ULN.
10. Creatinine level ≤1.5 × ULN or creatinine clearance >60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal (as determined by Cockroft-Gault equation).
11. Absolute neutrophil count ≥1.5 x 10^9/L.
12. Platelets ≥100 x 10^9/L.
13. Life expectancy estimated at ≥3 months.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Anti-cancer chemotherapy, radiotherapy, immunotherapy, or investigational agents within 7 days of the first dose of BBI608. Patients may begin BBI608 on a date determined by the investigator and medical monitor for the sponsor after a minimum of 7 days since last receiving anti-cancer treatment, provided that all treatment-related AEs have resolved or have been deemed irreversible.
2. Major surgery within 4 weeks prior to first dose.
3. Any known untreated brain metastases. Treated subjects must be stable for 4 weeks after completion of that treatment, with image documentation required. Patients must have no

clinical symptoms from brain metastases and must be either off steroids or on a stable dose of steroids for at least 2 weeks prior to protocol enrollment. Patients with known leptomeningeal metastases are excluded, even if treated.

4. Pregnant or breastfeeding.
5. Significant gastrointestinal disorder(s) that would, in the opinion of the Principal Investigator, prevent absorption of an orally available agent (e.g., Crohn's disease, ulcerative colitis, extensive gastric resection and small intestinal resection).
6. Unable or unwilling to swallow BBI608 capsules or tablets daily.
7. Prior treatment with BBI608.
8. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements.
9. For patients to be treated with a regimen containing 5-fluorouracil/leucovorin:
    a. Known hypersensitivity to 5-fluorouracil/leucovorin
    b. Known dihydropyrimidine dehydrogenase (DPD) deficiency
10. For patients to be treated with a regimen containing capecitabine:
    a. Known hypersensitivity to capecitabine
    b. Known dihydropyrimidine dehydrogenase (DPD) deficiency
    c. Significant gastrointestinal disorder(s) that would, in the opinion of the Principal Investigator, prevent absorption of an orally available agent
11. For patients to be treated with a regimen containing oxaliplatin:
    a. Neurosensory neuropathy $\geq$ grade 2 at baseline
    b. Known hypersensitivity to oxaliplatin or other platinum containing compounds
12. For patients to be treated with a regimen containing irinotecan:
    a. Known hypersensitivity to irinotecan
    b. Abnormal glucuronidation of bilirubin
13. For patients to be treated with a regimen containing bevacizumab:
    a. Current uncontrolled hypertension (systolic blood pressure [BP] > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management) as well as prior history of hypertensive crisis or hypertensive encephalopathy
    b. History of cardiac disease: congestive heart failure (CHF) $\geq$ NYHA Class II; active coronary artery disease, myocardial infarction within 6 months prior to study entry; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
    c. History of arterial thrombotic or embolic events (within 6 months prior to study entry)

d. Significant vascular disease (e.g., aortic aneurysm, aortic dissection, symptomatic peripheral vascular disease)

e. Evidence of bleeding diathesis or clinically significant coagulopathy

f. Major surgical procedure (including open biopsy, significant traumatic injury, etc.) within 28 days, or anticipation of the need for major surgical procedure during the course of the study as well as minor surgical procedure (excluding placement of a vascular access device or bone marrow biopsy) within 7 days prior to study enrollment

g. Proteinuria at screening as demonstrated by urinalysis with proteinuria ≥ 2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24 hour urine collection and must demonstrate ≤ 1g of protein in 24 hours to be eligible).

h. History of abdominal fistula, gastrointestinal perforation, peptic ulcer, or intra-abdominal abscess within 6 months

i. Ongoing serious, non-healing wound, ulcer, or bone fracture

j. Known hypersensitivity to any component of bevacizumab

k. History of reversible posterior leukoencephalopathy syndrome (RPLS)

14. For patients to be treated with a regimen containing regorafenib:

a. History of cardiac disease: congestive heart failure (CHF) ≥ NYHA Class II; active coronary artery disease, myocardial infarction within 6 months prior to study entry; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)

b. Current uncontrolled hypertension (systolic blood pressure [BP] > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management)

c. Interstitial lung disease with ongoing signs and symptoms at the time of screening

d. History of HIV infection or chronic hepatitis B or C (hepatitis B is allowed if no active replication is present; hepatitis C is allowed if no antiviral treatment is required)

e. Active clinically serious infections

f. History of arterial or embolic events (within 6 months prior to study entry)

g. Liver cirrhosis ≥ Child-Pugh class B with uncontrolled ascites (defined as not easily controlled with diuretic or paracentesis treatment)

h. History of RPLS

i. Ongoing serious, non-healing wound, ulcer, or bone fracture

j. Evidence of bleeding diathesis or a clinically significant coagulopathy (≥CTCAE Grade 3 within 4 weeks prior to the start of study)

k. Renal failure requiring hemo- or peritoneal dialysis

l. Persistent proteinuria of CTCAE grade 3 (>3.5g/24 hours)

m. Significant gastrointestinal disorder(s) that would, in the opinion of the Principal Investigator, prevent absorption of an orally available agent

n. Known hypersensitivity to regorafenib

3.3 Number of Patients

The exact number of patients estimated for this trial is dependent on the number of patient cohorts investigated based on the toxicity encountered. It is expected that, for each combination arm (except for irinotecan combination study arm for which RP2D in combination with BBI608 has already been established)*, approximately 9 to 12 patients will be enrolled in the dose escalation part of the study. Up to an additional 15 patients may be enrolled at RP2D in each arm. An additional 20 evaluable subjects will be enrolled on the hepatocellular carcinoma, cholangiocarcinoma, and gastric/GEJ, esophageal or pancreatic adenocarcinoma disease cohorts.

Safety of BBI608 at 480 mg by mouth twice daily (960 mg total daily dose) will be evaluated in each combination arm, including after RP2D establishment in that combination. DLT assessment will be performed as above with 6 patients enrolled at the dose of 480 mg by mouth twice daily (960 mg total daily dose). Up to an additional 15 evaluable patients may be enrolled in each cohort at the dose of 480 mg by mouth twice daily (960 mg total daily dose) as long as $\leq$1 of 6 patients experience a DLT at the 480 mg by mouth twice daily dose level (960 mg total daily dose).

Up to an additional 50 evaluable FOLFIRI/XELIRI-refractory CRC patients will be enrolled on the FOLFIRI (with bevacizumab if clinically indicated) study arm as an expansion cohort. FOLFIRI-refractory CRC patients will have failed treatment with FOLFIRI with or without bevacizumab regimen with failure defined as progression of disease during or <3 months after the last dose of FOLFIRI/XELIRI with or without bevacizumab.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label, Phase 1b, dose escalation study of oral BBI608 administered to patients with advanced gastrointestinal malignancy in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan. The study is designed to explore the safety, tolerability and pharmacokinetics of BBI608, and to define a recommended Phase 2 dose of BBI608 in combination with each one of the above regimens (except for irinotecan study arm for which RP2D in combination with BBI608 has been established).

Initially, 3 patients will be enrolled in each combination arm (except for the irinotecan study arm for which enrollment will begin with the expansion phase skipping DLT period assessment being that RP2D for BBI608 in combination with irinotecan has been established at the time of this amendment*) at a BBI608 dose level of 240 mg twice daily (480 mg total daily dose—Cohort I). If 0 out of 3 patients experience a DLT, then the BBI608 dose will be escalated to 480 mg twice daily (960 mg total daily dose—Cohort II) and 6 patients will be enrolled at this dose level. If 1 out of 3 patients in the 240 mg by mouth twice daily cohort experience a DLT, then an additional 3 patients will be enrolled in that arm. If a DLT occurs in ≥2 of the 6 patients in an arm, then the BBI608 dose will be reduced to 160 mg twice daily (320 mg total daily dose—Cohort Ib) and 6 patients will be enrolled at this does level.

If <1 of 6 patients experience a DLT at the 240 mg by mouth twice daily dose level, then BBI608 dose will be escalated to 480 mg by mouth twice daily (960 mg total daily dose) and 6 patients will be enrolled at this dose level. If ≤1 out of 6 patients experiences a DLT at 480 mg by mouth twice daily, this dose level will be considered the Recommended Phase 2 Dose (RP2D) for BBI608 in that combination.

If ≥2 out of 6 patients experience a DLT at 480 mg by mouth twice daily, then RP2D will be declared as the next lowest dose level at which ≤1 out of 6 patients experiences a DLT.

Cycles of therapy will consist of the patient taking BBI608 daily in combination therapy for 28 days. Tumor assessments will be performed every two cycles (eight weeks), or as otherwise clinically indicated.

Dose escalation scheme for BBI608

Cohort	Total Daily Dose[a] (mg)	Number of Patients
I	480 mg	3 [b,c]
Ib	320 mg	3 [b,d]
II	960 mg	6

[a.] Daily dose must be taken one hour prior to or two hours after meals

[b] If a BBI608-related DLT is seen in a 3 patient cohort an additional 3 patients will be enrolled at the same dose

[c]If ≥2 of 6 patients experience a DLT, then BBI608 dose will be reduced to 160 mg twice daily (total daily dose of 320 mg—Cohort Ib) and 6 patients will be enrolled at this dose level.

[d]If ≥2 patients experience a DLT at this dose level, the arm will be closed to accrual.

The recommended phase 2 dose (RP2D) for a given combination arm is defined as the dose level at which no more than one patient with DLT is observed among six patients for each combination. Once the RP2D has been reached for a given combination arm based on DLT assessment rules outlined above, up to 15 additional evaluable patients may be enrolled at RP2D. If a patient drops-out, another patient may be enrolled such that there are 15 evaluable patients available for analysis. An additional 20 evaluable subjects will be enrolled on the hepatocellular carcinoma, cholangiocarcinoma, gastric/GEJ, esophageal or pancreatic adenocarcinoma disease cohorts. Up to an additional 50 evaluable FOLFIRI/XELIRI-refractory CRC patients will be enrolled on the FOLFIRI (with bevacizumab if clinically indicated) study arm as an expansion cohort.

Number of Subjects with DLT at a Given Dose Level for a Given Combination Arm	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enter at least 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is the recommended phase 2 dose for this combination arm. Once the RP2D has been defined based on DLT assessment rules outlined in this section, up to 15 additional subjects will be enrolled followed by an additional 20 evaluable patients in each of the following groups: HCC, cholangiocarcinoma, gastric/GEJ, esophageal or pancreatic adenocarcinoma. Up to an additional 50 evaluable FOLFIRI/XELIRI-refractory CRC patients will be enrolled on the FOLFIRI (with bevacizumab if clinically indicated) study arm as an expansion cohort.

4.2 Rationale for Study Design

Considerable data has been collected from the Phase I monotherapy study of BBI608 (protocol BBI608-101) as well as phase 1b/II studies (BBI608-201, BBI608-224) conducted in advanced oncology patients who have failed multiple previous regimens.BBI608 has shown a favorable safety and PK profile, and encouraging signs of activity. Combination of cancer stem cell therapeutics with chemotherapy would allow simultaneous inhibition of cancer stem cells as well as non-stem tumor bulk cells. Given the clinical data thus far, and the encouraging *in vitro* and *in vivo* results seen with combination of BBI608 with 5-FU or oxaliplatin or irinotecan or regorafenib, further evaluation of BBI608 in combination therapy to treat gastrointestinal malignancies is warranted.

4.3 Selection of Dose

Dose escalation for BBI608 has been successfully conducted from 20 to 2000 mg total daily dose. MTD was not reached and RP2D was determined based on pharmacokinetics. Adverse events observed in the BBl608 monotherapy phase I trial have been generally mild (Grade 1-2) with the most common being diarrhea, nausea, anorexia and fatigue. Grade 3 events include fatigue and diarrhea. No bone marrow suppression or neuropathy was observed.

In phase 1b/II studies, BBI608 has been successfully combined at full dose (480 mg twice daily) with weekly paclitaxel or capecitabine, without any signs of adverse effects that differ from either agent administered as monotherapy.

Dosing of BBI608 in each combination arm of this trial will be initiated at 480 mg/day, which is 50% of the monotherapy RP2D for BBI608, and is also 50% of the RP2D of BBI608 in combination with weekly paclitaxel or capecitabine. Dosing of BBI608 in the FOLFIRI/XELIRI-refractory CRC expansion cohorts will be at 480 mg/day.

4.4 Criteria for Dose Escalation and Determination of Dose-Limiting Toxicity

Patients must have been treated with both BBI608 and the designated combination regimen to be evaluable for Dose-Limiting Toxicity (DLT). Patients evaluable for dose escalation are defined as having been exposed to at least 28 days of continuous daily administration of BBI608, starting from Cycle 1 Day 1 or having had a protocol defined DLT at any time within this period. Based on the tolerability and safety of evaluable patients, enrollment at the next dose level and/or enrollment of additional patients into the ongoing cohort for each combination arm will occur according to criteria described below:

- If zero treated patients experience a BBI608-related DLT (defined below) by Day 28 of Cycle 1, then dose escalation will occur.
- If one treated patient experiences a BBI608-related DLT by Day 28 of Cycle 1, then an additional three patients will be enrolled for a total of six patients treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (i.e. one out of six patients)
- If two or more treated patients at a dose level experience a BBI608-related DLT by Day 28 of Cycle 1, dose escalation will stop and this dose level will be considered the maximally administered dose. Three (3) additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose.
- The recommended phase 2 dose (RP2D) for a given combination arm is defined as the dose level at which no more than one patient with DLT is observed among six patients for each combination

The BBI medical Monitor and Principal Investigator will review all significant BBI608-related toxicities to determine if the dose escalation schedule requires modification. Intermediate doses may be assigned to a cohort after agreement between the BBI Medical Monitor and the Principal Investigator.

4.5 Dose-Limiting Toxicity

Dose-limiting toxicity is defined by the occurrence of any of the following toxicities possibly or probably related to BBI608 or BBI608 in combination with FOLFOX6 with and without bevacizumab, or CAPOX, or FOLFIRI with and without bevacizumab, regorafenib or irinotecan, which includes all following toxicities unless there is a clear alternative explanation. DLT will be scored during the first cycle of BBI608 treatment.

- Grade 4 hematological toxicity. In addition, Grade 3 thrombocytopenia associated with a clinically significant bleeding event will be considered a DLT
- Grade 3 or 4 non-hematological toxicity, except:

  - Grade 3 nausea/vomiting/anorexia, diarrhea, or fatigue will be considered a DLT only if it persists for 3 days despite optimal medical management
  - Alopecia will not be considered a DLT
- Any other toxicity that in the view of the Principal Investigator represents a clinically significant hazard to the patient, including delays or omissions of the backbone chemotherapy regimen.

Whether a DLT has occurred will be assessed during the 28 days of Cycle 1. DLT will be determined from adverse events, changes from baseline in physical examination findings and laboratory parameters. The incidence of adverse events and DLTs will be evaluated for each combination arm and for all patients (except for the irinotecan combination arm for which RP2D in combination with BBI608 has been established).

4.6 Study Duration

Patients will receive treatment with BBI608 until progression of disease (clinical or radiological), unacceptable toxicity or another discontinuation criterion is documented (see Section 5.7). It is expected that most patients will receive between one and four cycles of BBI608 for a treatment period of 4 to 16 weeks.

5 STUDY VISITS

5.1 Overview

Study Visits will consist of a Pre-Study Evaluation, during which the patient is evaluated to determine suitability for entry into the study, Weekly Evaluations during which the patient is regularly evaluated during conduct of the study, Monthly Evaluations, which begin after the completion of Cycle 1, and an End-of-Study Evaluation (See APPENDICES A through D for schedules of Assessments for each study arm).

Following the Pre-Study Evaluation and a determination by a Principal Investigator that the patient meets all inclusion/exclusion criteria and signs the informed consent, the patient will be considered enrolled in the study.

5.2 Informed Consent

Patients who agree to participate will sign the approved informed consent and will be provided a copy of the signed document.

Informed consent may be obtained within approximately one month prior to the first dose of BBI608. All screening procedures should be performed within 9 days of the first dose of BBI608 (unless otherwise noted).

5.3 Pre-Study Evaluations (Baseline)

After written informed consent is obtained according to ICH-GCP and local regulations, the patient will be evaluated for inclusion and exclusion criteria according to the eligibility criteria listed in Section 3.

The following will be evaluated and documented within seven days prior to first dose of BBI608:

- Medical history
- Physical examination
- Karnofsky performance status score (see APPENDIX E)
- Vital signs (weight, temperature, blood pressure, height, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Serum pregnancy test (if applicable)
- Tumor markers if applicable
- Record concomitant medication
- Baseline tumor biopsy, if applicable (can be scheduled for any time prior to first dose of BBI608 - see Section 6.6); additionally, archival tissue will be obtained per Appendix G once the patient has been enrolled.
- 12-lead electrocardiogram (ECG)
- Tumor measurement and staging [computed tomography (CT) scan or magnetic resonance imaging (MRI) scan acceptable]*

*All CT and MRI scans can be used for baseline assessment if they were performed within three weeks of the first scheduled dose of BBI608.

5.4 On-Study Assessments

5.4.1 FOLFOX6 Arm

5.4.1.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication
- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.1.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)

- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)
- FOLFOX6 regimen, IV infusion starting 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFOX therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFOX by 1-4 hours.

5.4.1.3 Cycle 1, Day 15

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- FOLFOX6 regimen, IV infusion starting 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFOX therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFOX by 1-4 hours.

5.4.1.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- FOLFOX6 regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608
- Dispense BBI608 (28 day supply plus 2 days)

Day 15

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Karnofsky performance status score
- Hematology (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication
- FOLFOX6 regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608

5.4.2 FOLFOX6 with Bevacizumab Arm

5.4.2.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication
- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.2.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)
- FOLFOX6 plus bevacizumab regimen, IV infusion starting 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFOX6 plus bevacizumab therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFOX6 plus bevacizumab by 1-4 hours.

5.4.2.3 Cycle 1, Day 15

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication

- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- FOLFOX6 plus bevacizumab regimen, IV infusion starting 3 hours after the first morning dose of BBI608
- Blood samples for pharmacokinetics, Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFOX6 plus bevacizumab therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFOX6 plus bevacizumab by 1-4 hours.

5.4.2.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- FOLFOX6 plus bevacizumab regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608
- Dispense BBI608 (28 day supply plus 2 days)

Day 15

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Karnofsky performance status score
- Hematology (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication
- FOLFOX6 plus bevacizumab regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608

5.4.3 CAPOX Arm

5.4.3.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication

- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.3.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)
- Dispense capecitabine supply for Cycle 1*
- CAPOX regimen, with oral capecitabine administration and oxaliplatin IV infusion starting 3 hours after the first morning dose of BBI608**
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (see APPENDIX F)

*Capecitabine must be administered starting in the morning of Cycle 1, Day 1. Following completion of Cycle 1, capecitabine administration at the begining of a new 3-week cycle may start with evening dosing, at the discretion of the Investigator.

** A 3 hour interval between the first daily dose of BBI608 and the administration of oxaliplatin and/or capecitabine is required on Days 1, 2, 22 and 23 of Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 should precede the administration of oxaliplatin and/or capecitabine by 1-4 hours.

5.4.3.3 Cycle 1, Day 22

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- CAPOX regimen, with oral capecitabine administration and oxaliplatin IV infusion starting about 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, Cycle 1 ONLY (see APPENDIX F)

* A 3 hour interval between the first daily dose of BBI608 and the administration of oxaliplatin and/or capecitabine is required on Days 1, 2, 22 and 23 of Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 should precede the administration of oxaliplatin and/or capecitabine by 1-4 hours.

5.4.3.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- CAPOX regimen, with oral capecitabine administration and oxaliplatin IV infusion starting 1-4 hours after the first morning dose of BBI608
- Dispense BBI608 (28 day supply plus 2 days)
- Dispense capecitabine supply for the given 28 Day Cycle

NOTE: Due to the 3 week nature of CAPOX cycles, the weeks that capecitabine and the day(s) that oxaliplatin are administered during the 28-day study cycle will vary from cycle to cycle.

5.4.4 FOLFIRI Arm

5.4.4.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication
- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.4.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)

- FOLFIRI regimen, IV infusion starting 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFIRI therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFIRI by 1-4 hours.

5.4.4.3 Cycle 1, Day 15

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- FOLFIRI regimen, IV infusion starting 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFIRI therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFIRI by 1-4 hours.

5.4.4.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- FOLFIRI regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608
- Dispense BBI608 (28 day supply plus 2 days)

Day 15

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Assess adverse events (AE)

- Record concomitant medication
- FOFLIRI regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608

5.4.5 FOLFIRI with Bevacizumab Arm

5.4.5.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication
- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.5.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)
- FOLFIRI plus bevacizumab regimen, IV infusion starting about 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFIRI plus bevacizumab therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFIRI plus bevacizumab by 1-4 hours.

5.4.5.3 Cycle 1, Day 15

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)

- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- FOLFIRI plus bevacizumab regimen, IV infusion starting about 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, Cycle 1 ONLY (see APPENDIX F)

*A 3 hour interval between the first daily dose of BBI608 and the initiation of FOLFIRI plus bevacizumab therapy is required only during Cycle 1, in order to standardize PK interpretation. Following completion of Cycle 1, the first daily administration of BBI608 should precede the administration of FOLFIRI plus bevacizumab by 1-4 hours.

5.4.5.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- FOLFIRI plus bevacizumab regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608
- Dispense BBI608 (28 day supply plus 2 days)

Day 15

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication
- FOFLIRI plus bevacizumab regimen, IV infusion starting 1-4 hours after the first morning dose of BBI608

5.4.6 Regorafenib Arm

5.4.6.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication

- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.6.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)
- Administer regorafenib about 3 hours after the first morning dose of BBI608*
- Dispense regorafenib (supply for 21 days out of 28 day cycle)**
- Blood samples for pharmacokinetics, red blood cell pellet Cycle 1 ONLY (see APPENDIX F)

* A 3 hour interval between the first daily dose of BBI608 and the administration of regorafenib is required on Days 1, 2, 15 and 16 of Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 should precede the administration of regorafenib by 1-4 hours.

5.4.6.3 Cycle 1, Day 15

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Administer regorafenib about 3 hours after the first morning dose of BBI608*
- Blood samples for pharmacokinetics, Cycle 1 ONLY (see APPENDIX F)

* A 3 hour interval between the first daily dose of BBI608 and the administration of regorafenib is required on Days 1, 2, 15 and 16 of Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 should precede the administration of regorafenib by 1-4 hours.

5.4.6.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- Dispense BBI608 (28 day supply plus 2 days)
- Dispense regorafenib (supply for 21 days out of 28 day cycle)

5.4.7 Irinotecan Arm

5.4.7.1 Week 0 (Day [-] 5)

A Day [-] 5 visit should ONLY occur during the first cycle of BBI608 administration. Patients who meet all inclusion and exclusion criteria will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- 12-lead electrocardiogram (ECG)*
- Record concomitant medication
- Dispense BBI608 (5 day supply plus 2 extra days)

* The 12-lead electrocardiogram on Cycle 1 Day [-5] should be obtained two hours *after* first BBI608 has been administered.

5.4.7.2 Cycle 1, Day 1

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Dispense BBI608 (28 day supply)
- Irinotecan IV infusion starting 1-4 hours after the first morning dose of BBI608

5.4.7.3 Cycle 1, Day 15

The patient will have the following assessments:

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Assess adverse events (AE)
- Record concomitant medication
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Irinotecan IV infusion starting 1-4 hours after the first morning dose of BBI608

5.4.7.4 Cycle 2 and Beyond

Day 1

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry (see Section 6.3)
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- Tumor markers (if applicable)
- Tumor biopsy (for Cycle 2 only, if applicable)
- Assess adverse events (AE)
- Record concomitant medication
- Irinotecan IV infusion starting 1-4 hours after the first morning dose of BBI608
- Dispense BBI608 (28 day supply plus 2 days)

Day 15

- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Assess adverse events (AE)
- Record concomitant medication
- Irinotecan IV infusion starting 1-4 hours after the first morning dose of BBI608
-

5.5 Tumor Evaluation Visits

Disease status and tumor response will be assessed at eight-week intervals until objective disease progression, or as clinically indicated. Standard imaging studies will be performed according to institutional procedures. Tumor response will be evaluated using the guidelines for Response Evaluation Criteria in Solid Tumors (RECIST 1.1) outlined in Section 9. De-identified radiologic image dictation report as well as de-identified copies of the radiologic images for independent review may be requested in cases where radiologic assessment is in question. However, the study Case Report Forms (CRFs) will include relevant lesion measurements as determined by the study site.

Patients will have confirmatory radiographic scanning within approximately 4 weeks of initial results of partial or complete response (PR or CR) according to RECIST 1.1.

Once clinical or radiological progression of disease during BBI608 therapy is documented, patients must be taken off treatment and may receive any therapy as determined by their treating physician.

5.6 End of Study Evaluation

All patients will be followed for a minimum of 30 days after the last dose of BBI608. If a patient is removed from the study due to drug-related adverse events, the patient will be followed until resolution of any drug-related AE occurring during the study or within 30 days of the last BBI608 dose, or for 30 days, whichever is longer. In the presence of toxic effects, follow-up visits will be required every four weeks until all study related toxicities have resolved to baseline (or < Common Terminology Criteria for Adverse Events [CTCAE] Grade 1), stabilized or are deemed irreversible.

The following assessments will be made during the end of study visit:

- Physical examination
- Karnofsky performance status score
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Biochemistry
- Urinalysis including fractional excretion of sodium phosphate (see Section 6.3)
- 12-lead ECG
- Tumor marker, if applicable
- Tumor measurement and staging if applicable
- Assess adverse events
- Record concomitant medications

Patients will be followed for Overall Survival.

5.7 Discontinuation from Study

Patients will be removed from the study at any time if they meet any of the following criteria:

- Documented radiologic or clinical progression of disease
- Noncompliance with any part of the study, as evaluated by the Principal Investigator and Medical Monitor
- Withdrawal of consent
- Investigator decision
- Lost to Follow-up
- Death
- Clinically unacceptable toxicities despite optimal treatment or dose reduction
- Pregnancy

6 STUDY PROCEDURES

6.1 Medical History

Medical history will include, but is not limited to, the following:

- Demography: date of birth, sex, ethnic origin, height, and weight
- Clinically significant prior diagnoses, surgeries, and current medications
- Prior cancer history, current cancer diagnosis, tumor stage at time of diagnosis and screening, KRAS, NRAS, BRAF and MSI mutation status, previous chemotherapy, including dates and duration of treatment, previous radiation therapy, including anatomic site, dose and date of treatment

Prior records, radiology reports, radiology imaging, or procedure notes may be required in order to verify components of study patient history.

6.2 Physical Examination

Complete physical examination including height, weight, blood pressure, heart rate, respiratory rate, temperature (oral, axillary or tympanic) and Karnofsky performance status score.

6.3 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, and urinalyses. All laboratory tests required during the study must be obtained at a primary laboratory designated by the Principal Investigator.

- Hematology: CBC including hemoglobin, white blood cell count with 5-part differential, platelets
- Biochemistry: electrolytes (sodium, potassium, and chloride), HCO_2, calcium, phosphorus, magnesium, total protein, albumin, glucose, and serum creatinine, blood urea nitrogen (BUN), AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin, and uric acid
- Routine urinalysis: dipstick including protein, specific gravity, glucose and blood as well as fractional excretion of sodium phosphate
- Serum pregnancy test for female patients of childbearing potential

6.4 Pharmacokinetic Assessments

Blood samples for the PK of BBI608 will be collected from all treated patients except for patients enrolled on Arm G (irinotecan). Collection, storage, and shipping of PK samples will be performed as described APPENDIX F: Pharmacokinetic Studies.

6.5 Pharmacodynamic Assessments

Pre-clinical and clinical studies conducted by BBI have identified several biomarkers in tumor tissues whose levels either increase or decrease upon exposure to BBI608. Tumor biopsies will be collected as described below. The goal of the proposed biomarker study is to examine the response of biomarkers in patients treated with BBI608. Subject tumor samples will be processed for determination of pharmacodynamic markers in malignant tissue by histopathology and CSC assays.

6.6 Tumor Biopsy

Patients who are identified by the Principal Investigator as having an easily accessible lesion, which could be biopsied with a minimally invasive procedure, will be asked to sign an additional consent. Patients with easily accessible tumors who consent to the optional biopsy should have a *baseline* biopsy prior to starting treatment with BBI608, and an *on-treatment* tumor biopsy which will be collected on Day 1 of Cycle 2 (+/- 2 days) of the first cycle of treatment with BBI608.

An easily accessible lesion is a lesion which, in the opinion of the Study Investigators, could be biopsied with a minimally invasive procedure, and with minimal risk to the patient. The baseline biopsy, if applicable, needs to be obtained no more than 1-week prior to the first dose of BBI608.

The *on-treatment* biopsy will be collected approximately 4-6 h after the first administration of BBI608 on Day 1 of Cycle 2. (If a patient withdraws from the study, or if a DLT occurs and the patient stops taking BBI608 prior to Day 1 of Cycle 2, then the *on-treatment* biopsy will be canceled.)

In addition, archival tissue samples from a previous resection or biopsy should be collected from all patients enrolled in the clinical trial if they are available.

Collection, storage, and shipping of tissue samples will be performed as described in Appendix G: Tumor Biopsies. Tumor samples may be used for the following investigations:

- Pharmacodynamics
- Pharmacokinetics (see section 6.4 and Appendix F)

Other investigations on tumor samples may be performed as determined by the study investigators and/or study sponsors. If the patient grants permission, tumor samples may be stored for additional future studies.

7 TREATMENT

7.1 BBI608

BBI608 capsules or tablets will be supplied to the pharmacy at the clinical sites. Study drug will be labeled as an investigational agent, limited by federal law. The pharmacist will dispense an appropriate number of each strength capsule or tablets to the Principal Investigator for in-clinic dosing. The appropriate quantity of capsules or tablets will be dispensed to the patient for each cycle (see Section 5.4 and Appendices A, B, C and D).

BBI608 is supplied in 80 mg capsules or tablets and should be stored at room temperature (15-25 degrees Celsius). These instructions must appear on the label for the container in which capsules or tablets are delivered to the patient.

7.1.1 Investigational Product Accountability

BBI will provide all study drug required for completion of this study. The recipient will acknowledge receipt of the drug indicating shipment content and condition. Damaged supplies will be replaced. Until dispensed to the patients, the 80 mg capsules or tablets will be stored in a temperature controlled, secure locked area, accessible to authorized personnel only, at room temperature (15-25 degrees Celsius).

Accurate records of all study drug dispensed from and returned to the study site are to be maintained. The study site must supply a copy of their drug destruction policy to BBI before authorization for destruction will be granted. Product accountability will be monitored throughout the study. Upon completion or termination of the study, and after inventory by a BBI monitor or designated representative, all unopened drug is to be returned to BBI, or designee, in the original containers.

7.1.2 BBI608 Administration

BBI608 will be administered continuously by mouth twice daily, with doses approximately 12 hours apart for 28 consecutive days. BBI608 should be administered approximately one hour prior to or two hours after meals, with the first dose given in the morning.

The dose of BBI608 to be administered depends on the dose level cohort to which the patient is enrolled. See Section 4.1 for details.

Intra-patient dose escalation is permitted if the new dose level cohort is complete and proven safe. Intra-patient dose escalation can occur following the agreement of both the Principal Investigator and the medical monitor of the Sponsor.

Intra-patient dose de-escalation is allowed due to adverse events, pharmacokinetic data, or pill burden, provided that the new dose level is below MTD (maximum tolerated dose) and the new dose level is agreed upon by the Principal Investigator and the medical monitor of the Sponsor.

7.1.3 FOLFOX6 with and without Bevacizumab, CAPOX, FOLFIRI with and without Bevacizumab, Regorafenib or Irinotecan Administration

Detailed instructions for the preparation, premedication, and administration of FOLFOX6 with and without bevacizumab, CAPOX, FOLFIRI with and without bevacizumab, regorafenib or irinotecan are provided in the Product Labels approved by Health Canada or US FDA.

ARM A- FOLFOX6 – Oxaliplatin 85 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously starting on Day1 of Cycle 1, after the first daily dose of BBI608**. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following oxaliplatin/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2 over 46-48 hours) continuous intravenous infusion This regimen will be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted.

ARM B- FOLFOX6 plus bevacizumab - Oxaliplatin 85 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously over 2 hours starting on Day1 of Cycle 1, following the first daily dose of BBI608*. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following oxaliplatin/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2 over 46-48 hours) continuous intravenous infusion. Bevacizumab 5 mg/kg will be administered intravenously following oxaliplatin/leucovorin infusion. This regimen will be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted.

ARM C- A CAPOX regimen will be administered orally (capecitabine) and IV (oxaliplatin). Starting on Day 1 of Cycle 1, capecitabine 850 mg/m^2 will be administered orally twice-daily following the first daily dose of BBI608* for 14 consecutive days and be repeated every 21 days. Oxaliplatin 130 mg/m^2 will be administered IV over 2 hours, following the first daily dose of BBI608* starting on Day 1 of Cycle 1 and be repeated every 21 days thereafter. In case of toxicity, dose adjustment is permitted. If capecitabine is tolerated at the 850 mg/m^2 twice daily dose, dosage may be increased to 1000 mg/m^2 twice daily as tolerated after the first cycle.

ARM D- A FOLFIRI** – Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously starting on Day 1 of Cycle 1, following the first dose of BBI608*. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted.

ARM E- FOLFIRI plus bevacizumab - Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously starting on Day 1 of Cycle 1, following the first dose of BBI608*. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. Bevacizumab 5 mg/kg will be administered intravenously following oxaliplatin/leucovorin infusion. This regimen will be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted.

ARM F- Regorafenib 120 mg will be administered orally once daily, with a low-fat meal, starting on Day 1 of Cycle 1, following the first daily dose of BBI608* and be continued for 21 consecutive days of every 28 days thereafter. In case of toxicity, dose adjustment is permitted. If regorafenib is tolerated in the first cycle, dosage may be increased to 160 mg once daily as tolerated after the first cycle.

ARM G- Irinotecan 180 mg/m^2 will be administered intravenously starting on Day 1 of Cycle 1, following the first dose of BBI608. This regimen will be repeated every 14 days thereafter. In case of toxicity, dose adjustment is permitted.

*A 3 hour interval between the first daily dose of BBI608 and the initiation of combination therapy is required on PK days during Cycle 1 only, in order to standardize PK interpretation. On all other days, the first daily administration of BBI608 should precede the administration of combination therapy by 1-4 hours.
** FOLFIRI/XELIRI-refractory patients enrolled as part of the 50 evaluable patient expansion cohort can resume FOLFIRI at the last dose that they received prior to progression on their prior FOLFIRI treatment.

7.2 Dose Modifications

7.2.1 BBI608

For any BBI608-related intolerable grade 3 or intolerable grade 2 adverse events, persisting despite optimized medical management, a dose holiday of 1-3 days followed by dose modification is recommended. The dose can be reduced by 1/3 or ½ (as allowed by capsule or tablet strength). For instance, if a patient requires a dose modification at the dose level of 240 mg twice daily, the dose can be reduced to 160 mg twice daily. If a patient requires a dose modification at the dose level of 480 mg twice daily, the dose can be reduced to 240 mg twice daily. Investigators should discuss dose modifications with the medical monitor for the sponsor. Patients should up-titrate dose with the goal of achieving full dose as tolerated.

If a toxicity is thought by the Investigator to be related to both BBI608 and the combination regimen (FOLFOX6 with and without bevacizumab, CAPOX, FOLFIRI with and without bevacizumab, regorafenib or irinotecan), then the dose modification rules for both BBI608 and the combination regimen should be followed.

7.2.2 FOLFOX6 with and without Bevacizumab, CAPOX, FOLFIRI with and without Bevacizumab, Regorafenib and Irinotecan

Dose modifications for toxicities expected from combination agents/regimen should be performed according to the Investigator, as per Product Labels approved by Health Canada or US FDA, respectively.

7.3 Treatment Compliance

A patient is considered compliant with the study protocol when study medication is administered at a compliance level of greater than 80%.

BBI608 compliance will be calculated using the following equation:

(Number of capsules or tablets actually ingested /number of capsules or tablets that should have been ingested per dose level) x 100 = % compliance

For any IV combination drug, compliance will be calculated using the following equation:

(Number of treatments administered /number of treatments that should have been administered) x 100= % compliance

For any oral combination drug, compliance will be calculated using the following equation:

(Number of capsules actually ingested /number of capsules that should have been ingested) x 100 = % compliance

7.4 Blinding

This is an open label study. Neither the patient nor the investigator and site staff will be blinded to the treatment administered.

7.5 Prior Treatment

Reasonable efforts will be made to determine all relevant prior treatments received by the patient within four weeks of the first BBI608 dose. All relevant information must be recorded on the appropriate patient's Case Report Form (CRF). All surgical procedure history, prior chemotherapy and radiation therapy must be recorded on the appropriate CRF.

7.6 Concomitant Medication

7.6.1 Permitted Treatment

All information regarding concomitant treatments (medications or procedures) must be recorded on the patient's CRF (including the name of the medication or procedure and duration of treatment).

Palliative and supportive care for disease-related symptoms will be offered to all patients in this study.

BBI608 was shown *in vitro* to inhibit individual CYP P450 isoforms 1A2, 2D6, 2C19, 3A4, and 2C9 with IC_{50}'s of 0.25 μM, 0.25 μM, 2.5 μM, 5 μM, and 0.5 μM respectively, under serum-free conditions. Since *in vitro*, BBI608 has shown the ability to inhibit these CYP P450 isoforms, concomitant use of agents that are substrates of these CYP P450 enzymes should be avoided unless deemed medically necessary by the primary investigator. Examples of commonly prescribed agents that are metabolized by these CYP P450 enzymes are:

NSAIDS: such as ibuprofen, naproxen
Proton pump inhibitors: such as lansoprazole, omeprazole
Oral hypoglycemic medications: sulfonylureas
Beta-blockers: metoprolol, carvedilol
Calcium channel blockers: amlodipine, diltiazem, nefedipine, verapamil
Antidepressants: paroxetine, imipramine, amitriptyline
Anti-epileptics: such as phenytoin, phenobarbitone
Anti-psychotics: such as haloperidol, risperidone
Antibiotics: such as clarithromycin, erythromycin
HMG CoA reductase inhibitor: atorvastatin, lovastatin, simvastatin
Anesthetics: such as halothane, enflurane;
HIV antivirals: such as saquinavir, indinavir, ritonavir
Immunomodulators (immunosuppressives): such as cyclosporine, tacrolimus
Steroids: such as hydrocortisone, estrodiol

BBI608 is metabolized by the CYP P450 isoform 1A2. Therefore, concomitant use of drugs which

inhibit CYP1A2 should be avoided unless deemed medically necessary by the primary investigator. Known drugs that inhibit CYP 1A2 include ciprofloxacin and other fluoroquinolones, Fluvoxamine Verapamil, amiodarone, interferon, methoxsalen, enoxacin, mexiletine, and ticlopidine.

Of note, no clinically apparent drug-drug interactions occurred during phase 1, phase 1b/2 studies conducted on BBI608 thus far.

In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Epoetin alfa (Epogen®, Procrit®)
- Hematopoietic growth factors, including filgrastim (Neupogen®), or other granulocyte colony stimulating factors (G-CSF), are permitted following documented and clinically significant neutropenia after the patient has completed at least one cycle of treatment with BBI608
- Prophylactic antiemetics may be administered according to standard practice
- Low dose corticosteroids used as an antiemetic regimen
- Megestrol acetate (Megace®)

7.6.2 Prohibited Treatment

- Any concurrent chemotherapy, radiotherapy, (palliative radiotherapy for non-target lesions may be permitted in certain cases as decided by the principal investigator and sponsor), hormonal therapy, or immunotherapy
- Other investigational agents

  Immunosuppressive therapies, including systemic corticosteroids such as prednisone 10 mg daily or equivalent (except when used intermittently in an antiemetic regimen)

8 SAFETY ASSESSMENTS

8.1 Adverse Events

8.1.1 Assessments

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study. All AEs considered to be related to BBI608 occurring after any administration of the study drug will be followed until the event resolves. AEs will be evaluated using the National Cancer Institute (NCI) CTCAE, Version 4.0.

Investigators are required to document all AEs occurring during the clinical trial, commencing with the first dose of BBI608 and including the protocol-defined post-treatment follow-up period (21 Code of Federal Regulations [CFR] §312.64[b]) on designated CRF pages. AEs occurring following the signature of the informed consent, but prior to the first dose of study drug will not be reported as AEs. It is also important to record all AEs that result in permanent discontinuation of the investigational product being studied, whether serious or non-serious.

Serious adverse events (SAEs), as defined below, must be reported to Boston Biomedical Inc. or its representative within 24 hours of knowledge of their occurrence.

8.1.2 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical investigational patient administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment. An AE can, therefore, be any unfavorable and unintended sign (including an

abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Laboratory data are to be collected as stipulated in this protocol, and toxicity trends will be analyzed utilizing objective toxicity criteria. Clinical syndromes associated with laboratory abnormalities are to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycemia).

Progression of disease is considered an efficacy outcome parameter and should not be captured as an AE. A non-serious AE is any untoward medical occurrence that does not meet any of the criteria for SAEs as defined below.

Patients should be instructed to report any AE that they experience to the Investigator. Investigators should assess the patient for AEs at each visit. AEs occurring during the clinical trial and the follow-up period should be recorded on the appropriate AE CRF. To capture the most potentially relevant safety information during a clinical trial, it is important that investigators record accurate AE terms on CRFs.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

8.2 Serious Adverse Events

8.2.1 Definitions

A serious adverse event (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events may be considered an SAE based upon appropriate medical judgment.

Under this protocol, scheduled hospitalizations or elective surgical/medical procedures or elective hospitalization will not be considered SAEs. Prolongation of a scheduled hospitalization can be considered an SAE. Complications associated with scheduled procedures are considered an AE.

8.2.2 Reporting Serious Adverse Events

Any SAE, including death, due to any cause that occurs during this investigation, whether or not related to the administration of study drug, must be reported to the Sponsor immediately (not to exceed 24 hours) by telephone, secured email or facsimile. The reaction must be completely described on the CRF and SAE report form.

Primary Medical Monitor Contact information:
Laura Borodyansky, MD Boston Biomedical, Inc 640 Memorial Drive Cambridge, MA 02139 Telephone: (617) 674-6800 ext 8705 Fax: (617) 674-6800 Email: lborodyansky@bostonbiomedical.com
Emergency Number**:** 339-364-5611

9 ASSESSMENT OF ANTI-TUMOR ACTIVITY

The following definitions and criteria (from Response Evaluation Criteria in Solid Tumors [RECIST 1.1, Eisenhauer et al., 2009]) should be used for the baseline evaluations of existing disease, and for the ongoing evaluation of tumor responses.

Measurable disease - presence of at least one measurable lesion.

Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥10 mm using conventional techniques or ≥10 mm with spiral CT scan. Malignant lymph nodes must be ≥15 mm in the shortest diameter.

Non-measurable lesions - all other lesions, including small lesions (longest diameter <10 mm with conventional techniques or <10 mm with spiral CT scan or ≥10 mm to ≤15 mm in short axis), i.e., bone lesions, ascites, pleural/pericardial effusion, cystic lesions and also abdominal masses that are not confirmed and followed by imaging techniques.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Lesions identified by clinical exam will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, and a measurement with a ruler to estimate the size of the lesion, is recommended.

9.1 Central Radiology Review

A central radiology review will be used for this study. A central imaging reviewer will provide an independent review of response and progression only for the FOLFIRI/XELIRI-refractory CRC patients enrolled onto the study on the FOLFIRI (with bevacizumab if clinically indicated) combination arm. Collection of all on-study CT/MRI scans for all FOLFIRI/XELIRI-refractory CRC patients enrolled on the study will be included as part of the review.

Films or electronic copies should be collected by the investigative sites and sent to the central image reader. Complete details regarding image handling and submission can be found in the Radiology Technical Manual.

9.2 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.
- All imaging methods should be performed according to institutional standards with each patient having consistency of methods beginning from baseline through the course of the study.

9.3 Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of five lesions total with a maximum of 2 lesions per organ, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

9.4 Response Criteria

	Evaluation of target lesions
Complete Response (CR):	Disappearance of all target lesions Any pathological lymph nodes must have reduction in short axis of <10mm
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started. In addition to the increase of 20%, the sum must also demonstrate an absolute increase of at least 5mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis)
Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

9.5 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence and is determined as indicated in the table below:

Target lesions	Non-Target lesions	Evaluation of New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10 PLANNED STATISTICAL METHODS

10.1 General Considerations

Phase Ib:

Because of the nature of this study, no formal statistical analysis is planned. Evaluation of the data will consist primarily of summary displays (i.e., descriptive statistics and graphs).

Phase II:

Efficacy in the FOLFIRI/XELIRI-refractory expansion cohort will be evaluated as a single stage design.

10.2 Determination of Sample Size

Phase Ib:

The sample size for this study was determined by clinical rather than statistical considerations. With cohort sizes of three to six patients, if the true underlying rates of DLT are 0.1, 0.2, 0.3, 0.4, and 0.5, there will be 91%, 71%, 49%, 31%, and 17% chances, respectively, of escalating to the next full dose.

Phase II:

Anti-tumor activity of the FOLFIRI/XELIRI-refractory CRC patients enrolled will be evaluated as a single stage design. Evaluable patients will include all FOLFIRI/XELIRI-refractory CRC patients who receive on-study tumor response assessment. This analysis will test the following:

$$\text{Ho: } \pi \leq 0.05$$

Versus

$$\text{Ha: } \pi > 0.05$$

If ORR response rate with FOLFIRI treatment alone is estimated at 5% and a true ORR response rate with FOLFIRI (with bevacizumab if clinically indicated) in combination with BBI608 is 12%, a sample size of 50 evaluable patients produces a two-sided 95% confidence interval with a width of 0.2, for a 95% exact confidence interval of 4.5%-24.5%.

10.3 Analysis Populations

All patients receiving at least one dose of BBI608 will be considered evaluable for safety analysis. Adverse event incidence rates will be described by the frequency of adverse events, categorized by NCI CTCAE version 4.0. Listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented.

Patients evaluable for dose escalation are defined as having been exposed to at least 28 days of continuous daily administration of BBI608, starting from Cycle 1 Day 1.

Patients who have received at least one cycle of study treatment and have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. Anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics.

10.4 Demographics and Baseline Characteristics

Patient characteristics will include a summary of the following:

- Patient demographics
- Baseline disease characteristics

- Pre-existing conditions
- Prior therapies
- Concomitant medications and treatments

Other patient characteristics will be summarized as appropriate

10.5 Statistical Analysis of Pharmacokinetic Variables

Timed blood sample collection for pharmacokinetic analysis will be performed on Days 1 (for all patients), 15 (for FOLFOX6 with and without bevacizumab and FOLFIRI with and without bevacizumab and regorafenib arms ONLY), and 22 (for CAPOX arm ONLY) during Cycle 1.

Timed blood sample collection for pharmacokinetic analysis will additionally be performed for patients who experience a dosing regimen modification.

These sample collections will be according to the parameters outlined in Sections 6.4, 6.5, and Appendices A, B, C and D.

Bioanalytical analysis of patient samples will be conducted at a centralized laboratory using GLP-validated assays. Plasma concentrations will be summarized by descriptive statistics, including mean, standard deviation, coefficient of variation, minimum, maximum, and median.

Concentration profiles will be analyzed by non-compartmental and/or non-linear least squares regression using WinNonLin. Pharmacokinetic parameters, including C_{max}, volume of distribution, distribution half-life, terminal half-life, and AUC will be evaluated.

10.6 Safety Analysis

Safety will be assessed by physical examination, and laboratory assessments. Adverse events will be graded according to the NCI CTCAE, version 4.0. The incidence of adverse events and DLTs will be evaluated for each dose level, and for all patients combined. Patients will be followed for adverse events for at least 30 days after the last dose of BBI608, or until recovered from all related BBI608 adverse events.

11 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the sponsorship of Boston Biomedical. Study drug, clinical supplies, and CRFs will be supplied by Boston Biomedical, or its representative. Representatives of Boston Biomedical will monitor the study to verify study data, medical records, and CRFs in accordance with current ICH GCPs and other applicable regulations and guidelines.

11.1 Compliance with the Protocol

The Investigator will notify the Sponsor of any deviations from the protocol. Such contact with the Sponsor will be made as soon as possible to permit a decision as to whether or not the subject (for whom the deviation from the protocol was effected) is to continue in the study. The case records will describe the deviation from the protocol and state the grounds for it.

11.2 Registration and Enrollment

This is an open-label, non-randomized study. Boston Biomedical should be notified as soon as a subject qualifies for entry in the protocol. Subjects will be registered by faxing Boston Biomedical or their designee, within 7 (+2) days prior to the 1st drug administration. At that time the dose level will be assigned. The subject will be enrolled into the study when the subject receives the 1st dose of study drug. Registration and enrollment forms and faxing instructions will be provided with the Case Report Forms (CRFs). The site should maintain a log of all subjects who are screened (i.e., who sign consent) but do not qualify for the study, or who do not receive study drug. The reason for disqualification should be noted in the log.

11.3 Removal, Replacement, or Early Withdrawals of Subjects

If a subject exits the study prior to receiving four weeks of study drug or does not receive four weeks of study drug for a reason other than DLT, an additional subject may be recruited to replace the subject.

12 COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS AND INFORMED CONSENT

12.1 Institutional Review Board

The protocol, any protocol modifications, informed consent form that will be used, and, if applicable, the permission to use private health information must be approved by the Investigator's IRB or Independent Ethics committee (IEC) before the study is initiated. Documentation of this approval (i.e., a copy of the document showing IRB/IEC approval including the chairperson's signature and the date of approval) must be provided to Boston Biomedical or its designee, and made available during an inspection by the FDA or other regulatory agency inspectors. The Investigator will submit to Boston Biomedical:

- A list of the names, occupations, and affiliations of the members of the IRB
- Documentation that the IRB is duly constituted or a General Assurance Number
- No supplies will be shipped until the IRB has given written approval of the protocol and informed consent and Boston Biomedical has received copies of the approvals

It is the responsibility of the Investigator to:

- Submit to the IRB/IEC for review any advertisements that will be used to recruit subjects
- During the conduct of the study, submit progress reports to the IRB, if required, and request review of the study
- Report, in writing, to the IRB all SAEs that occurred during the study or SAEs reported in other studies using study drug, per local IRB regulations
- Inform the IRB of any changes in the protocol and obtain documented IRB approval of the changes
- Maintain a file of study-related information, including all correspondence with the IRB/IEC
- Within 3 months of study completion, provide the IRB with a final report on the study

12.2 Compliance with Good Clinical Practice and Ethical Considerations

This study must be conducted in compliance with IRB/IEC informed consent regulation and the ICH GCP Guidelines. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the trial participants.

This study will be conducted according to the current revision of the Declaration of Helsinki (Revised Edinburgh, Scotland, 2000) and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

Before initiating a trial, the Investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), written informed consent form, patient recruitment procedures (e.g., advertisements) and written information to be provided to patients.
Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

12.3 Informed Consent and Permission to Use Private Health Information

The Investigator, or designee, is responsible for the content of the informed consent form, but the content must be submitted and approved by Boston Biomedical, prior to submission to the IRB. Before the start of required study procedures, the Principal Investigator or associate must obtain informed consent from each study participant (or the subject's parent/guardian) in accordance with ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. It should also include any additional information required by local laws relating to institutional review.

Informed consent must be obtained from the subject before any screening activity, washout of medication, or treatment (that is not part of routine care) is undertaken. Informed consent will be obtained by discussing with the subject the purpose of the study, the risks and benefits, the study procedures, and any other information relevant to the subjects.

The subject or his/her legal representative will document their informed consent by signing the current version of the written, IRB-approved, informed consent form in the presence of a witness.

The person, who conducted the informed consent discussion with the subject and/or guardian, must also sign the informed consent form. The subject should be given a copy of the informed consent form with all of the appropriate signatures.

The Principal Investigator will ensure that a copy of the signed consent is kept with the Clinical Trial Master File.

The Investigator or designee must explain to the patient subject that for evaluation of study results, that subject's private health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and ECs/IRBs, before enrolling that subject into the study. It is the Investigator's (or designee's) responsibility to obtain permission to use private health information from each subject, or if appropriate, the subject's legal guardian.

13 STUDY MANAGEMENT

13.1 Amendments to the Protocol

Once the protocol has been approved by the IRB, the Investigator will not modify it without obtaining the prior concurrence of Boston Biomedical. In turn, Boston Biomedical will inform the Investigator in writing of any amendment to the protocol. The Investigator must submit the protocol modifications and any informed consent modifications to the IRB, and approval must be obtained before the modifications are implemented. Boston Biomedical will submit protocol modifications to Health Canada.

13.2 Investigator Brochure and Information Materials

Before the study begins, the Investigator will receive an Investigator's Brochure describing all known contraindications, warnings, precautions, and adverse reactions associated with the administration of the study drug. If such information is revised while the study is in progress, the brochure will be amended or revised, and Boston Biomedical will provide the most current version to the Investigator.

13.3 Pre-investigational Documents

Prior to the shipment of the study drug(s), the Investigator will supply Boston Biomedical with the following:

- A signed Investigator Clinical Research Agreement
- A completed Form FDA 1572 signed by the Investigator
- Current curricula vitae and copy of current medical license for the Principal Investigator and Sub-Investigators listed on Form FDA 1572
- A completed financial disclosure form for all personnel listed on Form FDA 1572
- Signed and dated protocol signature page by the Principal Investigator
- A copy of the approval for this protocol from the IRB listed on Form FDA 1572
- A copy of the approval for the informed consent from the IRB listed on Form FDA 1572
- A copy of the IRB-approved informed consent
- Evidence of laboratory certification and a list of laboratory normal ranges for all laboratories listed on Form FDA 1572
- A list of the IRB members (for the IRB on Form FDA 1572) and the member occupations and affiliations; written verification that the IRB is duly constituted or the General Assurance Number

13.4 Drug Inventory Record

The Investigator, or a responsible party (research pharmacist or other) designated by the Investigator, must maintain an inventory record of drug received and dispensed. Boston Biomedical will provide forms to facilitate the inventory control. These forms must be used unless the Investigator has previously established a system that complies with FDA and/or Health Canada regulations and is approved by Boston Biomedical. The study drug must be dispensed only to the institution(s) specified on form FDA 1572.

13.5 Disposition of Used and Unused Study Drug

Upon completion or termination of the study and after inventory by a Boston Biomedical monitor or designated representative, all unopened drugs are to be returned to Boston Biomedical in the original containers. All used vials will be retained until released for destruction by the Boston Biomedical monitor. Unopened returned drugs, with completed Boston Biomedical forms for return shipment, should be shipped as instructed by the Sponsor.

13.6 Study Records

Boston Biomedical will provide the Investigator with drug shipment records, CRFs designed to collect the data specified for each individual, and other forms as necessary.

The Investigator and/or institution is required to prepare and maintain these forms in accordance with federal regulations (set forth in the Statement of Investigator Form FDA 1572) and to sign, date, and return them to the Sponsor.

Upon the request of authorized Boston Biomedical or appropriate regulatory agency personnel, the Investigator will make available for inspection subject source documents, e.g., records of each subject who participates in this study. This information will be treated as confidential.

13.7 Record Retention

Records must be maintained for 25 years:

If the Investigator leaves the institution where the study was conducted, he/she agrees that the records will be retained and will not be destroyed without prior notification of Boston Biomedical.

Boston Biomedical will notify the Investigator when records are no longer required.

13.8 Subject Confidentiality

Every effort will be made to keep all subject identities confidential. All reports and communications submitted to the Sponsor will be identified only by the subject's initials and subject number. The identity of an individual subject may not be disclosed in any publication relating to this study.

In connection with this study, representatives of the Health Canada, or other regulatory bodies outside of Canada, such as the United States Food and Drug Administration, and representatives of the local IRB may, in certain circumstances, review study source documentation including subject medical records.

13.9 Monitoring

In accordance with good clinical practices, the study will be monitored by Sponsor representatives. These representatives will have access to and will review source documents relating to this study, including subject medical records.

The status of drug storage, dispensing, and accountability will also be assessed during periodic visits.

At any time, each site may be audited either by Boston Biomedical personnel, or by a contractor acting on behalf of Boston Biomedical, or by a regulatory agency such as the FDA or Health Canada.

13.10 Case Report Form (CRF) Completion

A set of CRFs will be provided for each study subject. All forms must be filled out in non-erasable ink or typed. The Investigator will sign and date each CRF as indicated. Correction of data on a CRF will be made by crossing out the incorrect data in a manner that leaves the previous entry legible and writing the correct information next to the crossed out entry. "White-out" and erasures are not permitted. Each correction must be initialed and dated by the individual making the correction. After the CRFs have been collected by Boston Biomedical, all corrections will be made via a query resolution form, and no further corrections should be made on the site's copy of the CRF.

13.11 Final Site Report

The Principal Investigator or associate must notify the IRB when the study is closed and provide a final report to the IRB within 90 days of the last subject's completion of the study. A copy of this final report must also be provided to Boston Biomedical.

13.12 Final Study Report

At the conclusion of the study, after the data are analyzed, Boston Biomedical will prepare a final study report. A copy of this report will be provided to the Principal Investigator at each center.

The preparation of the final study report may be delegated to a contract research organization.

13.13 Use of Information

All personal information pertaining to subjects in this study and in any subsequent reports will be kept confidential. Subjects will be identified only by their initials and by a subject number. It is the responsibility of the Investigator to keep a subject listing for cross-referencing.

The Investigator understands that the information developed in the clinical study will be used by Boston Biomedical in connection with the development of the study drug. This information may be disclosed to other clinical investigators, the FDA, Health Canada, and other government agencies.

All information disclosed to the Investigator(s) by Boston Biomedical for the purpose of having the Investigator(s) conduct the clinical trial described in this protocol or generated by the Investigator(s) as results in the clinical trial shall be treated by the Investigator(s) as strictly confidential. The Investigator(s) shall not use such information other than for the purpose of conducting the clinical trial and may not disclose such information to others, except when such disclosure is to colleagues and/or employees who reasonably require the information to assist in carrying out the clinical trial and who are bound by like obligations of confidentiality. Notwithstanding, the Investigator(s) may use or disclose to others any information which: (i) was known to the Investigator(s) prior to the date of its disclosure, (ii) is now, or becomes in the future, publicly available; or (iii) is lawfully disclosed to the

Investigator(s) on a non-confidential basis by a third party who is not obligated to Boston Biomedical or any other party to retain such information in confidence.

13.14 Publication

Boston Biomedical acknowledges that the Investigator(s) have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. The Principal Investigator shall have the right to publish the results of research performed under this protocol, provided such publication does not disclose any Confidential Information or trade secrets of Boston Biomedical (other than the Clinical Data). If the Study is conducted as part of a multi-center protocol, Principal Investigator agrees not to independently publish their findings except as part of an overall multi-center publication, unless specifically approved in writing by Boston Biomedical. The Principal Investigator agrees to, prior to submitting a manuscript, abstract, or any other written or oral presentation describing the Data for publication or presentation, forward to Boston Biomedical a copy of the item to be submitted for publication or presentation. Upon reasonable request by Boston Biomedical within 30 days of receipt, the Principal Investigator agrees to withhold such publication an additional 60 days to permit the preparation and filing of related patent applications. In addition, Boston Biomedical shall have the right to require the Principal Investigator to delete from any publication or presentation any Confidential Information (other than the Clinical Data) of Boston Biomedical's and to require that any publication or presentation concerning the Study acknowledge the Sponsor's support.

13.15 Research Outside the Terms of this Protocol

Boston Biomedical has a legal responsibility to report fully to the regulatory authorities all the results of administration of its investigational drugs.

No investigative procedures other than those described in this protocol shall be undertaken on subjects enrolled in this study (unless required for the care of the subject), without the agreement of the IRB/Ethics Committee and Boston Biomedical. The nature and results of any such procedures must be recorded and reported by a method agreed between Boston Biomedical and the Investigator. The consent of the subjects must be obtained before any such procedures are undertaken.

The investigative drug provided to the Investigator for use under this protocol may not be used for any other purpose, including another study, compassionate use, or personal use.

APPENDIX A: SCHEDULE OF ASSESSMENTS FOR FOLFOX6 WITH OR WITHOUT BEVACIZUMAB (ARMS A AND B)

Tests & Procedures	Pre-Study Evaluation	On Study Evaluations (+/- 2 days)					End of Study Visit
			Cycle 1		Additional Cycles		
Week		0	1	3	1	3	
Day	up to 9 days before 1st dose of BBI608	[-]5	1	15	1	15	At least 30 days from last BBI608 dose
Written informed consent[1]	X						
Medical history	X						
Physical examination	X				X		X
Serum pregnancy test	X						
Karnofsky performance status score	X	X	X	X	X	X	X
Vital signs, Weight	X	X	X	X	X	X	X
Hematology[2]	X		X	X	X	X	X
Biochemistry[2]	X		X	X	X		X
Urinalysis[2]	X		X	X	X		X
12-Lead electrocardiogram	X	X					X
Tumor markers (if applicable)[2]	X				X		X
Tumor biopsy (if applicable)[3]	X				X		
Pharmacokinetics			X	X			
Tumor measurement & staging[4,5,6]	X[7]						X
Concomitant medications	X	X	X	X	X	X	X
Adverse events[8]			X	X	X	X	X
FOLFOX6 ± Bevacizumab[9]			X	X	X	X	
Dispense BBI608[10]		X	X		X		

1. Written informed consent may be obtained up to 1 month prior to first dose of BBI608
2. Refer to Section 6.3 for description of laboratory assessments.
3. Archival Tissue samples will be obtained per Appendix G once the patient has been enrolled.
4. Including tumor measurements, following RECIST 1.1.
5. At the end of cycle 2 and every other cycle thereafter, assessments must be made utilizing the same imaging method as baseline
6. If at any time during the tumor evaluation visits either a partial or complete response is observed, the same radiographic study should be repeated within four weeks for confirmation of response.
7. Unless CT/MRI has been performed within last three weeks.
8. Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.
9. FOLFOX6 with or without bevacizumab will be administered as per standard schedule.
10. BBI608 will be dispensed in a 5-day plus 2 extra day supply on day [-]5, 28 day supply on day 1, cycle 1 and 28 day plus 2 extra day supply at the beginning of each cycle thereafter.

APPENDIX B: SCHEDULE OF ASSESSMENTS FOR CAPOX ARM (ARM C)

Tests & Procedures	Pre-Study Evaluation	On Study Evaluations (+/- 2 days)				End of Study Visit
			Cycle 1		Additional Cycles	
Week		0	1	4	1	
Day	up to 9 days before 1st dose of BBI608	[-]5	1	22	1	At least 30 days from last BBI608 dose
Written informed consent[1]	X					
Medical history	X					
Physical examination	X				X	X
Serum pregnancy test	X					
Karnofsky performance status score	X	X	X	X	X	X
Vital signs, Weight	X	X	X	X	X	X
Hematology[2]	X		X	X	X	X
Biochemistry[2]	X		X	X	X	X
Urinalysis[2]	X		X	X	X	X
12-Lead electrocardiogram	X	X				X
Tumor markers (if applicable)[2]	X				X	X
Tumor biopsy (if applicable)[3]	X				X	
Pharmacokinetics			X	X		
Tumor measurement & staging[4,5,6]	X[7]					X
Concomitant medications	X	X	X	X	X	X
Adverse events[8]			X	X	X	X
Oxaliplatin administration[9]			X	X	Scheduled according to specific cycle	
Dispense BBI608[10]		X	X		X	
Dispense capecitabine[11]			X		X	

1. Written informed consent may be obtained up to 1 month prior to first dose of BBI608
2. Refer to Section 6.3 for description of laboratory assessments.
3. Archival Tissue samples will be obtained per Appendix G once the patient has been enrolled.
4. Including tumor measurements, following RECIST 1.1.
5. At the end of cycle 2 and every other cycle thereafter, assessments must be made utilizing the same imaging method as baseline
6. If at any time during the tumor evaluation visits either a partial or complete response is observed, the same radiographic study should be repeated within four weeks for confirmation of response.
7. Unless CT/MRI has been performed within last three weeks.
8. Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.
9. Oxaliplatin will be administered every 3 weeks
10. BBI608 will be dispensed in a 5-day plus 2 extra day supply on day [-]5, 28 day supply on day 1, cycle 1 and 28 day plus 2 extra day supply at the beginning of each cycle thereafter.
11. The appropriate amount of capecitabine will be dispensed at the start of a given cycle

APPENDIX C: SCHEDULE OF ASSESSMENTS FOR FOLFIRI WITH OR WITHOUT BEVACIZUMAB OR IRINOTECAN (ARMS D, E OR G)

Tests & Procedures	Pre-Study Evaluation	On Study Evaluations (+/- 2 days)					End of Study Visit
			Cycle 1		Additional Cycles		
Week		0	1	3	1	3	
Day	up to 9 days before 1st dose of BBI608	[-]5	1	15	1	15	At least 30 days from last BBI608 dose
Written informed consent[1]	X						
Medical history	X						
Physical examination	X				X		X
Serum pregnancy test	X						
Karnofsky performance status score	X	X	X	X	X	X	X
Vital signs, Weight	X	X	X	X	X	X	X
Hematology[2]	X		X	X	X	X	X
Biochemistry[2]	X		X	X	X		X
Urinalysis[2]	X		X	X	X		X
12-Lead electrocardiogram	X	X					X
Tumor markers (if applicable)[2]	X				X		X
Tumor biopsy (if applicable)[3]	X				X		
Pharmacokinetics[4]			X	X			
Tumor measurement & staging[5,6,7]	X[8]						X
Concomitant medications	X	X	X	X	X	X	X
Adverse events[9]			X	X	X	X	X
FOLFIRI ± Bevacizumab or Irinotecan[10]			X	X	X	X	
Dispense BBI608[11]		X	X		X		

1. Written informed consent may be obtained up to 1 month prior to first dose of BBI608.
2. Refer to Section 6.3 for description of laboratory assessments.
3. Archival Tissue samples will be obtained per Appendix G once the patient has been enrolled.
4. Pharmacokinetic analysis will be collected from study arms D and E only.
5. Including tumor measurements, following RECIST 1.1.
6. At the end of cycle 2 and every other cycle thereafter, assessments must be made utilizing the same imaging method as baseline
7. If at any time during the tumor evaluation visits either a partial or complete response is observed, the same radiographic study should be repeated within four weeks for confirmation of response.
8. Unless CT/MRI has been performed within last three weeks.
9. Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.
10. FOLFIRI with or without bevacizumab or irinotecan will be administered as per standard schedule.
11. BBI608 will be dispensed in a 5-day plus 2 extra day supply on day [-]5, 28 day supply on day 1, cycle 1 and 28 day plus 2 extra day supply at the beginning of each cycle thereafter.

APPENDIX D: SCHEDULE OF ASSESSMENTS FOR REGORAFENIB (ARM F)

Tests & Procedures	Pre-Study Evaluation	On Study Evaluations (+/- 2 days)				End of Study Visit
			Cycle 1		Additional Cycles	
Week		0	1	3	1	
Day	up to 9 days before 1st dose of BBI608	[-]5	1	15	1	At least 30 days from last BBI608 dose
Written informed consent[1]	X					
Medical history	X					
Physical examination	X				X	X
Serum pregnancy test	X					
Karnofsky performance status score	X	X	X	X	X	X
Vital signs, Weight	X	X	X	X	X	X
Hematology[2]	X		X	X	X	X
Biochemistry[2]	X		X	X	X	X
Urinalysis[2]	X		X	X	X	X
12-Lead electrocardiogram	X	X				X
Tumor markers (if applicable)[2]	X				X	X
Tumor biopsy (if applicable)[3]	X				X	
Pharmacokinetics			X	X		
Tumor measurement & staging[4,5,6]	X[7]					X
Concomitant medications	X	X	X	X	X	X
Adverse events[8]			X	X	X	X
Dispense BBI608[9]		X	X		X	
Dispense regorafenib[10]			X		X	

1.Written informed consent may be obtained up to 1 month prior to first dose of BBI608
2.Refer to Section 6.3 for description of laboratory assessments.
3.Archival Tissue samples will be obtained per Appendix G once the patient has been enrolled.
4.Including tumor measurements, following RECIST 1.1.
5.At the end of cycle 2 and every other cycle thereafter, assessments must be made utilizing the same imaging method as baseline
6.If at any time during the tumor evaluation visits either a partial or complete response is observed, the same radiographic study should be repeated within four weeks for confirmation of response.
7.Unless CT/MRI has been performed within last three weeks.
8.Patients will be followed until resolution of any drug-related AE or SAE occurring during the study or within 30 days of last BBI608 administration.
9.BBI608 will be dispensed in a 5-day plus 2 extra day supply on day [-]5, 28 day supply on day 1, cycle 1 and 28 day plus 2 extra day supply at the beginning of each cycle thereafter.
10.The appropriate amount of regorafenib will be dispensed at the start of a given cycle

APPENDIX E: PERFORMANCE STATUS

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

APPENDIX F: PHARMACOKINETIC STUDIES

Instructions for Collecting and Processing Blood PK Samples

Sampling to define the plasma pharmacokinetics of BBI608 will be performed all patients enrolled in each combination arm of the study. For the FOLFOX6 and FOLFIRI arms (with and without bevacizumab), PK samples are taken on Days 1-2 and 15-16 of cycle 1. For the CAPOX arm, samples are taken on Days 1-2 and 22-23 of cycle 1. For the regorafenib arm, samples are taken on Days 1-2 and 15-16 of cycle 1. For the irinotecan arm, PK samples will not be collected. The sampling schedules and summary of procedures that are to be used to establish times, collect samples, and process specimens for storage prior to analysis, to insure the acquisition of accurate pharmacokinetic data, are described below. The sampling schedules have been devised to accommodate treatment on an outpatient basis. Dosing of the first dose of drug (on day [-] 5) should be started on a Wednesday or Thursday.

Before starting the BBI608 administration, place a large gauge peripheral catheter (e.g., 19 or 20 gauge angiocath straight set with T-connector, or similar IV access device) within a vein in the arm of the subject for the collection of pharmacokinetic blood samples. Patency of the sampling catheter should be maintained between blood draws using either a heparin lock (e.g., 10 U/mL in normal saline) or a slow drip of Normal Saline for Injection, USP (e.g., 10 mL/hr). Blood may be obtained directly by venipuncture on days when only a single pharmacokinetic blood specimen is scheduled for collection. When sampling through the peripheral catheter, begin to clear the catheter approximately 1 minute before the specified sample time by withdrawing the lock solution and approximately 0.5 mL of blood into a syringe. Remove and properly dispose the syringe used to clear the catheter.

A battery-powered digital timer/stopwatch programmed to operate continuously as a 24-hr clock will be used to accurately monitor drug administration and sample collection times. The same timer must be allowed to run without interruption until the last blood specimen has been obtained from the subject during the first cycle of therapy. Timer readings will be noted at the precise time that the administration is started as well as at the beginning and ending times of the blood sample collection intervals. Readings of the digital timer must be directly recorded on a copy of the appropriate Pharmacokinetic Dosing and Blood Collection Time Form. All blood samples should be drawn within ± 3 minutes of the desired time.

Please note that blood and plasma must be protected from direct exposure to light and all sample processing procedures are to be performed in a room with indirect lighting. The volume of blood collected for each pharmacokinetic sample will be 3 mL. This volume has shown to be adequate for the pharmacokinetic assay. Samples are to be collected in plastic Vacutainer plasma collection tubes. Immediately wrap the tube with aluminum foil to protect it from exposure to light. Promptly mix the plasma collection tube by gently inverting 6-times, then place it on wet ice, and centrifuge (1,100-1,300 x g, 10 min, 4°C) within 5-10 minutes after collection. Separate the plasma from the blood cells pellet (please see Blood Cell Pellet section directly following for instructions for this portion of the sample) using a pipette and transfer approximately equal volumes into three self-standing opaque

amber polypropylene microcentrifuge cryogenic tubes with external threads. Affix a pre-printed label (protocol number, subject initials, subject number, sample collection date and time) to the cryotube, oriented lengthwise toward the upper part of the tube. Hand-written information on sample tube labels is absolutely prohibited. Completely cover the label with protective cryogenic freezer tape. Place the tube on crushed dry-ice until stored in a freezer maintained at ≤ -70°C. Any deviation from the sample collection time needs to be documented in the study subjects' case report forms and in their study binder.

The total volume of blood collected for pharmacokinetic studies, 84-120 mL, represents < 5% of the total blood volume for a 60 kg subject, during a 28-day treatment cycle. As pharmacokinetic data becomes available during the course of the trial, it may be necessary to modify the number of samples or the times at which they are collected to more accurately define the plasma concentration-time profile of the drug. However, the cumulative volume of blood collected for pharmacokinetic sampling will not exceed 240 mL, or approximately 5% of the total volume of a 60 kg subject during the first 4 weeks of study treatment.

Computer files for dose administration and sample collection time forms and specimen tube labels will be provided to the lab personnel in charge of labeling. The PK_Tube_Label files are templates, and the files are copied to user computers and the limited information pertaining to each subject studied, typically the subject entry no., is added by editing the computer file, and subsequently printed onto adhesive-backed labels. Hand-written information on sample tube labels is absolutely prohibited. There are separate sets of labels for blood collection vials and sample storage tubes. Blood collection vials should be pre-labeled.

Time points will be determined as the difference between the midpoint of the blood collection interval and starting time of dose administration. Concentration-time profiles of BBI608 will be analyzed by non-compartmental methods and/or nonlinear least squares regression using WinNonlin (Scientific Consulting, Inc.). Pharmacokinetic parameters and variables will be calculated according to standard equations.

Blood Cell Pellet

In addition to the plasma samples obtained for pharmacokinetic analysis (as outlined above), the blood cell pellet that results from centrifuging the patient blood samples is also requested. The cell fraction is required for comprehensive BBI608 PK and biomarker assessment.

At the Cycle 1, Day 1 (C1D1) visit, blood cells should be saved from the first four PK samples (-5, 60, 120, and 180 minutes) and must be shipped to Boston Biomedical within 24 hours—preferably on the same day the blood is drawn. To isolate the blood cells, retain the EDTA vacutainers once the plasma has been poured off and store these samples either on ice or at 4 °C. If, for any reason, the C1D1 cells fractions either cannot be obtained or are unsuitable for analysis by the sponsor, the cell fractions from the equivalent first four PK samples on the second PK day in Cycle 1 may be shipped instead. The samples should then be shipped on wet ice to Boston Biomedical.

Pharmacokinetic Sample Collection: FOLFOX6 and FOLFIRI Arms (±Bevacizumab) (CYCLE 1 ONLY)

Day	Procedure	Sample No.	Desired Time
1	Draw blood sample	PK-01	-5 min
	First daily BBI608 dose		0
	Draw blood sample	PK-02	60 min
	Draw blood sample	PK-03	120 min
	Draw blood sample	PK-04	180 min
	Begin Combination Regimen Administration[a]		180 min
	Draw blood sample	PK-05	240 min
	Draw blood sample	PK-06	300 min
	Draw blood sample	PK-07	360 min
	Draw blood sample	PK-08	420 min
	Draw blood sample	PK-09	480 min
	Draw blood sample	PK-10	540 min
	Draw blood sample	PK-11	600 min
	Draw blood sample	PK-12	660 min
2	Draw blood sample	PK-13	24 hours
	Draw blood sample	PK-14	30-32 hours[b]
Day	**Procedure**	**Sample No.**	**Desired Time**
15	Draw blood sample	PK-15	-5 min
	First daily BBI608 dose		0
	Draw blood sample	PK-16	60 min
	Draw blood sample	PK-17	120 min
	Draw blood sample	PK-18	180 min
	Begin Combination Regimen Administration[a]		180 min
	Draw blood sample	PK-19	240 min
	Draw blood sample	PK-20	300 min
	Draw blood sample	PK-21	360 min
	Draw blood sample	PK-22	420 min
	Draw blood sample	PK-23	480 min
	Draw blood sample	PK-24	540 min
	Draw blood sample	PK-25	600 min
	Draw blood sample	PK-26	660 min
16	Draw blood sample	PK-27	24 hours
	Draw blood sample	PK-28	30-32 hours[b]

[a]FOLFOX6/FOLFIRI ±Bevacizumab infusion

[b]PK draw can occur anywhere in this timeframe, however exact time of draw must be recorded

Pharmacokinetic Sample Collection: CAPOX arm (CYCLE 1 ONLY)

Day	Procedure	Sample No.	Desired Time
1	Draw blood sample	PK-01	-5 min
	First daily BBI608 dose		0
	Draw blood sample	PK-02	60 min
	Draw blood sample	PK-03	120 min
	Draw blood sample	PK-04	180 min
	Begin Combination Regimen Administration*		180 min
	Draw blood sample	PK-05	240 min
	Draw blood sample	PK-06	300 min
	Draw blood sample	PK-07	360 min
	Draw blood sample	PK-08	420 min
	Draw blood sample	PK-09	480 min
	Draw blood sample	PK-10	540 min
	Draw blood sample	PK-11	600 min
	Draw blood sample	PK-12	660 min
2	Draw blood sample	PK-13	24 hours
Day	**Procedure**	**Sample No.**	**Desired Time**
22	Draw blood sample	PK-15	-5 min
	First daily BBI608 dose		0
	Draw blood sample	PK-16	60 min
	Draw blood sample	PK-17	120 min
	Draw blood sample	PK-18	180 min
	Begin Combination Regimen Administration*		180 min
	Draw blood sample	PK-19	240 min
	Draw blood sample	PK-20	300 min
	Draw blood sample	PK-21	360 min
	Draw blood sample	PK-22	420 min
	Draw blood sample	PK-23	480 min
	Draw blood sample	PK-24	540 min
	Draw blood sample	PK-25	600 min
	Draw blood sample	PK-26	660 min
23	Draw blood sample	PK-27	24 hours

*Oxaliplatin IV infusion and capecitabine oral administration

Pharmacokinetic Sample Collection: Regorafenib arm (CYCLE 1 ONLY)

Day	Procedure	Sample No.	Desired Time
1	Draw blood sample	PK-01	-5 min
	First daily BBI608 dose		0
	Draw blood sample	PK-02	60 min
	Draw blood sample	PK-03	120 min
	Draw blood sample	PK-04	180 min
	Administer regorafenib		180 min
	Draw blood sample	PK-05	240 min
	Draw blood sample	PK-06	300 min
	Draw blood sample	PK-07	360 min
	Draw blood sample	PK-08	420 min
	Draw blood sample	PK-09	480 min
	Draw blood sample	PK-10	540 min
	Draw blood sample	PK-11	600 min
	Draw blood sample	PK-12	660 min
2	Draw blood sample	PK-13	24 hours
Day	**Procedure**	**Sample No.**	**Desired Time**
15	Draw blood sample	PK-15	-5 min
	First daily BBI608 dose		0
	Draw blood sample	PK-16	60 min
	Draw blood sample	PK-17	120 min
	Draw blood sample	PK-18	180 min
	Administer regorafenib		180 min
	Draw blood sample	PK-19	240 min
	Draw blood sample	PK-20	300 min
	Draw blood sample	PK-21	360 min
	Draw blood sample	PK-22	420 min
	Draw blood sample	PK-23	480 min
	Draw blood sample	PK-24	540 min
	Draw blood sample	PK-25	600 min
	Draw blood sample	PK-26	660 min
16	Draw blood sample	PK-27	24 hours

APPENDIX G: TUMOR BIOPSIES

Instructions for Collecting, Processing and Shipping Samples

Archival tissues:

Archival tissue samples should be collected from all patients enrolled in the clinical trial if they are available. Archive tissue labels should be coded with the protocol number, study site number, the patient's initials and the patient number. Paraffin embedded tissue blocks or prepared tissue slides should be shipped by courier to Boston Biomedical at the address listed below. Tissue blocks are preferred; however, if blocks are not available, 10-15 unstained, positively charged, 5 micron thickness slides may be sent.

Fresh Tumor Biopsies:

Tumor biopsies will be collected for immunohistopathology-based analysis of the target and its downstream genes and for the analysis of the effect of BBI608 on cancer stem cells. These samples will be used for research purposes only. Tumor biopsies for analysis should be collected by core biopsy or minimally invasive procedures. Tumor specimen samples should be processed sterilely into three parts: fixed, frozen, and fresh.

Fixed Tumor Biopsies for Immunohistochemistry:

The sample should be processed to yield paraffin embedded tissues using the study site's standard operating procedures. The samples should be labeled and coded with the protocol number, study site number, the patient's initials, the patient number and the sample collection date and time. The paraffin embedded tissue blocks should be shipped to Boston Biomedical at the address listed below.

Fresh and Frozen Tumor Biopsy Specimens for Cancer Stem Cell Assays:

Tumor biopsies for the analysis of the effect of BBI608 on cancer stem cells should be collected by core biopsy or similar minimally invasive procedures. Once the biopsy tissue is obtained, half of the biopsy tissue should be immediately placed in sterile fashion into CSC transport media provided by Boston Biomedical, stored and shipped at 4ºC. Overnight shipment should be arranged on the same day as the biopsy is performed. A label should be affixed to all sample tubes containing with the protocol number, study site number, the patient's initials, the patient number and the sample collection date and time. The other half should be immediately snap-frozen in liquid nitrogen, and then transferred to a polypropylene microcentrifuge cryogenic tube. The tissue sample should then be stored at ≤ -70ºC until being shipped to Boston Biomedical on dry ice to the address listed below.

Shipping information:

Please ship all tumor samples to the following address:

On the day that specimens are sent to Boston Biomedical, please contact Boston Biomedical by phone, fax or email to notify what is being sent and when the shipment is expected to arrive.

SPONSOR SIGNATURE

Study Title:	**A Phase Ib/II Clinical Study of BBI608 in Combination with Standard Chemotherapies in Adult Patients with Advanced Gastrointestinal Cancer**
Study Number:	BBI608-246
Amendment 1:	September 26th, 2015
Amendment 2:	August 17th, 2016
Amendment 3:	December 6th, 2016
Amendment 4:	June 23rd, 2017

This clinical study protocol is subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: _____Date: _____

[redacted]
Vice President of Clinical Development & Pharmacovigilance
Boston Biomedical, Inc.

INVESTIGATOR'S SIGNATURE

Study Title:	**A Phase Ib/II Clinical Study of BBI608 in Combination with Standard Chemotherapies in Adult Patients with Advanced Gastrointestinal Cancer**
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Amendment 1:	September 26th, 2015
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Amendment 4:	June 23rd, 2017

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Printed Name:_____

Signature: _____Date: _____

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