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NCIC CTG TRIAL: CO.23

HEALTH CANADA SUBMISSION
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NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A PHASE III RANDOMIZED STUDY OF BBI608 AND BEST SUPPORTIVE CARE VERSUS PLACEBO AND BEST SUPPORTIVE CARE IN PATIENTS WITH PRETREATED ADVANCED COLORECTAL CARCINOMA

NCIC CTG Protocol Number: **CO.23**

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(For contact information of study personnel see Final Page.)

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Boston Biomedical, Inc.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined herein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

I will provide copies of the protocol and access to all information furnished by NCIC CTG and Boston Biomedical, Inc. to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Boston Biomedical, Inc. and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Boston Biomedical, Inc. and NCIC CTG of any such disclosure.

I assume my own liability for any loss, damage, costs, and expense relating to a claim, to the extent such claim is the result of my own negligence or wilful misconduct, or failure to comply with this protocol or written instructions of the sponsor concerning the CO.23 study, or failure to comply with applicable law; or the negligence or wilful misconduct, or failure to comply with this protocol or written instructions of the sponsor concerning the CO.23 study, or failure to comply with applicable law of those for whose actions I am in law responsible.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to NCIC CTG. The study may be terminated at any time by NCIC CTG or Boston Biomedical, Inc. with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Boston Biomedical, Inc. and NCIC CTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Investigator (Qualified/Principal) Date
(printed name and signature)

Protocol Number: NCIC CTG CO.23

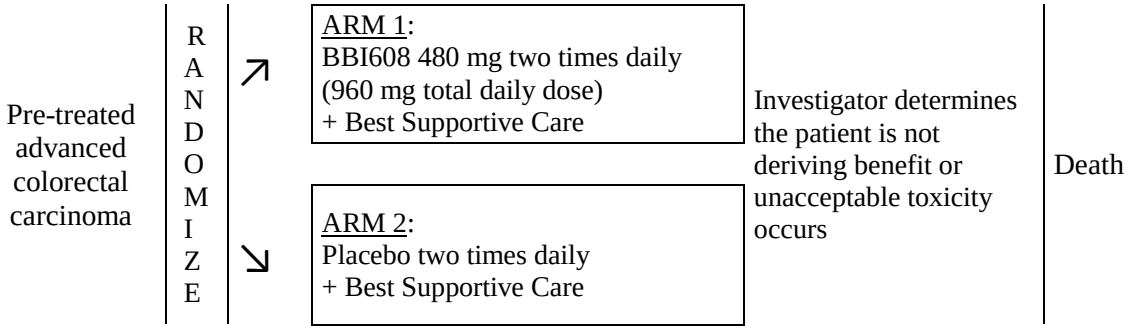
CENTRE: _____

TREATMENT SCHEMA

This is an international multi-centre, prospective, double-blind, randomized phase III trial of the cancer stem cell inhibitor BBI608 plus best supportive care *versus* matched placebo plus best supportive care (where best supportive care is defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible) in patients previously treated with combination chemotherapy for advanced (metastatic or locally advanced), unresectable, colorectal carcinoma, now refractory and for whom no further standard anticancer therapy is appropriate or available.

Stratification:

- ECOG performance status (0 *versus* 1)
- Tumour *K-ras* status (wild type *versus* mutated)
- Prior anti-VEGF therapy (yes *versus* no)
- Time from diagnosis of metastatic disease to randomization (< 18 months *versus* ≥ 18 months)



Endpoints:

Primary

- Overall Survival

Secondary

- Progression-Free Survival (PFS)
- Disease Control Rate (DCR)
- Safety Profile
- Quality of Life (using EORTC QLQ-C30)

Sample Size:

Planned sample size is 650 patients (325 on Arm 1 and 325 on Arm 2).

1.0 OBJECTIVES

1.1 Primary Objective

- To compare Overall Survival (OS), defined as the time from randomization until death from any cause, in patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care *versus* placebo plus best supportive care.

1.2 Secondary Objectives

- To compare Progression-Free Survival (PFS), defined as the time from randomization until the first objective observation of disease progression or death from any cause, in patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care versus placebo plus best supportive care;
- To compare the Objective Response Rate (OR), defined as the proportion of patients with a documented complete response or partial response (CR + PR) based on RECIST 1.1 criteria, in patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care versus placebo plus best supportive care;
- To compare the Disease Control Rate (DCR), defined as the proportion of patients with a documented complete response, partial response and stable disease (CR + PR + SD) based on RECIST 1.1 criteria, in patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care versus placebo plus best supportive care;
- To evaluate the safety profile of BBI608 administered daily in patients with pre-treated advanced colorectal carcinoma, with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE)
- To compare the Quality of Life (QoL), as measured using the EORTC QLQ-C30, in patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care versus placebo plus best supportive care;
- To compare the Health Utilities, as measured using the HUI3 Health Utilities Index, in patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care versus placebo plus best supportive care;
- To conduct a comparative economic evaluation of patients with pre-treated advanced colorectal carcinoma treated with BBI608 plus best supportive care versus placebo plus best supportive care;
- To explore the exposure/response relationships of BBI608 in patients with pre-treated advanced colorectal carcinoma using population pharmacokinetics with sparse PK sample collection;
- To explore an association between putative biomarkers (see Appendix VI) as determined from paraffin embedded tumour specimens and the potential for clinical benefit in terms of overall survival, progression-free survival, disease control rate, and objective response rate, from treatment with BBI608 in patients with pre-treated advanced colorectal carcinoma.
- To explore associations with baseline values and changes of putative biomarkers (see Appendix VI) in the blood and the potential for clinical benefit in terms of overall survival, progression-free survival, disease control rate, and objective response rate, from treatment with BBI608 in patients with pre-treated advanced colorectal carcinoma.
- To establish a comprehensive tumour bank linked to a clinical database for the further study of molecular markers in colorectal cancer.

Study Conduct Post-Unblinding

As a result of the interim analysis, the study has met the criteria for stopping (see section 14.5), and subsequently patients were unblinded.

However, post-unblinding, the trial will continue in centres with patients who have not yet met the primary study endpoint (death), and with patients currently on protocol therapy (active arm) and who may receive BBI608 on study based on the clinical judgement of the investigator and local REB approval that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also section 9.1.1 and 9.2.1). Patients will receive study supply BBI608 until any of the discontinuation criteria are met (see section 12.1). Patients will be followed for serious adverse events.

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common malignancy in Canada and the second most frequent cause of cancer related death *[NCIC 2011]*. In the United States, it is the third most commonly diagnosed malignant disease and third most frequent cause of cancer-related death *[ACS 2011]*. Approximately half of all diagnosed CRC patients will develop disseminated advanced disease, which in most cases will be fatal *[Saunders 2006]*. Standard treatment for unresectable metastatic disease currently includes first and second line 5-fluorouracil (5-FU) chemotherapy based regimen in combination with oxaliplatin or irinotecan. The vascular endothelial growth factor-A (VEGF_A) inhibitor, bevacizumab, has been shown to improve survival in combination with first and second line 5-FU based chemotherapy *[Welch 2010]*, while the VEGF soluble decoy receptor, aflibercept has been shown to improve overall survival in combination with the FOLFIRI regimen (irinotecan-5-fluorouracil-leucovorin) administered as second line therapy *[Van Cutsem, 2011]*. Additionally, the monoclonal antibody epidermal growth factor receptor (EGFR) inhibitors, cetuximab and panitumumab, have shown efficacy as third line monotherapy and in combination with earlier lines of therapy in patients with *K-ras* wild type tumours *[Karapetis 2008; Amado 2008; Tol 2010; Bokemeyer 2012]*. At this time, however, a patient with progressive disease on third line therapy has treatment options generally limited to an investigational regimen or best supportive care. Moreover, for the approximately 30-50% of colorectal tumours with an activating *K-ras* mutation *[Amado 2008],* effective treatment options are further limited. Given the morbidity associated with this disease, there is an urgent need to identify novel therapies which improve the outcome of patients with advanced chemorefractory CRC.

2.2 Cancer Stem Cells (CSC) and CRC

CSCs or cancer cells with stemness phenotypes are a sub-population of cancer cells that have self-renewal capability, are highly malignant and are considered to be fundamentally responsible for malignant growth, recurrence, drug-resistance and metastasis. Moreover, CSCs are highly resistant to chemotherapies and current targeted agents. CSCs have been isolated from almost all major tumour types, including CRC *[Bowman 2008; Clevers 2011; Gupta 2009; Hanahan 2011; Gupta 2011]*. Targeting stem cells, therefore, holds great promise for fundamentally advancing cancer treatment.

Accumulating evidence indicates that CSCs play a key role in the pathogenesis of CRC *[Todaro 2010]*. Cancer stem cells have been isolated from human colon carcinomas using various cell surface markers including CD133, CD44, CD24, CD29, CD166, Musashi-1, and Lgr5 *[Horst 2009; Du 2008; Levin 2010; Merlos-Suarez 2011; Kemper 2010]*. These CSCs isolated from CRC patients display tumour-initiating properties, as well as resistance to chemotherapeutics. These findings suggest that the development of cancer stem cell inhibitors represents a novel and compelling strategy for the treatment of CRC.

2.3 BBI608

Preclinical Rationale

BBI608 is the most advanced product candidate designed by Boston Biomedical, Inc. (BBI) to target CSCs. BBI608 is a small molecule that blocks self-renewal of, and induces cell death in, CSCs isolated from CRC and other types of cancer.

BBI608 inhibits STAT3, a proprietary CSC target discovered by scientists at Boston Biomedical. STAT3 is a known oncogene which is aberrantly activated in a wide variety of human cancers including all the major carcinomas as well as some hematologic tumours. In particular, nearly 200 peer-reviewed scientific articles have established dysregulation of STAT3 signalling as a key feature of human CRC. Moreover, elevated expression of phosphorylated STAT3 by immunohistochemistry from archival patient tumour samples has been associated with poor prognosis *[Morikawa 2011]*. These data provide strong rationale for the development of CRC therapies based on inhibition of STAT3 activity.

2.4 Clinical Experience with BBI608 in Patients with CRC

Unpublished data redacted

2.5 Summary

NCIC CTG CO.23 will primarily examine the effect of treatment with CSC inhibitor BBI608 on Overall Survival in patients with metastatic CRC who have failed all standard chemotherapy (including a thymidylate synthase inhibitor, an irinotecan-containing regimen, an oxaliplatin containing regimen and, for patients whose tumours are *K-ras* wild type, either of the EGFR inhibitors cetuximab or panitumumab) recommended by their oncologist, and for whom no standard anticancer therapy is available (see section 5.1). Additional assessments will include Progression-Free Survival, Disease Control Rate, Safety, Quality of life (QoL), Health Utilities, Population Pharmacokinetics and putative predictive molecular markers.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Name and Chemical Information

BBI608

3.2 Mechanism of Action

Unpublished data redacted

3.3 Pharmaceutical Data

Supplied: Boston Biomedical, Inc. will supply BBI608/matching placebo free of charge to study participants. Capsules of BBI608 at a dose strength of 80 mg are available for oral administration. BBI608 and placebo capsules are supplied in high density polyethylene bottles, and are heat induction sealed with a child-resistant closure.

Stability: Initial product use dating is 13.5 months from the date of manufacture and can be extended to a maximum of 5 years from date of manufacture assuming acceptable results at re-assay time-point testing.

Storage: BBI608/placebo capsules should be stored in a tightly closed container at a temperature between 2-25 ºC. DO NOT FREEZE.

Route of Administration: Oral administration.

4.0 TRIAL DESIGN

This is an international multi-centre, prospective, double-blind, randomized phase III trial of the cancer stem cell inhibitor BBI608 plus best supportive care *versus* matched placebo plus best supportive in patients previously treated with combination chemotherapy for advanced (metastatic or locally advanced), unresectable, colorectal carcinoma, now refractory and for whom no further standard anticancer therapy is appropriate or available.

4.1 Stratification

Patients will be stratified by:

1. ECOG Performance Status (0 *versus* 1)
2. *K-ras* tumour status (wild type *versus* mutant)
3. Prior anti-VEGF therapy (yes *versus* no)
4. Time from diagnosis of metastatic disease to randomization (< 18 months *versus* ≥ 18 months)

4.2 Randomization

Patients will be randomized according to a 1:1 ratio using a permuted block randomization procedure to receive one of the following treatments:

BBI608 plus best supportive care or placebo plus best supportive care to a planned sample size of 650 subjects, with best supportive care defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible.

Patients will be randomized to one of the following two arms (plus best supportive care):

Arm	Agent(s)	Dose	Route	Duration
1	BBI608	480 mg two times daily[1,2] (960 mg total daily dose)	oral	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and are, in the opinion of the investigator, continuing to derive benefit from protocol therapy (see section 12.2)
2	Placebo	two times daily[1,2]	oral	

[1.] Protocol treatment should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses.
[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment.

4.3 Inclusion of Women and Minorities

There will be no exclusions based on race or ethnicity in this trial. In the NCIC Clinical Trials Group as a whole, 60% of patients have been female and 40% have been male. The female preponderance reflects the number of studies performed in breast cancer. Recruitment to trials for disease sites that involve both males and females has been approximately in proportion to the gender incidence *[Marlin 1996]*. Insufficient data has been collected to test a similar relationship for racial/ethnic groups. This study, however, will be presented to patients through major cancer-treatment institutions of Canada, Australia and New Zealand, Japan and the United States of America, to which all racial/ethnic groups have equal access. The intention, therefore, is to recruit subjects from racial/ethnic groups in close approximation to the incidence of the disease in these groups.

Patients enrolled in this study will be representative of the mix of genders, races and ethnicities seen in the general population of patients with colorectal cancer. The effect of the intervention under investigation will be analyzed in gender, racial and ethnic subgroups, with recognition of the potentially limited statistical power of this analysis.

4.4 Potential Continuation of Treatment Post- Unblinding

Following unblinding, patients who have not yet met the primary study endpoint (death), and are currently on protocol therapy (active arm), may receive BBI608 on study based on the clinical judgement of the investigator and local REB approval that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also section 9.1.1 and 9.2.1). Patients will receive study supply BBI608 until any of the discontinuation criteria are met (see section 12.1).

5.0 STUDY POPULATION

The trial population will consist of subjects with advanced (metastatic or locally advanced) histologically confirmed colorectal cancer that is unresectable who have exhausted standard treatment options. Subjects will have failed standard chemotherapy based regimens containing a fluoropyrimidine, irinotecan and oxaliplatin, or are deemed unsuitable for such regimens by their treating physicians. Subjects with *K-ras* wild type tumours must have previously received cetuximab or panitumumab. Subjects treated previously with anti-VEGF therapy (e.g. bevacizumab or aflibercept) or regorafenib will be eligible, though previous treatment with these agents is not a requirement for enrolment.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed prior to calling for randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfil all of the following criteria to be eligible for admission to the study:

5.1.1 Patient consent for trial participation and optional tumour banking must be obtained appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure.

For all institutions, it will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the national sponsor that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, standard consent forms for the trial and optional tumour banking will not be provided but sample forms are posted on the CO.23 area of the NCIC CTG web-site (www.ctg.queensu.ca). A copy of the initial full board Research Ethics Board (REB) approval and approved consent forms must be sent to the central office. The patient must sign the consent forms prior to randomization. Please note that the consent forms for this study must contain a statement which gives permission for the NCIC CTG and monitoring agencies to review patient records (see section 16.3 for further details).

5.1.2 Must have histologically confirmed advanced (metastatic or locally advanced) colorectal cancer that is unresectable.

5.1.3 Received a prior thymidylate synthase inhibitor (e.g. 5-fluorouracil (5-FU), capecitabine, raltitrexed, UFT) for metastatic disease or as adjuvant therapy. Thymidylate synthase inhibitor may have been given in combination with oxaliplatin or irinotecan.

The intention of this criterion is to ensure that it is the conclusion of the investigator that this patient would not benefit from further therapy with a thymidylate synthase inhibitor and is therefore an appropriate candidate for treatment with best supportive care measures only.

5.1.4 Received and failed an irinotecan -containing regimen (i.e. single-agent or in combination) for treatment of metastatic disease, OR relapsed within 6 months of completion of an irinotecan-containing adjuvant therapy, OR have documented unsuitability for an irinotecan-containing regimen.

Failure is defined as either progression of disease (clinical or radiologic) or intolerance to the irinotecan-containing regimen, where intolerance is defined as discontinuation due to any of the following: severe allergic reaction or delayed recovery from toxicity preventing retreatment.

Documented unsuitability for irinotecan includes (but is not confined to) known hypersensitivity to irinotecan, abnormal glucuronidation of bilirubin, Gilbert's syndrome or previous pelvic/abdominal irradiation.

The intention of this criterion is to ensure that it is the conclusion of the investigator that this patient would not benefit from further therapy with irinotecan and is therefore an appropriate candidate for treatment with best supportive care measures only.

5.1.5 Received and failed an oxaliplatin-containing regimen (i.e. single-agent or in combination) for treatment of metastatic disease, OR relapsed within 6 months of completion of an oxaliplatin-containing adjuvant therapy OR have documented unsuitability for an oxaliplatin-containing regimen.

Failure is defined as either progression of disease (clinical or radiological) or intolerance to the oxaliplatin-containing regimen, where intolerance is defined as discontinuation due to any of the following: severe allergic reaction, persistent severe neurotoxicity or delayed recovery from toxicity preventing retreatment.

Documented unsuitability for oxaliplatin includes (but is not confined to) known hypersensitivity to oxaliplatin or other platinum compounds, pre-existing renal impairment, or Grade 2 or greater neurosensory neuropathy.

The intention of this criterion is to ensure that it is the conclusion of the investigator that this patient would not benefit from further therapy with oxaliplatin and is therefore an appropriate candidate for treatment with best supportive care measures only.

5.1.6 *For patients with colorectal cancer that is K-ras wild type:* Received and failed a cetuximab or panitumumab-containing regimen (i.e. single-agent or in combination) for treatment of metastatic disease OR have documented unsuitability for a cetuximab or panitumumab-containing regimen

Failure is defined as either progression of disease (clinical or radiological) or intolerance to the cetuximab- or panitumumab-containing regimen, where intolerance is defined as discontinuation due to any of the following: severe infusion reaction, persistent severe skin toxicity or delayed recovery from toxicity preventing retreatment.

Documented unsuitability for cetuximab includes (but is not confined to) known hypersensitivity to cetuximab or the presence of tumours with an activating *K-ras* mutation.

Documented unsuitability for panitumumab includes (but is not confined to) known hypersensitivity to panitumumab or the presence of tumours with an activating *K-ras* mutation.

The intention of this criterion is to ensure that it is the conclusion of the investigator that this patient would not benefit from further therapy with either cetuximab or panitumumab and is therefore an appropriate candidate for treatment with best supportive care measures only.

5.1.7 The only remaining standard available therapy as recommended by the Investigator is best supportive care.

5.1.8 Must have presence of measurable disease as defined by Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

5.1.9 Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease done within 14 days prior to randomization.

5.1.10 Must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

5.1.11 Must be ≥ 18 years of age. (Note that the lower age limit at each centre will be determined by that centre's policy regarding the age at which an individual may sign their own consent.)

5.1.12 *For male or female patient of child producing potential:* Must agree to use contraception or take measures to avoid pregnancy during the study and for 30 days after the last Protocol treatment dose.

Adequate contraception is defined as follows:

1. Complete abstinence from intercourse from four weeks prior to administration of the first dose until 28 days after the final dose of protocol treatment.
2. Consistent and correct use of one of the following methods of birth control:
   a. male partner who is sterile prior to the female subjects entry into the study and is the sole sexual partner for that female subject; or
   b. implants of levonorgesterol; or
   c. injectable progestagen; or
   d. any intrauterine device (IUD) with a documented failure rate of less than 1% per year; or
   e. oral contraceptive pill (either combined or progesterone only); or
   f. barrier methods including diaphragm or condom with a spermicide.

5.1.13 Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 72 hours prior to randomization. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhoea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL). Even women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy or practicing abstinence or where partner is sterile (e.g. vasectomy), should be considered to be of child bearing potential.

5.1.14 Must have alanine transaminase (ALT) ≤ 3 × institutional upper limit of normal (ULN) [≤ 5 × ULN in presence of liver metastases] within 14 days prior to randomization.

5.1.15 Must have hemoglobin (Hgb) ≥ 80 g/L within 14 days prior to randomization.

5.1.16 Must have total bilirubin ≤ 1.5 × institutional ULN [≤ 2.0 x ULN in presence of liver metastases] within 14 days prior to randomization.

5.1.17 Must have creatinine $\leq$ 1.5 × institutional ULN or Creatinine Clearance > 50 ml/min (as calculated by the Cockroft Gault equation) within 14 days prior to randomization.

5.1.18 Must have absolute neutrophil count $\geq$ 1.5 x 10^9/L within 14 days prior to randomization.

5.1.19 Must have platelet count $\geq$ 75 x 10^9/L within 14 days prior to randomization.

5.1.20 Other biochemistry which must be done within 14 days prior to randomization includes lactate dehydrogenase (LDH) and alkaline phosphatase.

5.1.21 Patient must consent to provision of, and investigator(s) must confirm access to and agree to submit at the request of the NCIC CTG Central Tumour Bank, a representative formalin fixed paraffin block of tumour tissue in order that the specific correlative marker assays proscribed in Appendix VI (Correlative Studies) may be conducted. Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the NCIC CTG must be sought prior to randomization of the first patient to allow cores (two 2 mm cores of tumour from the block) and a predetermined number of slides of representative tumour tissue to be substituted in response to the Central Tumour Bank request. Failure to submit any tissue samples on request will result in the patient being considered ineligible. Where no previously resected or biopsied tumour tissue exists, on the approval of the NCIC CTG, the patient may still be considered eligible for the study.

5.1.22 Patient must consent to provision of a sample of blood in order that the specific correlative marker assays proscribed in Appendix VI (Correlative Studies) may be conducted.

5.1.23 Patient is able (i.e. sufficiently fluent) and willing to complete the Quality of Life and Health Utilities questionnaires in one of the validated languages for the questionnaires. For a fluent patient who is blind, unable to read, or has an equivalent condition, facilitated completion of the questionnaires is allowed (e.g. reading of the questions to the subject by study staff [see Appendix VII, Section 8]). If a patient is unable to complete the questionnaire (due to illiteracy or other equivalent reason), the patient will still be eligible for the trial. Patients who are sufficiently fluent but refuse to complete the questionnaires will be considered ineligible for the trial. The baseline assessment must be completed within 14 days prior to randomization.

5.1.24 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits placed on patients being considered for this trial. (Call the NCIC CTG office (613-533-6430) if questions arise regarding the interpretation of this criterion). Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

5.1.25 In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient randomization.

5.1.26 The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other clinical studies during their participation in this trial while on study treatment.

5.2 Ineligibility Criteria

Patients who fulfil any of the following criteria are not eligible for admission to the study:

5.2.1 Anti-cancer chemotherapy or biologic therapy within the **lesser** of i) 21 days, or ii) the usual cycle length of the regimen (e.g. 14 days for FOLFOX), prior to the first planned dose of BBI608/placebo. An exception is made for capecitabine and regorafenib, where a minimum of 10 days since last dose must be observed prior to the first planned dose of BBI608/placebo.

Radiotherapy, immunotherapy, or investigational agents within four weeks of first planned dose of BBI608/placebo, with the exception of a single dose of radiation up to 8 Gray (equal to 800 RAD) with palliative intent for pain control up to 14 days before randomization.

5.2.2 Major surgery within 4 weeks prior to randomization.

5.2.3 Any known symptomatic brain metastases requiring steroids. Patients with treated brain metastases 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 randomization. Patients with known leptomeningeal metastases are excluded, even if treated.

5.2.4 Women who are pregnant or breastfeeding.

5.2.5 Gastrointestinal disorder(s) which, in the opinion of the Qualified/Principal Investigator, would significantly impede the absorption of an oral agent (e.g. active Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection).

5.2.6 Unable or unwilling to swallow BBI608/placebo capsules daily.

5.2.7 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, clinically significant 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.

5.2.8 Patients with a history of other malignancies except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for $\geq$ 5 years.

5.2.9 Prior treatment with BBI608.

5.2.10 Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy.

5.2.11 Any condition (e.g. psychological, geographical, etc.) that does not permit compliance with the protocol.

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing prior to randomization
History and Physical Exam including:	• Prior medical and therapeutic history[1] • Physical examination • Vital signs • Height, weight, ECOG performance status • Clinical tumour measurements	≤ 14 days
Hematology	• CBC + differential • Platelet count	≤ 14 days
Biochemistry	• Creatinine[2], Total Bilirubin, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	≤ 14 days
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	≤ 14 days
Cardiac Assessment	• ECG (12 lead)	≤ 28 days
Radiology & Imaging	• CT/MRI scan of chest/abdomen/pelvis with tumour measurement and evaluation by RECIST 1.1 criteria[3]	≤ 14 days
Correlative Studies & Tissue Banking	• Submission of representative block of diagnostic tumour tissue to central tumour bank	On request
	• Blood sample collection[4]	≤ 14 days
Other Investigations	• Serum or urine pregnancy test[5]	≤ 72 hours
	• Serum CEA	≤ 14 days
Adverse Events[6]	• Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms)	≤ 14 days
Quality of Life	• EORTC QLQ-C30	≤ 14 days
Health Utilities	• Health Utilities Index (HUI3)	≤ 14 days

1 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *K-ras* status of tumour, prior anticancer therapy and prior date(s) of disease progression. Note: Documentation of progression, as described in section 10.2, or intolerance, as described in sections 5.1.4, 5.1.5 and/or 5.1.6, must be submitted.

2 Baseline creatinine or creatinine clearance may be used to demonstrate eligibility as per section 5.1.17.

3 Standard tumour measurement procedures will be followed to assess response to therapy. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment

4 Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory procedure manual.

5 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

6 Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (see Appendix V).

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done through the NCIC CTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook" posted on the CO.23 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the CO.23 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with NCIC CTG.

The following information will be required:

- trial code (NCIC CTG CO.23)
- study site and investigator
- patient's initials (may be coded)
- confirmation of the requirements listed in section 5.1, including dates of essential tests and actual laboratory values
- completed eligibility checklist
- stratification factors (*K-ras* status of tumour, ECOG performance status, prior anti-VEGF therapy, time from diagnosis of metastatic disease)
- exception number – IF required and granted
- For NCIC CTG Centres - informed consent & tissue banking consent version dates, date signed by patient, name of person conducting consent discussion and date signed.

7.2 Stratification

The permuted block randomization procedure will balance between treatment arms within each of the following stratification factors:

- ECOG Performance Status (0 *versus*1)
- *K-ras* status (wild type *versus* mutant)
- Prior anti-VEGF therapy (yes versus no)
- Time from diagnosis of metastatic disease to randomization (< 18 months versus $\geq$ 18 months)

7.3 Registration/Randomization

Patients will be randomized 1:1 between the two treatment arms and the randomization will be provided electronically.

Note: The validity of results of the trial depends on the authenticity of, and the follow-up of, all patients entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis, unless the participant withdraws from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible patients admitted to the trial will be followed by the coordinating center. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

All randomized patients are to be followed until death or until sites are informed by NCIC CTG that further follow-up is no longer required. The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report plus an annual minimal follow-up form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

8.0 TREATMENT PLAN

Although the NCIC Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator.

In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient randomization.

8.1 Treatment Plan

All patients will receive best supportive care (where best supportive care is defined as those measures designed to provide palliation of symptoms and improve quality of life as much as possible).

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment will be offered to all patients on this trial. Details of interventions (e.g. medications such as antibiotics, analgesics, antihistamines, steroids, G-CSF, erythropoietin), procedures (e.g. paracentesis, thoracentesis), or blood products (e.g. blood cells, platelets, or fresh frozen plasma transfusions) should be recorded on the case report forms.

8.1.1 Drug Administration

Arm	Agent(s)	Dose	Route	Duration
1	BBI608	480 mg two times daily[1,2,3]	Oral	Daily administration
2	Placebo	two times daily[1,2,3]	Oral	Daily administration

[1.] Protocol treatment should be taken one hour before or two hours after a meal, two times daily, with approximately 12 hours between doses.

[2.] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment.

[3.] Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and are, in the opinion of the investigator, continuing to derive benefit from protocol therapy (see section 12.2).

Patients will receive protocol treatment (BBI608 or placebo) two times daily, one hour prior to or two hours after meals, with the first dose given in the morning and approximately 12 hours between doses.

Handling instructions for BBI608/placebo will be provided to all sites. Investigators may refer to the Investigator Brochure for detailed instructions.

8.1.2 Blinding / Unblinding

This is a double blind, placebo controlled study. Blinding is critical to the integrity of this clinical drug trial. If there is a need to break the blind this must be discussed with the NCIC CTG as per Appendix IX.

8.1.3 Patient Monitoring

For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit, which will occur every four weeks, and are to be instructed to call their physician to report any adverse events between visits.

8.1.4 Dose Modification

The major adverse events associated with the use of BBI608 are gastrointestinal issues (nausea, diarrhea, and abdominal cramping) and fatigue. Fatigue is often secondary to gastrointestinal events. There is no hematologic toxicity associated with BBI608.

The guidelines that follow outline dosing modifications and recommended interventions should the above adverse events occur.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix V). If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

8.1.5 Hematologic Adverse Events

No hematologic toxicity related to BBI608 treatment has been observed. Should a study subject experience a Grade 1 or 2 hematologic adverse event, dosing may continue while an alternate explanation is sought and/or a therapeutic intervention is undertaken.

In the unlikely event of a Grade 3 or 4 hematologic adverse event, continued dosing will be at the discretion of the study investigator. Since a Grade 3 or 4 hematologic event attributed to BBI608 has not been reported, a prompt evaluation for an alternate explanation is strongly recommended.

8.1.6 Non-Hematologic Adverse Events

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

Protocol Treatment-Related Adverse Event	Investigator Action
Grade 1 or tolerable Grade 2 Symptoms	Patient should remain at current dose. Attempt pharmacologic measures to minimize symptoms (see symptom specific treatment table below).
Intolerable Grade 2 Symptoms*	If intolerable symptoms persist despite optimized medical management, dose reduction and sufficient oral hydration are recommended. A dose holiday of ½ to 2 days prior to reduction can also be considered. Dosing should be reduced to the next Modification Level on the *dose modification table*. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be re-escalated in 80 mg increments every 3-7 days as tolerated.**
Grade 3 or 4 Symptoms*	A dose holiday of ½ to 2 days is recommended until symptoms are reduced to ≤ grade 2. Dosing should be reduced to the next Modification Level on the *dose modification table*. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be re-escalated in 80 mg increments every 3-7 days as tolerated.**
* If, during the course of re-escalation, a dosing regimen is not tolerated despite optimized medical management, dosing should return to the highest previously tolerated dosing regimen. ** Asymmetry between AM and PM dose is allowed during re-escalation (e.g. 320 mg AM/240 mg PM)	

Dose Modification Table:

Dose Level	Dose
Starting dose	480 mg twice daily (q12h)
Modification Level-1	240 mg twice daily (q12h), up titrate as tolerated**
Modification Level-2	80 mg twice daily (q12h), up-titrate as tolerated**
Modification Level-3	80 mg once daily*, up-titrate as tolerated**
* If 80 mg once daily is not tolerated, a dose holiday of 1-3 days followed by re-challenge at 80 mg once daily is recommended ** Asymmetry between AM and PM dose is allowed during re-escalation (e.g. 320 mg AM/240 mg PM)	

Symptom-specific full supportive treatment is defined as follows (unless contraindicated):

Toxicity / Adverse Event	Full Pharmacologic Supportive Treatment
Diarrhea/Abdominal Cramps	Maximal dose administration (as tolerated) of at least two of the following anti- diarrheal agents: • Loperamide • Diphenoxylate/Atropine • Systemic opioids (e.g. hydromorphone) • Tincture of Opium • Butylscopolamine, or hyoscyamine
Nausea/Vomiting	Maximal dose administration (as tolerated) from one or more of the following classes of agents, at the discretion of the investigator: • 5-HT_3 Receptor Antagonists (e.g. ondansetron) • Dopamine Antagonists (e.g. prochlorperazine, metclopromide) • Antihistamines (e.g. dimenhydrinate) • Benzodiazepines (e.g. lorazepam) • Anticholinergics (e.g. scopolamine) • Cannabinoids (e.g. dronabinol) • Glucocorticoids (e.g. dexamethasone) • Proton Pump Inhibitors, H-2 Receptor Antagonists (e.g. omeprazole, ranitidine)
Fatigue	Full supportive treatment of any concurrent gastrointestinal adverse events.

8.1.7 Other Situations

Change in Urine Colour and Odour:
Occasionally, subjects have reported an orange-brown colour change to their urine. Rarely, subjects also report a new odour to their urine. All subjects should be made aware of the possibility of these effects. Patients can be reassured that these effects have no long term consequences, and that the effects are completely reversible. Dosing can be continued in the presence of these events.

8.1.8 Concomitant Medications

Permitted Treatments:
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.

All palliative and supportive care measures may be administered to patients in either study arm at the Investigator's discretion. Incident palliative radiotherapy is permitted in both study arms while on study, but requirement of radiation to the target lesion(s) will qualify the patient as having disease progression.

Non-Permitted Treatments:
Patients entering this trial are to be refractory to all recommended chemotherapy. Therefore further chemotherapy OR other non-cytotoxic experimental agents should not be given to study patients.

8.1.9 Duration of Therapy

Subjects will take their allocated therapy orally two times daily, one hour before or two hours after a meal, with approximately 12 hours between doses. Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and are, in the opinion of the investigator, continuing to derive benefit from protocol therapy (see section 12). For details concerning toxicity, please consult section 8.1.5 and 8.1.6. For a complete list of general criteria for stopping study treatment, please see section 12.0.

8.1.10 Patient Compliance

Treatment compliance is defined as the ratio, expressed as a percentage, of the number of capsules (BBI608 or placebo) taken by a patient over the course of a time interval to the number of capsules intended to be taken over that same time interval.

Treatment compliance in both arms will be monitored by drug accountability, as well as the monitoring of patient-reported compliance.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

Evaluations will be performed at different intervals throughout the study. If dose delays occur for any reason on the study, other study assessments, including assessment by physician and Quality of Life questionnaires, will not be delayed, but should continue at the time indicated from randomization.

9.1 Evaluation During Protocol Treatment

Investigations		Timing from Randomization
Physical Examination	• Physical examination • Vital signs • Weight + ECOG Performance status	Every 4 weeks (every 28 days) after randomization [1]
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	
Economics	• Resource Utilization Assessment	
Other Investigations	• Serum or urine pregnancy test [2]	
	• Serum CEA	
Adverse Events [3]	• Adverse Event evaluation must be done at each study visit for the preceding 4 week reporting period[3]	
	• Adverse Event evaluation by phone to assess tolerability of dosing regimen [3]	Within 24-48 hrs of start of protocol treatment, and at 2 weeks (approximately 14 days) and 6 weeks (approximately 42 days) after randomization
Cardiology Assessment	• ECG	2 hours after first dose on first day of treatment and as clinically indicated thereafter
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumour measurement and evaluation by RECIST 1.1 criteria [4]	Every 8 weeks (every 56 days) after randomization [4]
Correlative Studies & Tissue Banking	• Submission of whole blood sample to central tumour bank [5]	At 4, 8 and 12 weeks after randomization[5]
Sparse PK Collection	• Submission of blood plasma samples to central lab[5]	At 4, 8 and 12 weeks after randomization[5]
Quality of Life	• EORTC QLQ-C30 [6]	At 4, 8, 12, 16 and 24 weeks after randomization
Health Utilities	• Health Utilities Index (HUI3) [6]	

1 Patients are to be assessed every 4 weeks (28 days) while on study medication and until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days.

2 In women of childbearing potential only a negative pregnancy test must be demonstrated every 4 weeks until 4 weeks after the administration of the final dose of protocol therapy. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

3 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (see Appendix V).

4 The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumour evaluations will continue until progressive disease is documented (as described in section 10). For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumour measurements and assessment must be reported.

5 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.

6 To be completed in clinic.

9.1.1 Patient Evaluation After Unblinding and Continued Protocol Treatment

Please refer and follow section 9.1 until permanent discontinuation of protocol treatment. The only exception is blood collection for pharmacokinetic analyses ("Sparse PK Collection") which can cease for all patients post-unblinding. Note that collection of specimens for correlative studies (tissue and blood) and for specimen banking ("Correlative Studies & Tissue Banking") should continue post-unblinding as per section 9.1.

9.2 Evaluation After Protocol Treatment Discontinuation

Investigations		Timing from Randomization
Physical Examination	• Physical examination • Vital signs • Weight + ECOG Performance status	Every 4 weeks (every 28 days) after randomization until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, and every 8 weeks (56 days) thereafter until deterioration to ECOG PS 4 or hospitalization for end of life care.
Economics	• Resource Utilization Assessment	
Adverse Events [1]	• Adverse Event evaluation must be done at each study visit for the preceding reporting period[1]	
Overall Survival	• Assess for survival of patient [2]	Every 4 weeks (every 28 days) after randomization until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, and every 8 weeks (56 days) thereafter.
Other Investigations	• Serum or urine pregnancy test [3]	Every 4 weeks (every 28 days) after randomization until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days
	• Serum CEA	
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	
Cardiology Assessment	• ECG	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days
Radiology & Imaging	• CT/MRI scan as per baseline assessment with tumour measurement and evaluation by RECIST 1.1 criteria [4]	Every 8 weeks (56 days) after randomization until objective disease progression is documented [4]
Correlative Studies & Tissue Banking	• Submission of whole blood sample to central tumour bank [5]	At 4, 8 and 12 weeks after randomization [5]
Quality of Life	• EORTC QLQ-C30 [6]	At 4, 8, 12, 16 and 24 weeks after randomization or until deterioration to ECOG PS 4 or hospitalization for end of life care [6]
Health Utilities	• Health Utilities Index (HUI3) [6]	

1 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (see Appendix V).
2 In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.
3 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
4 The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumour evaluations will continue until progressive disease is documented (as described in section 10).
5 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.
6 To be completed in clinic.

9.2.1 Patient Evaluation After Permanent Discontinuation of Protocol Therapy, Post-Unblinding

Sites should complete the evaluations for the current reporting period as per section 9.2. Subsequently, evaluations can switch as follows:

Investigations		Timing from Randomization
Physical Examination	• Physical examination • Vital signs • Weight + ECOG Performance status	Every 4 weeks (every 28 days) after randomization until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days.
Adverse Events [1]	• Adverse Event evaluation must be done at each study visit for the preceding reporting period[1] • Report ongoing AEs thought to be related to BBI608	Every 4 weeks (every 28 days) after randomization until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days, and every 8 weeks (56 days) thereafter.
Overall Survival	Assess for survival of patient [2]	
Other Anti-cancer Therapy		
Other Investigations	• Serum or urine pregnancy test [3]	Every 4 weeks (every 28 days) after randomization until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days
	• Serum CEA	
Hematology	• CBC + differential, Platelet count	
Biochemistry	• Creatinine, Total Bilirubin, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	
Urinalysis	• Dipstick (including protein, specific gravity, glucose and blood)	
Cardiology Assessment	• ECG	At the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days
Radiology & Imaging (only if done)	• CT/MRI scan as per baseline assessment with tumour measurement and evaluation by RECIST 1.1 criteria [4]	No longer required every 8 weeks after randomization until objective disease progression. However if radiology and imaging is done, please report the data in EDC on the disease assessment (target and non-target lesion) tables. [4]
Correlative Studies & Tissue Banking	• Submission of whole blood sample to central tumour bank [5]	At 4, 8 and 12 weeks after randomization [5]

1 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (see Appendix V).
2 In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.
3 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
4 The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumour evaluations will continue until progressive disease is documented (as described in section 10).
5 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 *Evaluable for Adverse Events:* All patients who have received at least one dose of BBI608/placebo will be evaluable for adverse events from the time of their first dose of BBI608/placebo.

10.1.2 *Evaluable for Overall Survival (OS):* All randomized patients will be included in the analysis of OS, which is defined as the time interval between the date of randomization and the date of death from any cause. Patients who are still alive at the time of the final analysis, or who have become lost to follow-up will be censored at their last date known to be alive.

10.1.3 *Evaluable for Progression Free Survival (PFS):* All randomized patients will be included in the analysis of PFS, which is defined as the time interval between the date of randomization and the date of objective disease progression or death, whichever comes first. If neither event has been observed, then the patient will be censored at the date of the last tumour assessment.

Disease progression is defined as objective progression per RECIST 1.1 *[Eisenhauer 2009]*. It is required to perform, whenever possible, a radiological confirmation of the clinical suspicion of tumour progression. In the situation where there is clinical suspicion of progression but objective progression cannot be determined per RECIST 1.1, disease is defined as clinical deterioration without objective evidence of progression.

An observed increase in tumour marker (e.g. CEA), regardless of the magnitude of increase, will **NOT** be considered evidence of objective disease progression.

The date of disease progression is defined as the date when the criteria for objective progression are first met.

10.1.4 *Evaluable for Disease Control Rate (DCR):* All patients who have been randomized will be included in the analysis of DCR which is defined as a composite of Stable Disease, Partial Response and Complete Response as classified according to the definitions set out below *[Eisenhauer 2009]*. For patients who discontinue protocol therapy prior to their first objective assessment of response, it is imperative that an objective response assessment be undertaken as close to the protocol specified schedule as possible in order to ensure patient data contributes appropriately to the interim assessment of DCR (see section 14.5).

10.1.5 *Evaluable for Quality of Life Assessment:* All patients who have completed the baseline quality of life questionnaire and at least one other QoL questionnaire are evaluable.

10.1.6 *Evaluable for Health Utilities:* All patients who have completed the baseline health utilities assessment questionnaire and at least one other health utilities assessment questionnaire are evaluable.

10.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee.

10.2.1 *Measurable Disease:* Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan, or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

10.2.2 *Non-measurable Disease:* All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

10.2.3 *Target Lesions:* When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

10.2.4 *Non-target Lesions:* All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

10.2.5 *Response:* All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target*. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases *[Eisenhauer 2009]*) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

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

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of $\geq$ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	tumour nodes < 10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	documented at least once $\geq$ 5 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	tumour nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without radiological progression having been observed at that time should be reported as "symptomatic deterioration". This is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

10.3 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

10.4 Stable Disease Duration

Stable disease duration will be measured from the time of randomization until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

10.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

10.5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

10.5.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions $\geq$ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

10.5.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case *[Eisenhauer 2009]*. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

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

10.5.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

10.5.6 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.0 SERIOUS ADVERSE EVENT REPORTING

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

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the NCIC CTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAE's which are subject to expedited reporting to NCIC CTG.

11.1 Definition of a Protocol Reportable Serious Adverse Event

- **All serious** adverse events must be reported in an expedited manner (see section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration).
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death;
  - is life-threatening;
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care);
  - results in persistent or significant disability or incapacity;
  - is a congenital anomaly/birth defect.
- NOTE: Serious adverse events which are unequivocally related to the underlying malignancy or disease progression do **NOT** require expedited reporting. These include such adverse events as admission for pain control, palliative care or paracentesis of malignant effusions.
- In addition, the following events will **NOT** be recorded as AEs (or SAEs):
  - lack of efficacy /disease progression (will be recorded separately on CRF);
  - laboratory abnormalities for protocol specified tests (these are derived electronically from actual values supplied and need not be reported separately in adverse event tables on CRFs);
  - elective hospitalization for medical, radiological or surgical procedures for treatment of disease or to simplify treatment for study procedures (will be recorded separately on CRF);
  - hospitalization for palliative care or pain control.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization and which are NOT definitively related to the underlying malignancy or disease progression but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.1.1 *Serious Adverse Event Reporting on Study Post-Unblinding*

Serious adverse events that are considered related (i.e. possibly, probably or definitely) to protocol therapy must continue to be reported in an expedited manner (see section 11.2) for patients receiving BBI608 on study after unblinding.

11.2 Serious Adverse Event Reporting Instructions

All protocol specified (section 11.1) reportable serious adverse events must be reported using the web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the NCIC CTG Generic Data Management Guidebook for EDC Studies posted on the CO.23 section of the NCIC CTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to NCIC CTG via EDC system.
Within 7 days:	Update Serious Adverse Event Report as much as possible and submit report to NCIC CTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to: CO.23 Study Coordinator
NCIC Clinical Trials Group
Fax No.: 613-533-2941

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to NCIC CTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the CO.23 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to NCIC CTG as indicated above. Once internet connectivity is restored, the information that was FAXED to NCIC CTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the NCIC CTG Safety Desk for further instructions (613-533-6430).

11.3 Other Protocol Reportable Events – Pregnancy/Exposure Reporting

In accordance with NCIC CTG's inclusivity in research policy, women of childbearing potential (WOCBP) may be enrolled in this clinical trial. WOCBP are defined as women who have had a menstrual period during the last year and have not had a hysterectomy. Precautions are required to be taken to prevent pregnancy during the clinical trial when the research population includes WOCBP. This includes pregnancy testing, use of effective methods of birth control, and pregnancy as an exclusion factor. The trial sample informed consent form includes *the potential for unidentified risks to the embryo/fetus.* It also includes general information on pregnancy prevention and the required minimum period during which birth control must be utilized.

11.3.1 Pregnancy Prevention

WOCBP and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in eligibility criteria 5.1.12. Investigators are advised to inform the female partners of male participants when appropriate and compliant with local policy.

A highly effective method of birth control is defined as those which result in a failure rate of <1% per year when used consistently and correctly.

11.3.2 Pregnancy Occurring in WOCBP Exposed to Study Agent

Any female participant who becomes pregnant during the course of the trial should be instructed to stop taking study medication immediately.

The investigator should provide counselling and discuss the risks and possible side effects to the embryo/fetus from BBI608. Monitoring should continue until conclusion of the pregnancy. The same should occur for female partners of a male participant, or any female exposed to BBI608 when appropriate and compliant with local policy.

11.3.3 Pregnancy/Exposure Reporting

The investigator is required to report to the sponsor any pregnancy where the embryo/fetus could have been exposed to BBI608. This means pregnancies occurring in female participants, female partners of male participants, or females exposed through direct contact with the agent during their pregnancy (for example, environmental exposure involving direct contact with the agent). Pregnancies occurring up to 30 days after the completion of BBI608 must also be reported.

The investigator is required to inform NCIC CTG within 24 hours of learning of the pregnancy using the SAE reporting form appropriate for the trial as indicated above. In the Adverse Event column please enter the following: “pregnancy, puerperium and perinatal conditions – other, specify” (fetal exposure). Please note that the NCIC CTG patient identification number must correspond to the participant in the main trial. Specifically, in the case of pregnancy in the female partner of a male participant, the male participant’s patient identification number should be used for reporting purposes.

The SAE form must be updated to reflect the outcome of the pregnancy. For example:

- “pregnancy, puerperium and perinatal conditions – other, specify” (normal live birth),
- “pregnancy, puerperium and perinatal conditions – other, specify” (therapeutic abortion), or
- another term under "pregnancy, puerperium and perinatal conditions" as applicable.

Information on the medical history of the parents that may relate to assessing any potential fetal outcomes is requested, *as is information on the health of the newborn*. The narrative section of the SAE form should be used to communicate all relevant information pertaining to the pregnancy.

11.4 NCIC CTG Responsibility for Reporting Serious Adverse Events to Regulatory Agencies

The NCIC CTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) and local country sponsors (for submission to applicable regulatory authorities), for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are related to protocol treatment:

- **Unexpected** adverse events are those which are not consistent in either nature or severity with information contained in the Investigator's Brochure
- Adverse events considered **related to protocol treatment** are those events which lack a plausible alternate explanation.

NCIC CTG, in consultation with Boston Biomedical Inc, will determine which SAEs meet the criteria for regulatory reporting.

11.5 NCIC CTG Reporting Responsibility to Boston Biomedical, Inc.

Boston Biomedical, Inc will be notified of all serious adverse events within 1 working day of receipt by NCIC CTG. Boston Biomedical will have electronic access to Serious Adverse Event information for the purposes of assisting the NCIC CTG as requested in determining which SAEs meet the criteria for regulatory reporting.

11.6 Boston Biomedical, Inc Reporting Responsibilities

Boston Biomedical will notify the NCIC CTG of all Safety Letters/Safety Updates (SUs) or Serious Adverse Events (SAEs) that are reported to regulatory authorities from other trials involving BBI608.

11.7 Reporting Safety Reports to Investigators

NCIC CTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the NCIC CTG trial CO.23 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the NCIC CTG trial CO.23 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by NCIC CTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients should stop protocol treatment in the following instances:

- Progressive Disease (see section 10.2.5), unless the Investigator believes the patient may be deriving benefit from therapy, in which case patient may continue treatment (see section 12.2).
- Pregnancy.
- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in section 8.1.5 and 8.1.6.
- Request by the patient.
- Post-unblinding, the trial will continue in centres with patients who have not yet met the primary study endpoint (death), and with patients currently on protocol therapy (active arm) who may receive BBI608 on study based on the clinical judgement of the investigator and local REB approval that this is in the patient's best interest, providing the patient is fully informed and provides consent (see also section 9.1.1 and 9.2.1). Patients will receive study supply BBI608 until any of the discontinuation criteria are met (as above).

Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution. In particular, for patients who discontinue protocol therapy prior to their first objective assessment of response, it is imperative that an objective response assessment be undertaken as close to the protocol specified schedule as possible in order to ensure patient data contributes to the interim assessment of DCR (see section 14.5).

12.2 Duration of Protocol Treatment

Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and are, in the opinion of the investigator, continuing to derive benefit from protocol treatment.

As BBI608 targets cancer stem cells, it is possible that continued therapy after progressive disease per RECIST 1.1 may provide clinical benefit. Therefore, subjects will be permitted to remain on BBI608/placebo beyond formal objective progression until the Investigator believes the patient is no longer deriving benefit from protocol therapy. Thus, subjects may remain on BBI608/placebo beyond formal objective progression by RECIST 1.1 during, or as a component of, palliative care.

12.3 Therapy After Protocol Treatment is Stopped

Treatment after all protocol therapy has been discontinued is at the discretion of the Investigator.

12.4 Follow-up Off Protocol Treatment

Follow-up will continue after treatment completion according to the plan described in the protocol (see section 9.2). Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.5 Emergency Unblinding

Details of the circumstances in which emergency unblinding is permitted and process to unblind patient treatment are contained in Appendix IX.

13.0 CENTRAL REVIEW PROCEDURES, TISSUE COLLECTION, AND CORRELATIVE STUDIES

13.1 Central Radiology Review

There will be no central radiology review for this study.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Tissue Collection

Protocol-Mandated Correlative Studies:
The submission of a representative block of the diagnostic tumour tissue (at the request of the NCIC CTG Central Tumour Bank if available) and of a sample of whole blood for correlative studies defined in Appendix VI is mandatory for participation in this trial. Where local centre regulations prohibit submission of blocks of tumour tissue, the approval of the NCIC CTG must be sought prior to randomization of the first patient to allow cores (two 2 mm cores of tumour from the block) and a predetermined number of slides of representative tumour tissue to be substituted in response to the Central Tumour Bank request. Failure to submit any tissue samples as directed (blood) or on request (tumour tissue) will result in the patient being considered ineligible. Where no previously resected or biopsied tumour tissue exists, on the approval of the NCIC CTG, the patient may still be considered eligible for the study.

The subsequent banking of collected diagnostic tissue or blood is not mandatory for participation in the study, but the participation of all centres is strongly encouraged. Blocks and blood will be carefully banked as part of the NCIC CTG tissue/tumour bank at Queen's University in Kingston, Ontario.

After patient consent, whole blood and paraffin tumour blocks will be the preferred tissue material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If tumour blocks are unavailable, then two 2 mm cores of tumour from the block and 30 specimen slides are preferred. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of colorectal cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymous and only identified by a coded number.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen's Department of Pathology to the appropriate pathology departments for a representative tumour block.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the patient.

All patients on whom a blood sample and/or diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

13.4 Sparse Pharmacokinetic Plasma Sample Collection

Plasma samples for sparse pharmacokinetics (PK) analysis will be obtained from all patients at the study visits occurring 4, 8 and 12 weeks after randomization.

Week 4 Study Visit:
The week 4 visit should be scheduled prior to 10 AM. On the day of the week 4 visit, patients should be instructed to wait to take their first daily dose of BBI608/Placebo until they arrive in clinic. After arrival in the clinic, but 5 minutes prior to administration of the first daily dose of BBI608/Placebo, a plasma sample will be obtained. A second plasma sample will be obtained between 2 and 4 hours after the first daily dose of BBI608/Placebo.

Week 8 Study Visit:
On the day of the week 8 visit, patients will be instructed to take BBI608/Placebo as normal. A single plasma sample will be obtained between 5 and 10 hours after the first daily dose of BBI608/Placebo.

Week 12 Study Visit:
On the day of the week 12 visit, patients will be instructed to take BBI608/Placebo as normal. A single plasma sample will be obtained at any time after the first daily dose of BBI608/Placebo on this day.

For all days during which a plasma sample is obtained for PK analysis, the precise time of all doses of BBI608/Placebo (on the day of sampling and the day prior) and the precise time of all PK sampling must be captured.

Samples will be processed, stored and shipped according to the instructions provided in the CO.23 Sparse PK sampling laboratory manual.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this study is to assess the effect of orally administered BBI608 plus best supportive care (BSC), in comparison to placebo plus best supportive care on the Overall Survival of patients with advanced histopathologically confirmed colorectal carcinoma who have exhausted all standard treatment options.

Secondary objectives include comparisons of Progression Free Survival, Disease Control Rate, Quality of Life, and Adverse Events between the two treatment arms.

This is a multi-centre, prospective, double blind, placebo controlled, randomized phase III trial. Patients will be randomized to receive either BBI608 plus best supportive care, or placebo plus best supportive care in a 1:1 ratio and will be stratified by ECOG performance status (0 *versus* 1), *K-ras* tumour status (wild type *versus* mutant), prior anti-VEGF therapy (yes *versus* no), and time from diagnosis of metastatic disease to randomization (< 18 months *versus* ≥ 18 months).

14.2 Study Endpoints and Analysis

Overall Survival

Overall Survival, the primary endpoint of this study, is defined as the time from randomization to death from any cause. Patients who are alive at the time of the final analysis or who have become lost to follow-up will be censored at their last date known to be alive. Patients will be analyzed in the arm to which they are randomized regardless of the treatment they received (intent-to-treat analysis). The survival experience of patients in both treatment groups will be summarized by the Kaplan-Meier method and compared primarily by a stratified log-rank test adjusting for stratification variables, at randomization. Secondary analyses based on stratified Cox proportional hazards model will also be performed. ECOG performance status (0 *versus* 1), *K-ras* tumour status (wild type *versus* mutant), prior anti-VEGF therapy (yes *versus* no), and time from diagnosis of metastatic disease to randomization (< 18 months *versus* ≥ 18 months) will be the stratification factors to define the stratified Cox proportional hazards model. Besides the treatment factor (BBI608+BSC *versus* placebo+BSC), the following factors at patient entry will be included in the stratified Cox proportional hazards model:

- Number of previous chemotherapy drug classes [irinotecan, oxaliplatin, anti-thymidylate synthase drug, EGFR inhibitor, VEGF inhibitor], including during adjuvant therapy (< 3 *versus* ≥ 3)
- Age (< 65 *versus* ≥ 65)
- Sex (male *versus* female)
- Number of organ sites involved at baseline (≤ 2 *versus* > 2)
- Presence of liver metastases (yes *versus* no)
- Primary tumour site (colon *versus* rectum)

A formal pre-planned subset analysis for the primary endpoint (OS) will be conducted to address the benefit of BBI608 between the groups defined by the above factors and the following:

- ECOG Performance Status (0 versus 1)
- K-ras (wild type versus mutant)
- Prior bevacizumab exposure (prior treatment versus treatment naïve)
- Prior anti-VEGF (e.g. bevacizumab, aflibercept, etc) therapy (yes *versus* no)
- Time from diagnosis of metastatic disease to randomization (< 18 months versus > 18 months)
- Race (white, black, Asian, other)
- Country (Canada, Australasia, USA, others)

Progression-Free Survival

Progression-Free Survival (PFS) is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. If a patient has not progressed or died at the time of final analysis, PFS will be censored on the date of the last tumour assessment. This includes patients who are lost to follow-up or have withdrawn consent. All analyses for OS will also be performed for PFS, using similar methodology.

Disease Control Rate

Disease Control Rate (DCR) is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1. The primary estimate of DCR will be based on all patients randomized.

Safety Analysis

All patients who have received at least one dose of BBI608/Placebo will be included in the safety analysis. The incidence of adverse events will be summarized by type of adverse event and severity using the NCI Common Terminology Criteria for Adverse Events Version 4.0. A Fisher's exact test will be used to compare adverse events between the two arms if required.

Quality of Life Analysis

The Quality of Life (QoL) of patients will be assessed using EORTC QLQ-30. The EORTC QLQ-30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functional domains, a global quality of life domain, three symptom domains, and six single items. Scoring of the EORTC QLQ-30 data will be completed following the procedures recommended by the EORTC Study Group on Quality of Life. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100. The quality of life data will be analyzed to look for statistically and clinically significant differences between the BBI608 *versus* placebo groups. Questionnaire compliance rates will be ascertained for each group at each measurement time point. Mean baseline scores for each subscale and summary scores will be calculated.

The primary endpoints in QoL analysis are the mean EORTC QLQ-C30 QoL change scores from baseline at time 2 (8 weeks) and time 4 (16 weeks) for the physical function and global health status/quality of life subscale scores. These time points have been chosen a priori as experience from the CO.17 and CO.20 studies suggests patient compliance is expected to be sufficient to complete meaningful analyses at these times and the effects of BBI608 would be expected to be evident by 8-12 weeks, the approximately mean time to progression for the control arms of CO.17 *[Jonker 2007]* and CO.20 *[Siu, 2012]*. Wilcoxon tests will be used to compare the difference at each of these two time points between two treatment arms for each of these two subscales. The Hochberg method *[Hochberg 1988]* will be used to adjust for four comparisons in the primary analyses. The proportion of patients in either arm with at least a 10 unit(s) deterioration in change scores at both 8 and 16 weeks will be compared by means of Fisher's exact test.

Secondary QoL analyses will include the standard NCIC CTG QoL Response Analysis categorizing patients as either having improved, stable, or worsened QoL as follows *[Osoba 2005]*. Again, a change score of 10 points from baseline is defined a priori as clinically relevant. For functional scales and global health status, patients will be considered to have QoL improvement if reporting a score 10-points or better than baseline at any time of QoL assessment. Conversely, patients will be considered worsened if reporting a score minus 10-points or worse than baseline at any time of QoL assessment without any improvement. Patients whose scores fall between 10-point changes from baseline at every QoL assessment will be considered as stable. In contrast to functional scales, for the determination of patient's QoL response, classification of patients into improved and worsened categories will be reversed for symptom scales.

14.3 Sample Size and Duration of Study

The primary study endpoint is Overall Survival (OS). The study is designed to have a power of 90% and a two-sided alpha of 5% to detect a 23% reduction in the continuous risk of death (HR 0.77, which corresponds to an increase of median survival from 4.6 to 6.0 months). It is estimated that 615 events will be required to detect this reduction which would be observed by randomizing 650 patients over approximately 26 months and following them for additional 12 months.

14.4 Safety Monitoring

Adverse events will be monitored on an on-going basis by the central office and their frequencies reported annually at investigators' meetings.

14.5 Interim and Final Analyses

There will be two interim analyses in this study to be presented to the Independent NCIC CTG Data Safety and Monitoring Committee (DSMC). The first will use the DCR at first response assessment to project whether continued treatment with BBI608 would be futile. This analysis will be performed 10 weeks after the 96th patient has been randomized. The primary analysis will be based on DCR calculated as the proportion of 96 patients randomized. An analysis based on evaluable patients who have CR, PR, or SD assessed will also be presented. The trial would be stopped by the DSMC if both of the following conditions are met: (1) the observed percentage increase in DCR, calculated as the ratio of the difference in DCRs between BBI608+BSC and placebo+BSC arms over the DCR in placebo+BSC arm, is less than 30%; and (2) the observed absolute difference in DCR between BBI608+BSC and placebo+BSC arms is less than 10%.

Based on historical data from phase III studies of third and fourth line therapy *[Jonker, 2007; Van Cutsem, 2007; Grothey, 2012]*, the DCR in the placebo+BSC arm is expected to be approximately 10-15% *versus* 60% in the active treatment arm, as observed in the BBI608 phase I expanded colorectal cohort. Assuming that the true DCR in the placebo+BSC arm is 15%, then if the true DCR in the BBI608+BSC arm is 32% or higher, the chance that the trial would be continued is approximately 90%. On the other hand, if the true DCR in the BBI608+BSC arm is 16.5% or lower, the chance that the trial would be stopped is approximately 64%.

This trial was activated on April 15, 2013 and a total of 257 patients were randomized as of May 7, 2013. The 96th patient was randomized on January 10, 2014. Since there was one patient who withdrew consent virtually at time of randomization, it was decided the first interim analysis would also include the 97th patients, who was randomized on the same day. The cleaning of the data which are required for the first interim analysis was completed on April 17, 2014 and a database was locked for analysis on the same day. Both primary analysis based on all randomized patients included in the first interim analysis and sensitivity analysis based on patients evaluable for disease control at first response assessment were presented to DSMC on May 16, 2014. After reviewing the results, DSMC recommended closing the trial to further accrual. On May 23rd, 2014 the trial was officially closed to further accrual, and investigators were instructed to inform patients of *first interim analysis* findings and of their treatment allocation. All patients were directed to discontinue protocol therapy. Given that no safety concerns were identified by the DSMC, in cases in which a patient appears to be deriving benefit from BBI608 and is tolerating treatment well, open-label continuation of BBI608 was permitted on a case-by-case basis provided approval of the local REB and patient consent to continue BBI608 treatment. At the time of accrual closure, 282 patients had been randomized to this study.

Due to premature closure of the trial the analysis plan is amended as follows: analysis will be conducted as interim analysis 2 and final analysis. *Interim analysis 2* will be based on patient data accumulated before a clinical cut-off date of May 23rd, 2014 and the primary analysis population being patients enrolled on or before March 28 ("ITT-March" population). The date May 23rd 2014 is chosen as cut-off for *interim analysis 2* as the trial was closed to further accrual and patients on study were unblinded to their treatment allocation on May 23rd. March 28th 2014 is used to define primary ITT-March population so as to select patients with meaningful exposure to the study therapy. Using ITT-March population for primary analysis will also help minimize bias induced by premature closure of the trial to further accrual. All patients randomized on or before May 23rd, 2014 will comprise ITT-May population which will be used to perform secondary analysis.

The final analysis will be performed when 90% of the events (195 events in 217 ITT- March patients) have been observed. With 195 events, the study will have 70% power to detect a hazard ratio of 0.70 (2.0 month difference in median survival between the two treatment arms) at a two-sided 0.05 level. This number of events would yield 43% power to detect the original target hazard ratio of 0.77 (1.4 month difference in median survival between the two treatment arms) with an overall two-sided alpha of 5%.

An exploratory analysis will be conducted to provide a randomized estimate of treatment effect from at least 8 weeks study drug exposure by adjusting for protocol adherence and for limited time on trial. Treatment effect on survival and on PFS will be estimated for three separate periods i) an initial time period when dose intensity was suboptimal ii) a second time period for all additional patients enrolled up to March 28th and iii) for remaining patients enrolled up to May 23rd. An adjusted overall treatment effect will be estimated as a weighted average of these 3 periods adjusted for exposure within each.

14.6 Biomarker Evaluation

The following analysis will be performed to investigate the relationship between endpoints and biomarker levels (e.g. STAT3, phospho-STAT3, β-catenin):

For each biomarker, Cox Proportional Hazards model will be used to model the relationship between Overall Survival, Progression-Free Survival and duration of response with baseline value of the biomarker. The model will also include assigned treatment, interaction between treatment and biomarker, and will be stratified by baseline ECOG performance status.

For biomarkers with post-baseline measurements, similar analysis will be done with change from baseline of a biomarker as a covariate, for each of the time points. An additional model that includes prognostic factors may be investigated.

The relationship between the endpoint and binary biomarkers (e.g. baseline phospho-STAT3 status, β-catenin) will be also examined using the log-rank test, stratified by treatment and baseline ECOG performance status. Subgroup analysis by the status of the binary biomarker may also be performed. The Kaplan-Meier method will be used to describe overall survival, progression-free survival and duration of response by the status of the biomarker (e.g. phospho-STAT3-high vs. phospho-STAT3-low) and by treatment group.

The relationships between the binary response variable (e.g. objective response, DCR) with baseline values of biomarkers as well as with their change from baseline at different time points will be investigated using logistic regression that includes assigned treatment, biomarker value and treatment-by-biomarker interaction, stratified by baseline ECOG performance status. Additional model that includes prognostic factors may be investigated. Relationship between the response and binary biomarkers (e.g. baseline phospho-STAT3 status or STAT3 status) will also be examined using the CMH test, stratified by treatment and baseline ECOG performance status. Subgroup analysis by the status of the binary biomarker may also be performed.

Exploratory analyses, additional to those described in this section, such as alternative modeling approaches and analyses of other biomarkers are expected and may be performed. All analyses described in this section are based on availability of data.

14.7 Exploratory Analyses

Overall Survival in the Predefined Biomarker-positive Population

An analysis of Overall Survival (OS) in a predefined biomarker-positive population will be performed. In this analysis, biomarker positive patients will be defined as having nuclear β-catenin positivity on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) archival tissue. OS is defined as the time from randomization to death due to any cause. All analyses for OS in the ITT-March and ITT-May populations will also be performed for OS in the biomarker-positive population, using similar methodology.

Sparse Pharmacokinetic Analysis

Exploratory analyses will be performed on the bioanalytic data obtained from sparse plasma sampling in order to characterize the population pharmacokinetics of BBI608. Demographic and pathophysiologic factors that affect plasma concentration of BBI608 in this population of patients with pre-treated advanced colorectal carcinoma will be examined. The exposure-response relationship between clinical and safety endpoints and BBI608 exposure will also be examined.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the NCIC CTG chair of the study.
- A limited number of the members of the NCIC Clinical Trials Group, the Australasian Gastrointestinal Trials Group and Boston Biomedical Inc. may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.
- In the event of a separate paper dealing with the health economic outcomes, the first author will generally be the Health Economics Coordinator on the trial committee.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the NCIC Clinical Trials Group and conducted in collaboration with the Australasian Gastrointestinal Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the NCIC CTG Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results

NCIC CTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the NCIC CTG web site (http://www.ctg.queensu.ca).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the NCIC CTG Senior Investigator, Senior Biostatistician, Study Coordinator, NCIC CTG and AGITG Study Chairs and Boston Biomedical, Inc. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

The conduct of this trial must comply with local laws and national regulations (e.g. in Canada with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act), in the United States of America with applicable US FDA Regulations) relevant to the use of new therapeutic agents in the country of conduct.

16.2 Inclusivity in Research

Individuals must not be excluded from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of NCIC CTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a NCIC CTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is NCIC CTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into NCIC CTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. NCIC CTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

Informed consent will be obtained for each participant/potential participant in an NCIC CTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, NCIC CTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. NCIC CTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Principal Investigator to delegate the responsibility for conducting the consent discussion.

NCIC CTG requires that each participant sign a consent form prior to their enrolment in the study to document his/her willingness to take part. NCIC CTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

NCIC CTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject. This process must be thoroughly documented.

16.3.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the pregnant female is not a participant in the main trial, consent should be obtained via use of the *exposure/*pregnancy follow-up consent form.

In the case of information collected about a newborn, consent should be provided by the legal guardian. In cases where the legal guardian is the participant in the main trial, consent is obtained via the main consent. If the legal guardian is not the trial participant, consent should be obtained via the exposure/pregnancy follow-up consent.

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy*/exposure*. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the NCIC CTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the NCIC CTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the NCIC CTG), it is the responsibility of the principal investigator to notify the NCIC CTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the NCIC CTG or locally by the centre, it is the responsibility of the principal investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Principal Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by NCIC CTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

NCIC CTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

16.6 Centre Performance Monitoring

This trial is eligible for inclusion in the Centre Performance Index. There are minimum standards for performance. Data is to be submitted by electronic data capture (EDC) according to the schedule in Appendix IV (Documentation for Study).

16.7 On-Site Monitoring/Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, NCIC CTG site monitoring will be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as pharmacy, essential document binders, standard operating procedures (including electronic information) and ethics documentation.

At any time, your site may be subject to an inspection by a regulatory agency such as the Health Canada Inspectorate or the FDA. Your site may also be subject to an audit by NCIC CTG. Further, the drug company which produces BBI608, Boston Biomedical Inc., has reserved the right to audit participating centres. Audits may only be conducted after consultation with NCIC CTG.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except patient reported outcomes (Quality of Life, Health Utilities). For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the CO.23 area of the NCIC CTG web-site (www.ctg.queensu.ca).

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study (i.e., Pre-treatment)	2 hours after the first dose of BBI608, then as clinically indicated	Every 4 weeks/ 28 days[1]	Every 8 weeks/ 56 days	At 4 weeks (day 28),8 weeks (day 56), &12 weeks (day 84)	At 4 weeks (day 28),8 weeks (day 56),12 weeks (day 84), 16 weeks (day 112) & 24 weeks (day 168)	At 4 weeks (28 days) post-protocol treatment[1]	At 4 weeks (28 days) post-protocol treatment, & every 8 weeks (56 days) thereafter (until deterioration to ECOG PS 4 or hospitalization for end of life care)
History & Physical								
History & Physical Exam	X[2]		X					X
ECOG PS	X		X					X
Weight	X		X					X
Height	X							
Vital signs	X		X					X
Hematology[3]								
CBC + differential	X		X				X	
Platelet count	X		X				X	
Biochemistry[3]								
Creatinine[4], Total Bilirubin, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	X		X				X	
Urinalysis	X		X				X	
Economics								
Resource Utilization Assessment			X					X
Cardiology Assessment								
ECG	X	X					X	
Radiology & Imaging[5]								
CT/MRI scan (as per baseline assessment)	X			X[6]				
Correlative Studies & Tissue Banking								
Submission of representative block of diagnostic tumour tissue to central bank[7]								
Blood, plasma, serum, RBC pellet, buffy coat	X				X			
Pharmacokinetics								
Blood collection for sparse PK analysis					X[8]			

continued on next page …

Required Investigations	Pre-study (i.e., Pre-treatment)	2 hours after the first dose of BBI608, then as clinically indicated	Every 4 weeks/ 28 days[1]	Every 8 weeks/ 56 days	At 4 weeks (day 28),8 weeks (day 56),&12 weeks (day 84)	At 4 weeks (day 28),8 weeks (day 56),12 weeks (day 84), 16 weeks (day 112) & 24 weeks (day 168)	At 4 weeks (28 days) post-protocol treatment[1]	At 4 weeks (28 days) post-protocol treatment, & every 8 weeks (56 days) thereafter (until deterioration to ECOG PS 4 or hospitalization for end of life care)
Other Investigations								
Pregnancy test, serum or urine (if applicable)[9]	X		X[10]				X[10]	
Serum CEA	X		X				X	
Adverse Events								
Adverse Event assessment [11. 12]	X		X					X
Quality of Life								
EORTC QLQ-C30	X					X[13]		
Health Utilities								
Health Utilities Index (HUI3)	X					X[13]		
Overall Survival								
Assess for survival of patient			X					X[14]

1 Patients are to be assessed every 4 weeks (28 days) while on study medication and until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days.

2 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *K-ras* status of tumour, prior anticancer therapy and prior date(s) of disease progression. Note: Documentation of progression, as described in section 10.2, or intolerance, as described in sections 5.1.4, 5.1.5 and/or 5.1.6, must be submitted.

3 Bloodwork Timing: Pre-treatment blood draws may be done up to 14 days prior to randomization. Every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.

4 Baseline creatinine or creatinine clearance may be used to demonstrate eligibility as per section 5.1.17

5 Tumour measurement and evaluation by RECIST 1.1 criteria. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumour evaluations will continue until progressive disease is documented (as described in section 10). For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumour measurements and assessment must be reported.

6 **IMPORTANT NOTE**: For the first 96 patients, for the first 8-week scan, disease assessment MUST be entered into EDC expeditiously, due to the early stopping rule (DCR at first response assessment to project whether continued treatment with BBI608 would be futile) – see section 14.5

7 On request by the central tumour bank

8 Please refer to the specific Sparse PK sampling laboratory manual for full details about blood collection, storage, and shipment

9 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.

10 In women of childbearing potential only a negative pregnancy test must be demonstrated every 4 weeks until 4 weeks after the administration of the final dose of protocol therapy.

11 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (see Appendix V).

12 Adverse event assessment by phone will be performed at 24-48 hours after start of protocol treatment, and at 2 and 6 weeks (i.e. approximately days 14 and 42, respectively)after randomization to assess for tolerability of dosing regimen.

13 To be completed in clinic. The patient's responses to the questionnaire questions should be entered into EDC for the applicable reporting period. Note that the completed paper questionnaires can be kept on-site and do not have to be submitted to NCIC CTG.

14 In the event that the patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.

Evaluation Post-Unblinding & Permanent Discontinuation

Following unblinding, patients who have not yet met the primary study endpoint (death), and are currently on protocol therapy (active arm) may receive BBI608 on study based on the clinical judgement of the investigator and local REB approval that this is in the patients' best interest, providing the patient is fully informed and provides consent, if this agent is not a nationally licenced medicinal product and/or are not funded by the normal health care infrastructure. Please refer to sections 9.1.1 and 9.2.1.

Required Investigations	At 4 weeks (28 days) post-protocol treatment[1]	Every 8 weeks (56 days) thereafter (until deterioration to ECOG PS 4 or hospitalization for end of life care)
History & Physical		
History & Physical Exam	X	
ECOG PS	X	
Weight	X	
Vital signs	X	
Hematology		
CBC + differential	X	
Platelet count	X	
Biochemistry		
Creatinine, Total Bilirubin, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	X	
Urinalysis	X	
Cardiology Assessment		
ECG	X	As clinically indicated
Radiology & Imaging[2]		
CT/MRI scan (as per baseline assessment)		No longer required for patients who did not have objective disease progression prior to unblinding. But please report disease assessment data in EDC if done.
Correlative Studies & Tissue Banking		
Submission of representative block of diagnostic tumour tissue to central bank[3]		See table above
Blood, plasma, serum, RBC pellet, buffy coat		See table above
Adverse Events		
Adverse Event assessment for ongoing and related to BBI608[4,5]		X
New Anti-cancer Therapy		
Reporting of new anti-cancer therapy		X
Overall Survival		
Assess for survival of patient		X[6]

1 Patients are to be assessed every 4 weeks (28 days) while on study medication and until the first regularly scheduled 4 week assessment at which the patient has been off study therapy for a minimum of 28 days.

2 Tumour measurement and evaluation by RECIST 1.1 criteria. The same method of assessment and the same technique should be used to identify and report each lesion at baseline and at reassessment during treatment. Tumour evaluations will continue until progressive disease is documented (as described in section 10). For patients who remain on protocol therapy after objective disease progression has been documented, no further imaging assessments are mandated, but where these occur as a component of care, tumour measurements and assessment must be reported.

3 On request by the central tumour bank

4 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (see Appendix V).

5 Adverse event assessment by phone will be performed at 24-48 hours after start of protocol treatment, and at 2 and 6 weeks (i.e. approximately days 14 and 42, respectively)after randomization to assess for tolerability of dosing regimen.

6 In the event that the patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact.

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare 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.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Details of Drug Distribution, Supply and Control/Accountability are provided in the Drug Supply Instructions available on the CO.23 website.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "NCIC CTG EDC Generic Data Management Guidebook" posted on the CO.23 area of the NCIC CTG web-site (www.ctg.queensu.ca).

The electronic CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Timing	To be completed electronically	Supporting Documentation Required[1]
Eligibility Checklist		At the time of randomization	• Consent form[2] • Relevant pathology report(s) • KRAS reports • Relevant operative report(s) • Relevant radiology reports[3] (including CT/MRI abdomen/pelvis, CT/MRI chest, chest x-ray)[3] • Tumour Measurement Worksheet[3] • ECG report
Baseline Report		Within 2 weeks of randomization	
Correlative Studies Report (Tumour and Blood)	Continuous running-log folder See sections 6.0 and 9.0	Information pertaining to **baseline/pretreatment** (i.e. tumour specimen information and blood collection for correlative studies) must be completed within 2 weeks of randomization. **Tissue to be submitted immediately upon request.**	• Consent form[2] • Diagnostic pathology report *(for tumour tissue only)*
		Information pertaining to **post randomization** blood collection samples (i.e. whole blood, plasma, serum, RBC pellet, buffy coat) for correlative studies and banking should be completed within 2 weeks after collection of final blood specimen.	
		Information pertaining to blood collection for Pharmacokinetics must be completed in EDC **in real-time, as soon as the sample is collected.**	
Concomitant Medication Report	Continuous running-log folder		
Treatment Report	Every 4 weeks (28 days)	Within 2 weeks of the end of each 4 week reporting period	*If available/applicable:* • CT/MRI abdomen/pelvis report[3] • CT/MRI chest[3] • Other radiology reports[3] • Tumour Measurement Worksheet[3] • ECG report
End of Treatment Report[4]	As soon as permanent off treatment status is confirmed.	Within 2 weeks of end of treatment	ECG report

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Electronic Folder	Timing	To be completed electronically	Supporting Documentation Required[1]
Telephone Follow-Up Report	AE assessment by phone at 24-48 hours, 2 weeks (approx. day 14) and at 6 weeks (approx. day 42) from start of protocol treatment	Within 2 weeks of collection of the AE information by phone	
Follow-up Report[5]	Every 8 weeks (56 days)	Within 2 weeks of the end of each 8 week reporting period	*If available/applicable:* • CT/MRI abdomen/pelvis report[3] • Tumour Measurement Worksheet[3] • CT/MRI chest report[3] • Other radiology reports[3] • ECG report
Minimal Follow-up Report	Annual	Within 6 weeks of contact	If available/applicable: • Autopsy report • CT/MRI report
Relapse/Progression Report	Upon the patient's objective disease progression / relapse	Within 4 weeks of confirmation	Relevant radiology, operative and pathology reports
Death Report	Upon patient's death	Within 4 weeks of patient death	Autopsy/post-mortem report, if performed
Serious Adverse Event (SAE) Report[6]	Within 24 hours of event At time of event and reported to NCIC CTG	Within 1 working day[6]	

1 Please scan and upload all required source documentation into EDC. A reminder to please ensure the patient's identifiers (e.g. name) are blacked-out on all source documentation.

2 For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated.

3 **Important note**: radiology reports to assess disease are due (i.e. must be scanned and uploaded to EDC) expeditiously for first 96 pts.

4 The 4 week (28 day) post-treatment investigations (i.e. PE, biochemistry, hematology) are required to be reported on this form, if not already reported on the final Treatment Report.

5 The aim of this folder: To collect follow-up information on all patients who have permanently discontinued BBI608/placebo.

6 See section 11.0 Serious Adverse Event Reporting for details.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

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

APPENDIX VI - CORRELATIVE STUDIES

Exploratory Biomarker Analysis

Rationale:

The correlative science component of the CO.23 trial will include tumour and blood based assays to identify biomarkers of benefit from BBI608 therapy, as well as biomarkers of BBI608 resistance. The purpose of these studies is to explore the relationship of gene expression to the response of the subjects' disease to therapy. The research aims to validate molecular markers (markers are genes products, either RNA or protein, with measurable changes in abundance, sequence, or through post-translational modification) that can be used to predict appropriate therapeutic treatment regimens. The ultimate goal of identifying molecular markers is to improve subject responses and other measures of clinical benefit by matching an individual subject's tumour diagnostic profile with an anticancer agent that has demonstrated a therapeutic advantage in subjects with a similar diagnostic profile.

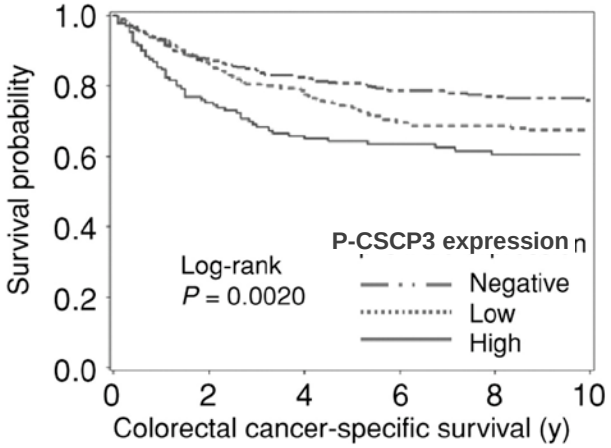
STAT3 has been identified as Signal Transducer and Activator of Transcription-3. The STAT family of transcriptional regulators are activated in response to extracellular signaling proteins, including cytokines and growth factors. When ligands bind to cell surface receptors, the receptor-associated JAK tyrosine kinases become activated and in turn phosphorylate a single tyrosine residue in the STAT molecule. The phosphorylated STATs then dimerize and enter the nucleus where they bind to specific DNA sequences in the promoters of target genes to regulate transcription. Downstream target genes induced by STAT3 binding include survivin, cyclin D1 and c-Myc. These genes, therefore, represent a selection of potentially relevant biomarkers of activity for BBI608. Additional potential downstream targets of STAT3, for example, those recently determined by genome-wide screening using the chromatin immunoprecipitation (ChIP) assay *[Snyder 2008]* or other techniques, may also be investigated. Archival tumour genomic DNA will be purified and analysed for the downstream targets and correlated with clinical outcomes.

Baseline phospho-STAT3 expression by IHC has been reported to correlate with clinical outcome *[Morikawa 2011]*. These authors evaluated a bank of 724 archival colorectal tumour tissue samples and defined high phospho-STAT3 expression in 18%, low expression in 34%, and no expression in 48%. Cancer-specific and overall survival was higher in those with absent phospho-STAT3 staining (Figure 1).

STAT3 is closely linked to another important oncogene, β-catenin. β-catenin contributes to tumorigenesis and metastasis in a range of cancers and is notable in colorectal cancer for promoting tumorigenesis as a result of APC mutation *[Morin 2007]*. In addition to its over-expression, β-catenin localization has important clinical implications. Membranous β-catenin is involved in maintaining cell-cell junctions and promoting a less-aggressive epithelial phenotype. By contrast, nuclear β-catenin is associated with the CSC-promoting and metastasis-promoting epithelial-to-mesenchymal transition (EMT) and is present in cells at the invasive front of colorectal tumours *[Brabletz 2005, Kawada 2006]*. STAT3 and β-catenin reciprocally regulate each other's expression; furthermore, STAT3 activation causes β-catenin to accumulate in the nuclei of colorectal cancer cells. This accumulation contributes to increased CSC abundance and consequently worse prognosis for a subset of colorectal cancer patients *[Kawada 2006]* (Figure 2). In CRC, there is a significant correlation between archival tissue staining positive for phospho-STAT3 and for nuclear β-catenin by immunohistochemistry (IHC) (92.5%, $p<0.01$) *[Kawada 2006].* Approximately 60-70% of CRC patients are expected to have nuclear localization of β-catenin on IHC of archival tissue *[Aamodt 2010, Kawada 2006]*.

In this study, archival tumour phospho-STAT3 and β-catenin localization will be correlated with clinical outcome to confirm these proteins as prognostic factors, but also to analyze whether phospho-STAT3 and β-catenin expression are biomarkers of benefit from BBI608 therapy.

Figure 1 – Correlation of phospho-STAT3 expression with survival in patients with colorectal cancer, from Morikawa *et al.*



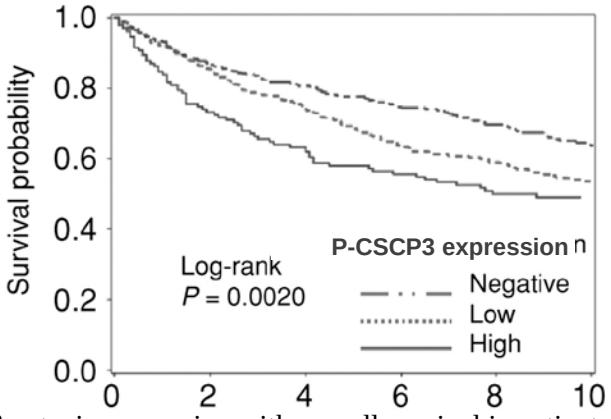
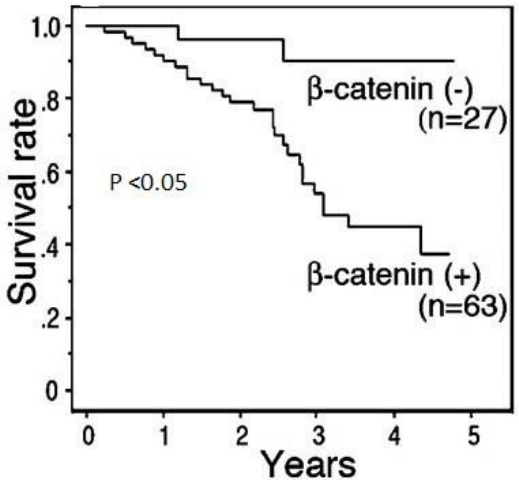


Figure 2 – Correlation of β-catenin expression with overall survival in patients with colorectal cancer, from Kawada *et al.*



Using data from this and other trials, the relationship between a number of molecular markers associated with the STAT3, β-catenin and other related pathways, and the clinical outcomes of BBI608 therapy will be explored. Multiple molecular markers in a paraffin-embedded tumour tissue sample can be determined by analyzing RNA and protein in the tissue sample.

In addition to analysis of potential biomarkers of benefit from BBI608 therapy, an analysis of markers of resistance to BBI608 will be conducted using serial plasma samples which will be drawn at baseline as well at 4, 8 and 12 weeks post initiation of therapy. This analysis may involve SNPs, CYPS, and metabolomics.

Paraffin-embedded tumour specimens, or cores (two 2 mm cores of tumour from the block) and unstained slides obtained from paraffin embedded specimens will be required for the patient to be enrolled on the trial. The patient must consent to provision of, and investigator(s) must confirm access to and agree to submit at the request of the NCIC CTG Central Tumour Bank, a representative formalin fixed paraffin block of tumour tissue in order that the correlative studies may be conducted.

Blood samples will be collected prior to dosing with BBI608 and then at weeks 4, 8 and 12 during BBI608 therapy.

APPENDIX VII - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

   The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule at:

   - 4, 8, 12, 16 and 24 weeks or until deterioration to ECOG PS 4 or hospitalization for end of life care

   In order to minimize missing quality of life data, if the patient is no longer attending clinic during the scheduled follow-up period, the patient should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. To facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

   The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

   There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in a language for which the questionnaire is available. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads a language for which the questionnaire is available, but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire *(for reason other than illiteracy in a language for which the questionnaire is available)*

   An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

   If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **CO.23**

This **page** to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Patient Initials: _____ (first-middle-last)

AGITG Site No: _____ *(AGITG centres only)*

Institution:_____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (✓)

☐ Prior to randomization

OR

During chemotherapy (timing from randomization):

☐ Week 4/Day 28 ☐ Week 8/Day 56 ☐ Week 12/Day 84 ☐ Week 16/Day 112 ☐ Week 24/Day 168

OR

After chemotherapy has stopped (timing from randomization):

☐ Week 4/Day 28 ☐ Week 8/Day 56 ☐ Week 12/Day 84 ☐ Week 16/Day 112 ☐ Week 24/Day 168

Were ALL questions answered? ☐ Yes ☐ No → If no, reason: _____

Was assistance required? ☐ Yes ☐ No →If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed:_____-_____- __ _

yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (CO.23)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX VIII - HEALTH UTILITIES ASSESSMENT

Introduction

The assessment of overall health benefits is complicated by the need for a measure that can combine various benefits, such as overall survival, progression free survival, and quality of life into a single measure of benefit. Patients may value particular benefits differently. There is no obvious way to add together independently collected benefits for an individual or for a trial to yield a measure of overall benefit. Health utilities are a measure of how people value particular health outcomes. They provide a common denominator that can be combined with survival to form a measure of overall health benefits.

Such a measure of overall health benefit can then be used as part of a health economic analysis. Health economic analyses assess the benefits and costs of an intervention, for consideration whether the intervention may be worth its "costs" -- including financial, toxicity, and social costs.

The collection of information about health utilities is becoming more common in clinical protocols. In clinical trials, health utilities are most often collected using a patient self-reported questionnaire (similar to the collection of quality of life data).

Health utility and quality of life assessments provide different but complementary information.

- Health utility is a measure of preference for a given health state that acknowledges the risk and uncertainty of outcomes in choices patients face and in clinical decision-making.
- They can be used as a weighting factor to adjust survival by quality of life.
- Depending on whether a disease-specific or generic quality of life instrument is used, often only utility assessments may be able to compare patient groups with different disease sites.
- Utilities provide a single meaningful measure that can be incorporated in health policy and health economic analyses.
- Utilities provide a single measure that can be compared across different diseases or conditions.

Health utilities data can be used in a variety of ways:

- to try and achieve the best possible outcome for patients and populations
- to evaluate the extent of change in health benefits of an individual, group, or population across time
- to evaluate new treatments, technologies, and patient management strategies
- to support approval of new drug applications or patient management strategies
- to try to provide the best value for health care dollars within and across diseases and health
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of new therapies or patient management strategies will most likely be based on a combination of health benefit and cost data. This may be formally done using health utilities as part of a health economic analysis.

Instructions for Administration of a Health Utilities Questionnaire

The instructions below are intended as a guide for the administration of the Health Utilities Questionnaire

1. Preamble

   Health utilities data are collected for research purposes, and will not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

The usual scheduled times to obtain the questionnaires are as follows:

- pre-randomization or pre-registration (baseline)
- during treatment
- during follow-up

The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pre-treatment Assessment

It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g. psychological distress, social disruption, symptoms, side-effects, *et cetera*.

The Clinical Research Associate (CRA) should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

The health utilities questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

The health utilities questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule at 4, 8, 12, 16, and 24 weeks or until deterioration to ECOG PS 4 or hospitalisation for end of life care.

In order to minimize missing health utilities data, if the patient is no longer attending clinic during the scheduled follow-up period, the patient should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. To facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how overall health is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If…

The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Four situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:

If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

D. The patient is no longer attending clinic during the scheduled follow-up period.

Should the patient no longer be attending clinic, he/she should be contacted by phone to ask him/her to complete the questionnaire and mail it to the clinic. In order to facilitate this, ensure that after randomization all patients are provided with 2 blank questionnaires and 2 clinic-addressed stamped envelopes. When the questionnaire is returned, the date on which the questionnaire was received should be recorded on the questionnaire. The date on which the questionnaire was completed should be noted on the appropriate case report form, as well as where and why the patient completed the questionnaire outside of the clinic. If the patient has deterioration to ECOG PS 4 or hospitalization for end of life care they need not be contacted for questionnaire completion.

6. Waiving the Health Utilities Component

The only time that we will not require a patient to complete the health utilities questionnaires is if s/he is not literate in a language for which the questionnaire is available. In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Health Utilities Questionnaire

If a patient speaks and reads a language for which the questionnaire is available, but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Health Utilities Questionnaire *(for reason other than illiteracy in a language for which the questionnaire is available)*

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the HUI3 assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Health Utilities Questionnaire – **ENGLISH**

NCIC CTG Trial: CO.23

This page to be completed by the Clinical Research Associate

Patient Information:

NCIC CTG Patient Serial No: _____ Patient Initials: _____ (first-middle-last)

AGITG Site No: _____ *(AGITG centres only)*

Institution: _____ Investigator: _____

Scheduled time to obtain health utilities assessment: please check (✓)

☐ Prior to randomization

OR

During chemotherapy (timing from randomization):

☐ Week 4/Day 28 ☐ Week 8/Day 56 ☐ Week 12/Day 84 ☐ Week 16/Day 112 ☐ Week 24/Day 168

OR

After chemotherapy has stopped (timing from randomization):

☐ Week 4/Day 28 ☐ Week 8/Day 56 ☐ Week 12/Day 84 ☐ Week 16/Day 112 ☐ Week 24/Day 168

Were ALL questions answered? ☐ Yes ☐ No → If no, reason: _____

Was assistance required? ☐ Yes ☐ No →If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: _____-_____- __ _

yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

Health Utilities Index Mark 3 (HUI3) Questionnaire

NCIC CTG: CO.23

This questionnaire contains a set of questions which ask about various aspects of your health. When answering these questions please think about your health and your ability to do things on a day-to-day basis, during the past week. For each question, please select one answer that best describes your level of ability or disability during the past week. Please answer all the questions yourself by circling the letter (a, b, c, …) beside the answer that best applies to you. Choose the best single response that applies to you. There are no right or wrong answers; what we want is your opinion about your abilities and feelings. To define the past week period, please think about what the date was 7 days ago and recall the major events that you have experienced during this period. Please focus your answers on your abilities, disabilities and how you have felt during the past week.

You may feel that some of these questions do not apply to you, but it is important that we ask the same questions of everyone. Also, a few questions are similar; please excuse the apparent overlap and answer each question independently.

The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

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1. Which one of the following best describes your ability, during the past week, to see well enough to read ordinary newsprint?

   a. Able to see well enough without glasses or contact lenses.

   b. Able to see well enough with glasses or contact lenses.

   c. Unable to see well enough even with glasses or contact lenses.

   d. Unable to see at all.

2. Which one of the following best describes your ability, during the past week, to see well enough to recognize a friend on the other side of the street?

   a. Able to see well enough without glasses or contact lenses.

   b. Able to see well enough with glasses or contact lenses.

   c. Unable to see well enough even with glasses or contact lenses.

   d. Unable to see at all.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

3. Which one of the following best describes your ability, during the past week, to hear what was said in a group conversation with at least three other people?

   a. Able to hear what was said without a hearing aid.

   b. Able to hear what was said with a hearing aid.

   c. Unable to hear what was said even with a hearing aid.

   d. Unable to hear what was said, but did not wear a hearing aid.

   e. Unable to hear at all.

4. Which one of the following best describes your ability, during the past week, to hear what was said in a conversation with one other person in a quiet room?

   a. Able to hear what was said without a hearing aid.

   b. Able to hear what was said with a hearing aid.

   c. Unable to hear what was said even with a hearing aid.

   d. Unable to hear what was said, but did not wear a hearing aid.

   e. Unable to hear at all.

5. Which one of the following best describes your ability, during the past week, to be understood when speaking your own language with people who do not know you?

   a. Able to be understood completely.

   b. Able to be understood partially.

   c. Unable to be understood.

   d. Unable to speak at all.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

6. Which one of the following best describes your ability, during the past week, to be understood when speaking with people who know you well?

   a. Able to be understood completely.

   b. Able to be understood partially.

   c. Unable to be understood.

   d. Unable to speak at all.

7. Which one of the following best describes how you have been feeling during the past week?

   a. Happy and interested in life.

   b. Somewhat happy.

   c. Somewhat unhappy.

   d. Very unhappy.

   e. So unhappy that life was not worthwhile.

8. Which one of the following best describes the pain and discomfort you have experienced during the past week?

   a. Free of pain and discomfort.

   b. Mild to moderate pain or discomfort that prevented no activities.

   c. Moderate pain or discomfort that prevented some activities.

   d. Moderate to severe pain or discomfort that prevented some activities.

   e. Severe pain or discomfort that prevented most activities.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

9. Which one of the following best describes your ability, during the past week, to walk? Note: Walking equipment refers to mechanical supports such as braces, a cane, crutches or a walker.

   a. Able to walk around the neighbourhood without difficulty, and without walking equipment.

   b. Able to walk around the neighbourhood with difficulty; but did not require walking equipment or the help of another person.

   c. Able to walk around the neighbourhood with walking equipment, but without the help of another person.

   d. Able to walk only short distances with walking equipment, and required a wheelchair to get around the neighbourhood.

   e. Unable to walk alone, even with walking equipment. Able to walk short distances with the help of another person, and required a wheelchair to get around the neighbourhood.

   f. Unable to walk at all.

10. Which one of the following best describes your ability, during the past week, to use your hands and fingers? Note: Special tools refers to hooks for buttoning clothes, gripping devices for opening jars or lifting small items, and other devices to compensate for limitations of hands or fingers.

   a. Full use of two hands and ten fingers.

   b. Limitations in the use of hands or fingers, but did not require special tools or the help of another person.

   c. Limitations in the use of hands or fingers, independent with use of special tools (did not require the help of another person).

   d. Limitations in the use of hands or fingers, required the help of another person for some tasks (not independent even with use of special tools).

   e. Limitations in the use of hands or fingers, required the help of another person for most tasks (not independent even with use of special tools).

   f. Limitations in the use of hands or fingers, required the help of another person for all tasks (not independent even with use of special tools).

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

11. Which one of the following best describes your ability, during the past week, to remember things?

    a. Able to remember most things.

    b. Somewhat forgetful.

    c. Very forgetful.

    d. Unable to remember anything at all.

12. Which one of the following best describes your ability, during the past week, to think and solve day to day problems?

    a. Able to think clearly and solve day to day problems.

    b. Had a little difficulty when trying to think and solve day to day problems.

    c. Had some difficulty when trying to think and solve day to day problems.

    d. Had great difficulty when trying to think and solve day to day problems.

    e. Unable to think or solve day to day problems.

13. Which one of the following best describes your ability, during the past week, to perform basic activities?

    a. Eat, bathe, dress and use the toilet normally.

    b. Eat, bathe, dress or use the toilet independently with difficulty.

    c. Required mechanical equipment to eat, bathe, dress or use the toilet independently.

    d. Required the help of another person to eat, bathe, dress or use the toilet.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

14. Which one of the following best describes how you have been feeling during the past week?

    a. Generally happy and free from worry.

    b. Occasionally fretful, angry, irritable, anxious or depressed.

    c. Often fretful, angry, irritable, anxious or depressed.

    d. Almost always fretful, angry, irritable, anxious or depressed.

    e. Extremely fretful, angry, irritable, anxious or depressed; to the point of needing professional help.

15. Which one of the following best describes the pain or discomfort you have experienced during the past week?

    a. Free of pain and discomfort.

    b. Occasional pain or discomfort. Discomfort relieved by non-prescription drugs or self-control activity without disruption of normal activities.

    c. Frequent pain or discomfort. Discomfort relieved by oral medicines with occasional disruption of normal activities.

    d. Frequent pain or discomfort; frequent disruption of normal activities. Discomfort required prescription narcotics for relief.

    e. Severe pain or discomfort. Pain not relieved by drugs and constantly disrupted normal activities.

16. Overall, how would you rate your health during the past week?

    a. Excellent.

    b. Very good.

    c. Good.

    d. Fair.

    e. Poor.

This box to be completed by the clinical research associate: Pt. Serial #:_____Pt. Initials: _____

17. How did you complete the questionnaire? Please select the one answer that best describes your situation.

    a. By myself, without any help from anyone else.

    b. By myself, except someone else circled the answers on the questionnaire form for me.

    c. With the help of someone else.

    d. This questionnaire was completed by a family member, without help from the subject or patient.

    e. This questionnaire was completed by a nurse or other health professional, without help from the subject or patient.

       Please specify type of health professional: _____

    f. This questionnaire was completed by another person, without help from the subject or patient.

       Please specify relationship to subject or patient: _____

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

APPENDIX IX - BLINDING / UNBLINDING

Emergency Unblinding

BBI608 and matching placebo are identical in appearance as are the bottles in which they are provided. Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's urgent management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding (i.e. almost all urgent situations can be managed by discontinuing study drug).

If a patient is unblinded, they are considered to be off BBI608/placebo treatment. Therefore the need to break the blind must first be discussed and approved by the NCIC CTG. For any treatment code unblinding, the reason and parties involved must be documented in the patient's medical record. Treatment identification information should be kept confidential.

Please note: *Requests to unblind for information only or to permit participation in other clinical trials will not be considered until the trial has been unblinded and reported.*

Unblinding Procedure:
To unblind the treatment for a patient you must contact NCIC CTG and receive the approval from an NCIC CTG Senior Investigator whenever possible.

The Emergency Unblinding Form is to be submitted ONLY once the unblinding has been approved and has occurred. Further instructions about this form can be found below.

8am-4pm (EST): Please send an email to the Study Coordinator or Senior Investigator including the trial code, patient identification, patient initials, last treatment kit (if applicable) and the reason for the unblinding request. Once approval is obtained from the Senior Investigator, authorized personnel at NCIC CTG will unblind the patient and send the unblinding information via email to the Investigator who requested the unblinding.

(4pm-8am EST) and statutory holidays: Please phone the following number as appropriate:

North America calls: 877-617-2810 Toll Free

International calls: 613-541-3280

You will be required to provide basic information regarding the trial code, patient identification, last treatment kit (if applicable), and the reason for the unblinding request as well as contact information of the caller (and the Investigator/treating physician to whom the information is to be relayed if different from the caller). The unblinding information will be conveyed to the Investigator by phone and may also be followed with a confirmation email or fax.

LIST OF CONTACTS

NCIC CTG	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to allocation.	Julia Baran *or* Vicki Classen Clinical Trials Assistants, NCIC CTG Email: jbaran@ctg.queensu.ca vclassen@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, Protocols	Available on NCIC CTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Nadine Magoski *or* Yvonne Murray Study Coordinators NCIC CTG Email: nmagoski@ctg.queensu.ca ymurray@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Chris O'Callaghan Senior Investigator NCIC CTG Email: cocallaghan@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Derek Jonker, Study Chair Email: djonker@ottawahospital.on.ca	613-737-7700 x70168	613-247-3511
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Chris O'Callaghan Senior Investigator, NCIC CTG or: Nadine Magoski *or* Yvonne Murray Study Coordinators, NCIC CTG	613-533-6430	613-533-2941
DRUG ORDERING See Appendix III for full details.			
REQUESTS FOR UNBLINDING	During office hours (8 am-4 pm EST): Nadine Magoski *or* Yvonne Murray Study Coordinators NCIC CTG Email: nmagoski@ctg.queensu.ca ymurray@ctg.queensu.ca or: Dr. Chris O'Callaghan Senior Investigator NCIC CTG Email: cocallaghan@ctg.queensu.ca	613-533-6430	613-533-2941
	After office hours (4 pm-8 am EST): North American calls (toll free): 877-617-2810 International calls: 613-541-3280		