BOSTON BIOMEDICAL
Sumitomo Dainippon Pharma Global Oncology

TITLE:	**A Phase 3 Study of BBI-608 in combination with 5-Fluorouracil, Leucovorin, Irinotecan (FOLFIRI) in Adult Patients with Previously Treated Metastatic Colorectal Cancer (CRC)**
PROTOCOL NUMBER:	**CanStem303C (aka BB608-303CRC)**
FDA IND NUMBER	**100,887**
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STUDY DRUG:	**BBI-608 (aka BBI608, Napabucasin)**
SPONSOR:	[redacted]
DATE OF ORIGINAL PROTOCOL:	**29 October 2015**
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AMENDMENT	**7.0 (Global)**

The following personnel have approved this protocol:

Signed: **Date:**

[redacted]

Confidentiality Statement

PROTOCOL AMENDMENT HISTORY

Document	Version Date
Original protocol	29 October 2015
Amendment 1	14 April 2016 (Global)
Amendment 2	14 July 2016 (Global)
Amendment 2.1	18 October 2016 (Local – Singapore, Korea)
Amendment 2.2	07 November 2016 (Local – Belgium)
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Amendment 5.0	16 February 2018 (Global)
Amendment 5.1	26 April 2018 (Local – Korea)
Amendment 6.0	25 September 2018 (Global)
Amendment 7.0	25 October 2019 (Global)

SYNOPSIS

Study Title:	**A Phase 3 Study of BBI-608 in combination with 5-Fluorouracil, Leucovorin, Irinotecan (FOLFIRI) in Adult Patients with Previously Treated Metastatic Colorectal Cancer (CRC).**
Study Number:	*CanStem303C (aka BB608-303CRC)*
Study Phase:	3
Study Drug:	BBI-608, a novel investigational small molecule anticancer drug that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the signal transducers and activators of transcription 3 (STAT3) pathway, which has been implicated in cancer stem cell viability.
Primary Objectives:	• To compare overall survival (OS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2) • To compare OS in the pSTAT3-positive (pSTAT3(+)) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)
Secondary Objectives:	<u>Key Secondary Objectives:</u> • To compare progression free survival (PFS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI • To compare PFS in the pSTAT3(+) Subpopulation patients treated with BBI 608 plus biweekly FOLFIRI versus biweekly FOLFIRI • To compare disease control rate (DCR) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI • To compare DCR in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI • To compare overall response rate (ORR) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI • To compare ORR in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI <u>Other Secondary Objectives:</u> • To compare the Quality of Life (QoL), as measured using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30), in the General Population patients treated with BBI-608 plus bi-weekly FOLFIRI versus bi-weekly FOLFIRI • To compare the QoL, as measured using the EORTC-QLQ-C30, in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI • To evaluate the safety profile of BBI-608 administered daily plus biweekly FOLFIRI with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0 in the General Population and the pSTAT3(+) Subpopulation

Study Design:	This is an international multi-center, prospective, open-label, randomized, adaptive design Phase 3 trial of the cancer stem cell pathway inhibitor BBI-608 plus standard bi-weekly FOLFIRI (Arm 1) versus standard bi-weekly FOLFIRI (Arm 2) in patients with previously treated metastatic colorectal cancer (mCRC). The hypotheses in General Population and pSTAT3(+) Subpopulation for OS in the study will be tested. An interim analysis will be conducted to check the decision rules of futility, population and hypothesis selection, and event count adjustment. The Sponsor and the CRO have implement blinding plans to minimize bias prior to the interim and final analyses. In this study, adult patients with mCRC following progression on first-line FOLFOX or XELOX with or without bevacizumab will be randomized in a 1:1 ratio to BBI-608 plus biweekly FOLFIRI (Arm 1) or biweekly FOLFIRI (Arm 2). Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. Patients will be stratified according to geographical region (North America/Western Europe/Australia, vs. Japan/Korea vs. rest of the world); time to progression from start of first line therapy (<6 months vs. ≥6 months); *RAS* mutation status (mutant vs. wild type), bevacizumab as part of their protocol treatment (yes vs. no), and location of the primary tumor (left vs. right colon). The study will proceed in 14-day (2-week) cycles. BBI-608 will be administered orally, twice daily, with doses separated by approximately 12 hours. Standard FOLFIRI will be administered biweekly, on Day 1 of each 14-day study cycle. BBI-608 administration will begin 2 to 5 days prior to the first FOLFIRI infusion in patients randomized to Arm 1. In Investigator selected patients, bevacizumab will be administered per product label and institutional standards. Tumor assessments will be performed every 8 weeks after randomization until 6 months of treatment and every 12 weeks thereafter until objective disease progression. Retrospective analysis of archival tumor tissue samples will be performed at the time of the interim analysis to determine pSTAT3 status of randomized patients.
Study Population:	The study will enroll patients with histologically confirmed adenocarcinoma of the colon or rectum that is metastatic (Stage IV, mCRC). Patients will have failed treatment with first-line combination therapy of oxaliplatin and a fluoropyrimidine with or without bevacizumab for metastatic disease, with failure defined as radiologic progression during or ≤6 months after the last dose of first-line therapy. Patients who discontinued first-line therapy due to toxicity may be enrolled as long as progression occurred ≤6 months after the last dose of first-line therapy. Patients receiving any other systemic chemotherapy in the metastatic setting will be excluded. All patients must have received a minimum of 6 weeks of the first-line regimen that included oxaliplatin and a fluoropyrimidine with or without bevacizumab in the same cycle. Prior neoadjuvant or adjuvant systemic treatment is allowed as long as no more than 2 prior systemic chemotherapy regimens were administered with no more than 1 prior regimen permitted in the metastatic setting. For participants with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as a single systemic regimen. Re-challenge with oxaliplatin is permitted and will be considered part of the first-line regimen for metastatic disease, with both initial oxaliplatin treatment and subsequent re-challenge being considered as 1 regimen. Patients with measurable or non-measurable disease may be included. Other inclusion criteria for all patients include: age ≥18 years.; ECOG performance status ≤1 and adequate hepatic, renal, and bone-marrow function.

Test Product, Dose, and Mode of Administration:	Patients in this study will receive BBI-608 orally, daily, at 240 mg bid (480 mg total daily dose). In each cycle BBI-608 will be taken daily for 2 weeks (14 days). BBI-608 will be administered twice daily, 1 hour prior or 2 hours after meals, with the first dose taken in the morning and doses separated by approximately 12 hours. Patients will receive BBI-608 in combination with FOLFIRI. Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. FOLFIRI chemotherapy infusion will start at least 2 hours following the first daily dose of BBI-608 and will be administered every 2 weeks. If bevacizumab is added to the FOLFIRI regimen, bevacizumab infusion should start at least 2 hours following the first dose of BBI-608 starting on Cycle 1 Day 1 and will be administered every 2 weeks. Irinotecan/leucovorin infusion will follow bevacizumab infusion in patients selected by the Investigator to receive standard dose of bevacizumab (5 mg/kg). Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously, over approximately 90 minutes and 2 hours, respectively, starting on Day 1 of Cycle 1, immediately following bevacizumab infusion or at least 2 hours following the first daily dose of BBI-608 if bevacizumab is not administered. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle. Dose modification of BBI-608 and/or FOLFIRI is allowed. Dose modification of bevacizumab is per product label and institutional standards.
Duration of Treatment:	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events (AEs) requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST criteria. If 1 or all components of the FOLFIRI regimen is/are discontinued due to toxicity, BBI-608 should be continued until another discontinuation criterion is met. If BBI-608 is discontinued due to toxicity, FOLFIRI should be continued until another discontinuation criterion is met.
Statistical Methods:	The primary study endpoints are OS in the General Population and the pSTAT3(+) Subpopulation. The hypotheses for the study are as follows: For the General Population, the null and alternative hypotheses are: H_{10}: BBI-608 + FOLFIRI ≤ FOLFIRI in the General Population H_{11}: BBI-608+FOLFIRI > FOLFIRI in the General Population For the pSTAT3(+) Subpopulation, the null and alternative hypotheses are: H_{20}: BBI-608 + FOLFIRI ≤ FOLFIRI in the pSTAT3(+) Subpopulation H_{21}: BBI-608+FOLFIRI > FOLFIRI in the pSTAT3(+) Subpopulation A multiplicity adjustment strategy will be developed to control the overall Type I error rate with respect to several sources of multiplicity in this trial. This multiplicity adjustment will employ the Hochberg-based gatekeeping procedure to account for the analysis of the treatment effect on the primary (OS) and key secondary (PFS, DCR, ORR) endpoints in the General Population and the pSTAT3(+) Subpopulation. For the General Population, this study is designed to have a power of 90% and a 1-sided α=0.025 to detect a 20% reduction in the risk of death (HR 0.80 which

corresponds to an increase of median survival from 12.54 to 15.68 months) in the General Population. The above design assumptions account for the anticipated varying control hazard rates for the bevacizumab versus no-bevacizumab stratification levels. It is assumed that approximately 30% of subjects will receive bevacizumab with expected mOS for the control arm FOLFIRI+bevacizumab subjects being 13.66 months while 70% of the subjects will not receive bevacizumab and have expected mOS of 12.06 months [*Van Cutsem 2012*]. Without adjusting for multiplicity, it is estimated that 850 events in the General Population will be required to detect this reduction, which would be observed by randomizing 1250 patients (General Population) over 26 months with patient follow up for an additional 14 months, for a total study duration of 40 months. It is anticipated that up to 5% dropout rate will occur over the entire study.

For the pSTAT3(+) Subpopulation, without adjusting for multiplicity, and assuming 310 events (approximately 36% of 850) in pSTAT3(+) Subpopulation, there will be approximately 88% nominal power at 1-sided α=0.025 to detect a 30% reduction (HR [BBI-608+FOLFIRI vs. FOLFIRI] = 0.70) in the risk of death in the pSTAT3(+) Subpopulation.

The overall power of the study will be approximately 90% (for both the General Population and the pSTAT3(+) Subpopulation) after the multiplicity control procedure is considered.

The interim analysis will be conducted when 425 deaths occur (50% of total number of 850 deaths) in the General Population. The OS results at the interim analysis will be reviewed by a Data Safety and Monitoring Board (DSMB). The recommendations from DSMB on the study design and conduct will be based on the following decisions:

- Futility stopping: terminate the trial or terminate pSTAT3(-) and pSTAT3 status unknown subpopulation due to lack of efficacy (futility).
- Patient population and hypothesis selection: select the most appropriate patient population and hypothesis (hypothesis in General Population, and/or hypothesis in pSTAT3(+) Subpopulation) for evaluating the significance of the treatment effect at the final analysis.
- Event count adjustment: remain the current events size or increase the target number of events in 1 of or both pre-defined patient populations.

Statistical Analysis for Primary and Key Secondary Endpoints:

Overall survival in the General Population and the pSTAT3(+) Subpopulation, the primary endpoints of this study, are defined as the time from randomization to death from any cause. 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 (listed in Section 3.1) for the General Population and unstratified log-rank test for the pSTAT3(+) Subpopulation.

The progression free survival 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 for the General Population and unstratified log-rank test for the pSTAT3(+) Subpopulation. Differences of DCR between the two treatment arms for the General Population, will be compared using a 1-sided Cochran-Mantel-Haenszel test stratified for stratification factors. Treatment difference of DCR and its 95% confidence interval based on harmonic mean method adjusting stratification factors will be provided. For the pSTAT3(+) Subpopulation, differences of DCR between the two arms will be compared using a 1-sided Z-test via normal approximation. Treatment difference of DCR and its 95% confidence interval based on normal approximation (unstratified) will be provided. Differences of ORR between the two arms will be analyzed the same as DCR for the General Population and for the pSTAT3(+) subpopulation.

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ABBREVIATIONS

Abbreviation	Definition
ALT	Alanine transaminase
ADR	Adverse drug reaction
AE	Adverse event
BID	Twice a day (Latin word “bis in die”)
BP	Blood pressure
CHF	Congestive heart failure
CHO	Chinese hamster ovary
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration equation
CR	Complete response
CRO	Contract Research Organization
CRC	Colorectal cancer
CSC	Cancer stem cells
CSR	Clinical study report
CSS	Cut-section Stability
CTA	Clinical Trial Assay
CTEP	Cancer Therapy Evaluation Program
DCR	Disease control rate
DPD	Dihydropyrimidine dehydrogenase
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life questionnaire
FOLFIRI	Fluorouracil, Leucovorin, Irinotecan
FOLFOX	Leucovorin, Fluorouracil, Oxaliplatin
FSH	Follicle stimulating hormone
Hgb	Hemoglobin
HRT	Hormone replacement therapy

Abbreviation	Definition
IB	Investigator Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IUD	Intrauterine device
mCRC	Metastatic colorectal cancer
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PR	Partial response
pSTAT3	Activated signal transducers and activators of transcription 3
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
RPLS	Reversible posterior leukoencephalopathy syndrome
RTSM	Randomization and trial supply management
SAE	Serious adverse event
SD	Stable disease
STAT3	Signal transducers and activators of transcription 3
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal
WOCBP	Women of child bearing potential

STUDY ACKNOWLEDGEMENT/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 resources 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 Boston Biomedical, Inc. and/or the designated Contract Research Organization (CRO) 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.

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. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Boston Biomedical, Inc. of any such disclosure.

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 Boston Biomedical Inc., and/or the designated CRO. The study may be terminated at any time by 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 must be kept in confidence in the same manner as the contents of this protocol.

Study CanStem303C

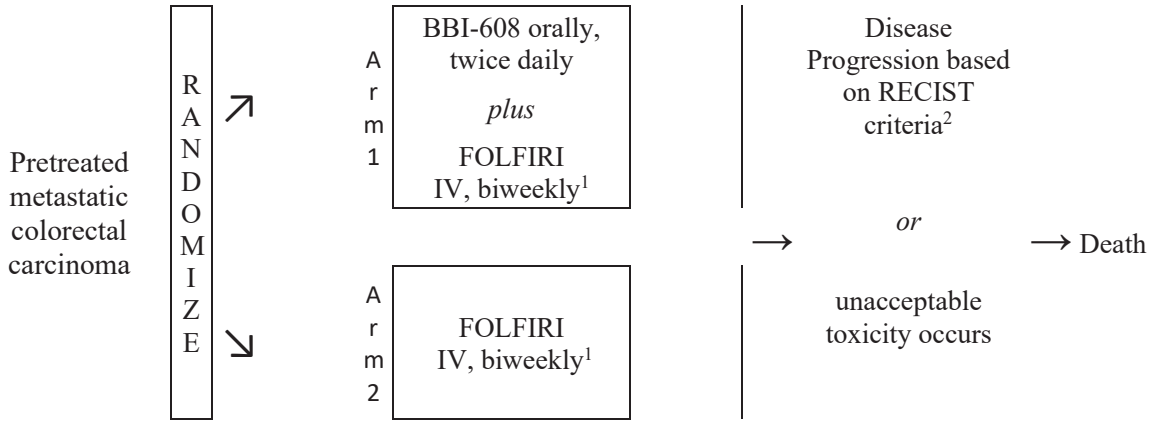
Principal Investigator (Signature)	**Date**
Principal Investigator (Printed Name)	
Center	

STUDY TREATMENT SCHEMA

This is an international multi-center, prospective, open-label, randomized, adaptive design Phase 3 trial of the cancer stem cell pathway inhibitor BBI-608 plus standard bi-weekly FOLFIRI (Arm 1) *versus* standard bi-weekly FOLFIRI (Arm 2) in patients with previously treated metastatic colorectal cancer (mCRC). Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. The safety and PK parameters will be evaluated in a lead-in cohort, if required, in each region/country according to the regulatory request. The trial will enroll patients from North America, Europe, Australia, Asia, and Japan; it is anticipated that 25% to 30% of patients will be enrolled from the United States.

Stratification:

- Geographical region (North America/Western Europe/Australia, Japan/Korea vs. Rest of the World)
- Time to progression from start of first line therapy (<6 months *versus* ≥6 months)
- Tumor *RAS* status (wild type *versus* mutated)
- Bevacizumab as part of study protocol treatment (yes *versus* no)
- Location of the primary tumor (left colon *versus* right colon)



[1]Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible

[2]If no other standard therapies are available at the time of disease progression based on RECIST 1.1 criteria, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI-608 may be continued in monotherapy.

1. OBJECTIVES

1.1. Primary Objectives

- To compare overall survival (OS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) *versus* biweekly FOLFIRI (Arm 2)
- To compare OS in the activated signal transducers and activators of transcription 3 (pSTAT3)-positive (pSTAT3(+)) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2)

1.2. Secondary Objectives

1.2.1. Key Secondary Objectives

- To compare progression free survival (PFS) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI *versus* biweekly FOLFIRI
- To compare PFS in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
- To compare disease control rate (DCR) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI *versus* biweekly FOLFIRI
- To compare DCR in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI
- To compare overall response rate (ORR) in the General Population patients treated with BBI-608 plus biweekly FOLFIRI *versus* biweekly FOLFIRI
- To compare ORR in the pSTAT3(+) Subpopulation patients treated with BBI-608 plus biweekly FOLFIRI versus biweekly FOLFIRI

1.2.2. Other Secondary Objectives

- To compare the Quality of Life (QoL), as measured using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30), in the General Population patients treated with BBI-608 plus bi-weekly FOLFIRI *versus* bi-weekly FOLFIRI
- To compare the QoL, as measured using the EORTC-QLQ-C30, in the pSTAT3(+) Subpopulation patients treated with BBI 608 plus biweekly FOLFIRI versus biweekly FOLFIRI
- To evaluate the safety profile of BBI-608 administered daily plus biweekly FOLFIRI with safety assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0 in the General Population and the pSTAT3(+) Subpopulation

2. BACKGROUND INFORMATION AND RATIONALE

2.1. Colorectal Cancer

Colorectal cancer (CRC) is the second and third most commonly diagnosed type of cancer in females and males, respectively, with more than 1.24 million cases diagnosed in 2008 alone [*Mokarram 2017*]. 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-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/PlGF soluble decoy receptor, aflibercept, has been shown to improve OS 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 tumors [*Karapetis 2008; Amado 2008; Tol 2010; Bokemeyer 2012*]. For the approximately 30% to 50% of colorectal tumors with an activating K-ras mutation [*Amado 2008*], effective treatment options are further limited. At this time, a patient with K-ras mutant tumor and progressive disease on second line therapy has treatment options generally limited to anti-angiogenic drugs including regorafenib monotherapy with a modest survival benefit of 1.4 months [*Grothey 2013*], ramucirumab in combination with FOLFIRI providing a survival benefit of 1.6 months [*Tabernero 2015*], TAS-102, an oral fluoropyrimidine analogue and thymidine phosphorylase inhibitor, recently proven to improve overall survival by 1.8 months in patients with refractory CRC over best supportive care [*Mayer 2015*], an investigational regimen, or best supportive care.

Cancer stem cells (CSC), 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 responsible for malignant growth, recurrence, drug-resistance, and metastasis. Moreover, CSCs are highly resistant to chemotherapies and current targeted agents. Accumulating evidence indicates that CSCs play a 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 tumor-initiating properties, as well as resistance to chemotherapeutics. These findings suggest that the development of cancer stem cell inhibitors represents a novel strategy for the treatment of CRC.

2.2. Napabucasin (BBI-608)

Napabucasin (BBI-608) is a small molecule that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the STAT3 pathway which has been implicated in CSC viability. It has the potential to treat CRC and other types of cancer by inhibiting self-renewal and survival of CSCs and inducing apoptosis in both CSCs and heterogeneous cancer cells.

Recent studies have uncovered the presence of CSCs (also called tumor initiating cells) and have found them to have self-renewal capability which may contribute to malignant growth, relapse, and metastasis [*Clevers 2011; Zhou 2009; Schwartz-Cruz-y-Celis 2011; Chaffer 2011; Rasheed*

2011]. Isolation of CSCs has been reported in various major human cancer types, including breast, colon, prostate, melanoma, pancreatic, lung, head/neck, ovarian, glioblastoma multiforme, liver, esophageal, and hematological malignancy [*Clevers 2011; Zhou 2009; Schwartz-Cruz-y-Celis 2011; Gupta 2009; Hannahan 2011; Gupta 2011; Boman Wicha 2008*]. CSCs are resistant to conventional therapies, therefore, a targeted agent with activity against cancer stem cells is being explored [*Lobo 2007*].

Napabucasin (BBI-608) is hypothesized to inhibit the STAT3 pathway. The signal transducers and activators of transcription 3 (STAT3) gene is an oncogene that belongs to a family of transcription factors activated in response to cytokines and/or growth factors to promote proliferation, survival, and other biological processes and is activated by phosphorylation of a critical tyrosine residue [*Darnell 2005*]. Upon tyrosine phosphorylation, STAT3 forms homo-dimers and translocates to the nucleus, binds to specific DNA-response elements in target gene promoters, and induces gene expression [*Darnell 2005*]. STAT3 activates certain genes involved in tumorigenesis, invasion, and metastasis, including Bcl-xl, Akt, c-Myc, cyclin D1, VEGF, and survivin. The constitutive activation of STAT3 is frequently detected in primary human CRC cells and established human CRC cell lines [*Ma 2004; Corvinus 2005; Kusaba 2005*], and elevated levels of pSTAT3 were correlated with the tumor invasion, nodal metastasis, and the stage ($p<0.05$) [*Ma 2004; Kusaba 2005*]. Constitutive STAT3 activation in CRC cells is associated with invasion, survival, and growth of CRC cells and colorectal tumor model in mice *in vivo* [*Corvinus 2005; Lin 2005; Xiong 2008; Tsareva 2007*]. These reports indicate that STAT3 is one of the oncogenic pathways activated in CRC and may serve as a therapeutic target.

Data from CRC patients treated with napabucasin have indicated that pSTAT3 positivity may be a predictive biomarker for napabucasin treatment (and have also confirmed that pSTAT3 positivity is a prognostic indicator of survival, as is cited in the scientific literature [*data available upon request*]). Several peer-reviewed scientific articles have established dysregulation of STAT3 signaling as a key feature of human CRC. Park *et al* [*2008*] showed that levels of activated STAT3 (pSTAT3) are significantly associated with increasing T- and clinical stages in CRC. Kusaba *et al* [*2005, 2006*] correlated pSTAT3 levels with increasing T- and Duke's stages and the presence of lymph vessel invasion and showed poor prognosis for OS in a first study of CRC, and with increasing T-stages and the presence of vein invasion and lymph node metastases in a second study of CRC. When a meta-analysis was performed combining data on gastrointestinal cancers, including gastric and colorectal cancers, higher levels of pSTAT3 were shown to correlate with worsened overall patient survival [*Li 2015*], signifying the role of pSTAT3 in cancer types throughout the gastrointestinal system. Lastly, pSTAT3(+) is present in about 70% of colorectal carcinomas and approximately 18% of colorectal adenomas [*de Jong 2014*].

2.2.1. Safety Profile

The predominant adverse drug reactions (ADRs) associated with napabucasin are gastrointestinal in nature. Napabucasin treatment may result in diarrhea, abdominal pain, nausea, vomiting, and decreased appetite (anorexia). Refer to the current Investigator Brochure (IB) for additional information on the safety profile of napabucasin.

2.2.2. Napabucasin Monotherapy in Last Line Metastatic Colorectal Cancer

Study CO.23 was a Phase 3 international, multicenter, randomized controlled trial of napabucasin monotherapy (480 mg PO BID) *vs*. placebo in refractory CRC patients. The primary endpoint for the CO.23 trial was OS. The key secondary endpoints include PFS, ORR, DCR, safety, and QoL. Exploratory endpoints include biomarker (pSTAT3) analyses.

To be considered eligible, patients were required to have failed available standard therapy including 5-FU based regimens, irinotecan, oxaliplatin, and EGFR inhibitor if KRAS wild type. The original planned sample size was 650 patients. Accrual was stopped after 282 patients were randomized following a pre-planned interim analysis based on DCR that met protocol-defined stopping criteria for futility. The study did not meet its primary objective.

Final analysis was conducted after completion of follow-up of the 282 patients. The demographic variables and known prognostic factors were balanced between the study arms. No significant differences were observed between the study arms in OS in the ITT population. Study results for primary and secondary endpoints are summarized in Table 1 (final clinical study report [CSR] is pending at the time of this Amendment).

Table 1: Summary of CO.23 Primary and Secondary Endpoints Analysis (ITT Population; N=282)

Statistic	Napabucasin (N=138)	Placebo (N=144)	Hazard Ratio [95%CI], p value
Median OS (mos.)	4.4	4.8	1.13 [0.88 – 1.46], p=0.336
Median PFS (mos.)	1.82	1.82	0.98 [0.76 – 1.26], p=0.831
DCR	17 (12.3%)	18 (12.5%)	---

Of the 282 randomized patients, 251 patients provided diagnostic tumor samples for biomarker evaluation (evaluation was performed by blinded third party assessment). Of these 251 patients, 55 were determined to be pSTAT3(+) and 167 were determined to be pSTAT3(-) and were included in exploratory analyses (Table 2); 29 patients had samples which were not evaluable. In concordance with the literature, presence of the biomarker (pSTAT3(+)) was shown to be a negative prognostic factor in patients receiving placebo. In patients receiving napabucasin, prolonged OS was observed in pSTAT3(+) patients compared to pSTAT3(+) placebo patients, indicating a potential positive predictive effect. In pSTAT3(-) patients, OS was numerically smaller in patients randomized to napabucasin as compared to pSTAT3(-) patients randomized to placebo, but the difference is not clinically meaningful.

Of note, the initial analysis of the correlation of biomarker status and clinical benefit *[Jonker 2018]* included patients with non-evaluable tumor tissue with pSTAT3(-) patients by default. The analysis presented here corrects for this by removing those non-evaluable patients from the pSTAT3(-) group.

Table 2: Study CO.23 Median Overall Survival by Biomarker Status – Intent-to-Treat Population

Subset	Median OS (months)		Hazard Ratio [95%CI]
	Napabucasin (n=138)	Placebo (n=144)	
All Patients (n=282)[a]	4.4	4.8	1.13 [0.88-1.46]
pSTAT3(+) (n=55)[b]	5.1	3.0	0.41 [0.23-0.73]
pSTAT3(-) (n=167)[c]	4.2	5.1	1.33 [0.97-1.83]

a Of the 282 patients in Study CO.23, 251 were evaluated for pSTAT3 positivity: 55 were pSTAT3(+), 167 were pSTAT3(-), 29 were not evaluable
b Of the 55 pSTAT3(+) patients, 29 were randomized to napabucasin and 26 were randomized to placebo
c Of the 167 pSTAT3(-) patients, 83 were randomized to napabucasin and 84 were randomized to placebo

The safety profile was consistent with the observations in earlier phase trials. Refer to the current IB for more information on the safety profile of napabucasin.

2.2.3. Napabucasin in Combination with FOLFIRI for Colorectal Cancer

BBI608-246 was a multi-arm Phase 1/2 clinical trial of napabucasin in combination with several standard anti-cancer regimens for advanced gastrointestinal malignancies. The primary objectives of the study were to determine the safety, tolerability, PK characteristics, and recommended Phase 2 dose (RP2D) of napabucasin in combination with each of the backbone regimens. Secondary objectives were to evaluate preliminary anti-tumor activity. Study accrual is complete, and analysis is ongoing.

Patients were eligible if they had a gastrointestinal malignancy that was recurrent, metastatic, or locally advanced, and if they were a candidate for treatment with 1 of the following backbone regimens: FOLFOX6 (±bevacizumab), FOLFIRI (±bevacizumab), CAPOX, irinotecan, or regorafenib. Patients were assigned to a backbone regimen according to investigator assessment. The backbone regimen was administered in combination with napabucasin at a dose assigned according to the dose-escalation protocol. Once RP2D was identified, patients were dosed with either 240 mg twice-daily (480 mg total daily) or 480 mg twice-daily (960 mg total daily), continuously, depending on the assigned backbone cohort.

One cohort included patients with advanced CRC who were administered napabucasin 240 mg twice daily (480 mg total daily) in combination with standard FOLFIRI (5-FU 400 mg/m^2 intravenous bolus followed by 5-FU 1200 mg/m^2/day continuous 48-hour intravenous infusion [total 2400 mg/m^2] with leucovorin 400 mg/m^2 and irinotecan 180 mg/m^2 every 14 days). If indicated and assigned by the investigator, bevacizumab was given at 5 mg/kg intravenously every 14 days. In case of toxicity, dose adjustment of either napabucasin or FOLFIRI or bevacizumab was permitted.

An analysis was performed on 82 patients in this cohort using safety and efficacy data available as of 01 September 2017. All patients had received previous systemic therapy, 36 (44%) had received 1 prior regimen, 18 (22%) had received 2 prior regimens, and 28 (34%) had received 3 or more prior systemic regimens. Additionally, 34 (41%) patients had received prior treatment with FOLFIRI. A total of 16 (19.5%) patients achieved objective response per RECIST 1.1 criteria, including 1 patient with complete response (CR) and 15 with partial response (PR). An additional 41 patients experienced stable disease (SD), and the DCR, proportion with CR, PR, or

SD was 69.5%. Of 48 patients with progression events and 52 patients who have died, the median progression-free survival (mPFS) is 5.9 months and the median overall survival (mOS) is 12.9 months.

Adverse events as of 01 September 2017 reported in ≥10% of the patients in this cohort are shown in Table 3.

Refer to the current IB for detailed safety data from this study..

Table 3: BBI608-246 Adverse Events in ≥10% of Patients (Napabucasin PLUS FOLFIRI [±bev])

Preferred Term	All Patients (N=164)
	n (%)
Diarrhoea	145 (88.4)
Nausea	106 (64.6)
Fatigue	98 (59.8)
Vomiting	82 (50.0)
Decreased appetite	76 (46.3)
Abdominal pain	70 (42.7)
Neutropenia	39 (23.8)
Alopecia	39 (23.8)
Constipation	37 (22.6)
Anaemia	28 (17.1)
Hypokalaemia	27 (16.5)
Dyspnoea	27 (16.5)
Dehydration	25 (15.2)
Weight decreased	24 (14.6)
Pyrexia	23 (14.0)
Cough	23 (14.0)
Urinary tract infection	23 (14.0)
Neutrophil count decreased	22 (13.4)
Insomnia	21 (12.8)
Oedema peripheral	20 (12.2)
Stomatitis	18 (11.0)
Mucosal inflammation	18 (11.0)
Back pain	18 (11.0)
Chromaturia	18 (11.0)
Headache	17 (10.4)

2.3. Pre-clinical Rationale

Refer to the current IB for a detailed summary of nonclinical data.

2.4. Summary

Napabucasin (BBI-608) at a dose of 240 mg BID (480 mg total daily) has been well tolerated as monotherapy and when combined with a standard regimen of FOLFIRI with or without bevacizumab. The clinical activity observed in Study CO.23 and Study BBI608-246, and the unmet medical need for additional effective therapies for patients with advanced CRC, provides a rationale for further clinical investigation. Study CanStem303C is designed to evaluate the role of napabucasin added to standard FOLFIRI (±bevacizumab) as second line therapy for advanced CRC.

3. TRIAL DESIGN

This is an international multi-center, prospective, open-label, randomized, adaptive design Phase 3 trial of BBI-608 plus standard bi-weekly FOLFIRI *versus* standard bi-weekly FOLFIRI in patients previously treated for advanced metastatic CRC. Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, is permissible.

3.1. Stratification

Patients will be stratified by:

1. Geographical region (North America/Western Europe/Australia, Japan/Korea *vs.* Rest of the World)
2. Time to progression on first-line therapy (<6 months vs. ≥6 months from start of first line therapy)
3. *RAS* mutation status (mutant vs. wild type)[1]
4. Bevacizumab as part of study protocol treatment (yes vs. no)
5. Location of the primary tumor (left colon vs. right colon)[2]

[1]*RAS* mutant status refers to any known mutation in *KRAS* or *NRAS* mutations in exons 2, 3, and 4 resulting in decrease of response to anti-EGFR treatment.
[2]Lesions proximal to the splenic flexure will be considered right colon and lesions at splenic flexure and distal to it will be considered left colon.

3.2. Randomization

Patients will be randomized according to a 1:1 ratio using a permuted block randomization procedure to receive BBI-608 plus standard bi-weekly FOLFIRI or standard bi-weekly FOLFIRI. Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible.

Patients will be randomized to 1 of the following 2 arms:

Arm	Agent(s)	Dose and Route	Duration
1	BBI-608	240 mg orally 2 times daily[1,2]	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria. [4,5]
	FOLFIRI	Standard FOLFIRI IV, once every 2 weeks[3]	
2	FOLFIRI	Standard FOLFIRI IV, once every 2 weeks[3]	

[1] BBI-608 should be taken 1 hour before or 2 hours after a meal, 2 times daily, with approximately 12 hours between doses. BBI-608 administration will begin 2 days prior to the FOLFIRI infusion on Day 1 of Cycle 1. These 2 days are referred to as Run-in Day 1 and Run-in Day 2. The run-in day period may be extended by up to 3 additional calendar days. Run-in Day 1 should occur within 2 calendar days of patient randomization.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking BBI-608 with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. FOLFIRI chemotherapy infusion will start at least 2 hours following the first daily dose of BBI-608 and will be administered every 2 weeks. Irinotecan/leucovorin infusion will follow bevacizumab infusion in patients selected by the Investigator to receive standard dose of bevacizumab (5 mg/kg). Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously, over approximately 90 minutes and 2 hours, respectively, starting on Day 1 of Cycle 1, following bevacizumab infusion or at least 2 hours following the first dose of BBI-608 if bevacizumab is not administered. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

[4] If any component of FOLFIRI is discontinued due to toxicity or any other reason deemed appropriate by the clinical investigators, BBI-608 should be continued until another criterion for stopping treatment is met. If BBI-608 is discontinued due to toxicity, FOLFIRI should be continued until another criterion for stopping treatment is met.

[5] If no other standard therapies are available at the time of disease progression based on RECIST 1.1 criteria, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI-608 may be continued as monotherapy.

3.3. Pharmaceutical Data

3.3.1. BBI-608

Supplied:

BBI-608 is supplied in 80-mg strength capsules.

Stability:

Initial product use dating is 24 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:

BBI-608 capsules should be stored in a tightly closed container at a temperature between 15°C to 25ºC (59°F to 77°F).

Route of Administration:

Patients should take BBI-608 orally twice daily, approximately 1 hour prior to or 2 hours after meals, with the first dose given in the morning and the second dose given approximately 12 hours later (ideally between 10 and 14 hours from the previous dose).

3.3.2. FOLFIRI

Please refer to the FOLFIRI component locally approved labels for product description, stability information, storage instructions, route of administration, as well as for the management of patients, regarding contraindications, patient monitoring, dose adjustments in case of toxicity, and drugs prohibited or used with caution.

In France, please refer to the following website to obtain the most updated version of the SmPC for the FOLFIRI components and bevacizumab: http://base-donnees-publique.medicaments.gouv.fr

3.3.3. Additional Chemotherapy Permissible for Combination with FOLFIRI: Bevacizumab

Please refer to the locally approved label for bevacizumab for product description, stability information, storage instructions, and route of administration.

3.4. Inclusion of Women and Minorities

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

4. STUDY POPULATION

The trial population will consist of patients with advanced (metastatic) histologically confirmed CRC. Patients will have failed treatment with 1 regimen containing a fluoropyrimidine and oxaliplatin with or without bevacizumab in the metastatic setting. Selection of the most appropriate patient population and hypothesis for evaluating the significance of the treatment effect at the final analysis will be made based on the rules and hypothesis described in Section 13.5.

4.1. Inclusion Criteria

Questions about eligibility criteria should be addressed prior to 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, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases.

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

4.1.1 Written, signed consent for trial participation must be obtained from the patient appropriately in accordance with applicable ICH guidelines and local and regulatory requirements prior to the performance of any study specific procedure.

4.1.2 Must have histologically confirmed advanced CRC that is metastatic.

4.1.3 Must have failed treatment with 1 regimen containing only a fluoropyrimidine and oxaliplatin with or without bevacizumab for metastatic disease. All patients must have received a minimum of 6 weeks of the first-line regimen that included oxaliplatin and a fluoropyrimidine with or without bevacizumab in the same cycle. Treatment failure is defined as radiologic progression during or ≤6 months after the last dose of first-line therapy.

No additional prior lines of therapy in the metastatic setting will be allowed. Patients who discontinued first-line therapy due to toxicity may be enrolled for as long as progression occurred ≤6 months after the last dose of first-line therapy.

Patients who show tumor progression while on maintenance therapy with a fluoropyrimidine with or without bevacizumab after prior fluoropyrimidine-oxaliplatin with or without bevacizumab induction therapy are eligible.

Prior neoadjuvant or adjuvant systemic treatment is allowed as long as no more than 2 prior systemic chemotherapy regimens were administered with no more than 1 prior regimen permitted in the metastatic setting. Patients who received oxaliplatin/fluoropyrimidine-based neoadjuvant or adjuvant therapy and have disease recurrence or progression >6 months from their last dose of neoadjuvant or adjuvant treatment (or >6 months from surgery if no adjuvant therapy was administered) will be required to receive fluoropyrimidine/oxaliplatin-based therapy with or without bevacizumab for metastatic disease.

For participants with rectal cancer, sequential neoadjuvant and adjuvant therapy will count as a single systemic regimen.

Re-challenge with oxaliplatin is permitted and will be considered part of the first-line regimen for metastatic disease, with both initial oxaliplatin treatment and subsequent re-challenge being considered as 1 regimen.

Patients receiving any other systemic therapy in the metastatic setting will be excluded.

4.1.4 FOLFIRI therapy is appropriate for the patient and is recommended by the Investigator.

4.1.5 Imaging investigations including CT/MRI of chest/abdomen/pelvis or other scans as necessary to document all sites of disease performed within 21 days prior to randomization. Patients with either measurable disease or non-measurable evaluable disease are eligible.

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

4.1.7 Must be ≥18 years of age.

4.1.8 For male or female patient of child bearing potential: Must agree to use contraception or take measures to avoid pregnancy during the study and for 180 days for female and for male patients, of the final FOLFIRI dose. Patients who receive single agent BBI-608 without FOLFIRI must agree to use contraception or take measures to avoid pregnancy during the study and for 30 days for female patients and 90 days for male patients, of the final BBI-608 dose.

Female patients of child bearing potential treated with bevacizumab, per investigator choice, must agree to use contraception or take measures to avoid pregnancy during the study and for 6 months, of the final bevacizumab dose.

Adequate contraception is defined as follows:

- Complete true abstinence: when this is in line with the preferred and usual lifestyle of the subject.
- Consistent and correct use of one of the following methods of birth control:
  - Male partner who is sterile prior to the female subject's entry into the study and is the sole sexual partner for that female subject; or
  - Implants of levonorgestrel; or
  - Injectable progestogen; or
  - Any intrauterine device (IUD) with a documented failure rate of less than 1% per year; or
  - Oral contraceptive pill (either combined or progesterone only); or
  - One barrier method for example diaphragm with spermicide or condom with spermicide in combination with either implants of levonorgestrel or injectable progestogen, any IUD with a documented failure rate of less than 1% per year, or oral contraceptive pill (either combined or progesterone only).

4.1.9 Women of child bearing potential (WOCBP) must have a negative serum or urine pregnancy test within 5 days 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 amenorrhea >12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level >35 mIU/mL). Women who are using oral, implanted or injectable contraceptive hormones or mechanical products such as an IUD 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.

4.1.10 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.

4.1.11 Must have hemoglobin (Hgb) ≥9.0 g/dL within 14 days prior to randomization. Must not have required transfusion of red blood cells within 1 week of baseline Hgb assessment.

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

4.1.13 Must have creatinine ≤1.5 × institutional ULN or Creatinine Clearance >50 ml/min as calculated by the Cockcroft-Gault equation (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation may also be used) within 14 days prior to randomization.

4.1.14 Must have absolute neutrophil count ≥1.5 × 10^9/L within 14 days prior to randomization.

4.1.15 Must have platelet count ≥100 × 10^9/L within 14 days prior to randomization. Must not have required transfusion of platelets within 1 week of baseline platelet assessment.

4.1.16 Patient must have adequate nutritional status with body mass index (BMI) ≥18 kg/m^2 and body weight of ≥40 kg with serum albumin ≥3 g/dL.

4.1.17 Other baseline laboratory evaluations, listed in Section 5, must be done within 14 days prior to randomization.

4.1.18 Patient must consent to provision of, and Investigator(s) must confirm access to and agree to submit a representative formalin fixed paraffin block of tumor tissue in order that the specific biomarker assays may be conducted (Section 12.2.1 and Section 13.2). Submission of the tissue is to occur prior to randomization unless approved by the Sponsor. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block ***and*** 10-30 unstained slides of whole sections of representative tumor tissue are preferred. Where two 2 mm cores of tumor from the block are unavailable, 10 to 30 unstained slides of whole sections of representative tumor tissue alone are acceptable. Where no previously resected or biopsied tumor tissue exists or is available, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

4.1.19 Patient must consent to provision of a sample of blood in order that the specific correlative marker assays may be conducted (Section 12.2.1).

4.1.20 Patients must be accessible for treatment and follow-up. Patients registered on this trial must receive protocol treatment and be followed at the participating center. This implies

there must be reasonable geographical limits placed on patients being considered for this trial. Investigators must ensure that the patients randomized on this trial will be available for complete documentation of the treatment, response assessment, adverse events, and follow-up.

4.1.21 Protocol treatment is to begin within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization.

4.1.22 The patient is not receiving therapy in a concurrent clinical study and the patient agrees not to participate in other interventional clinical studies during their participation in this trial while on study treatment. Patients participating in surveys or observational studies are eligible to participate in this study.

4.2. Exclusion Criteria

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

4.2.1 Anti-cancer chemotherapy or biologic therapy if administered prior to the first planned dose of study medication (BBI-608 or FOLFIRI) within period of time equivalent to the usual cycle length of the regimen. An exception is made for oral fluoropyrimidines (e.g. capecitabine, S-1), where a minimum of 10 days since last dose must be observed prior to the first planned dose of study medication.

Standard dose of bevacizumab (5 mg/kg) may be administered prior to FOLFIRI infusion, per Investigator decision, for as long as permanent decision to include or exclude bevacizumab is made prior to patient randomization.

Radiotherapy, immunotherapy (including immunotherapy administered for non-neoplastic treatment purposes), or investigational agents within four weeks of first planned dose of study medication, 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.

4.2.2 More than 1 prior chemotherapy regimen administered in the metastatic setting.

4.2.3 Major surgery within 4 weeks prior to randomization.

4.2.4 Patients with any known brain or leptomeningeal metastases are excluded, even if treated.

4.2.5 Women who are pregnant or breastfeeding. Women should not breastfeed while taking study treatment and for 4 weeks after the last dose of BBI-608 or while undergoing treatment with FOLFIRI and for 180 days after the last dose of FOLFIRI.

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

4.2.7 Unable or unwilling to swallow BBI-608 capsules daily.

4.2.8 Prior treatment with BBI-608 or possible hypersensitivity to BBI-608 or one of the excipients which include azo dyes sunset yellow and allura red.

4.2.9 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.

a. Known infection with human immunodeficiency virus (HIV), and/or active infection with hepatitis B (patients who have had an HBV immunization are eligible), or hepatitis C.
b. Patients with clinically significant ascites or pleural effusions.

4.2.10 Known hypersensitivity to 5-fluorouracil/leucovorin

4.2.11 Known dihydropyrimidine dehydrogenase (DPD) deficiency

4.2.12 Known hypersensitivity to irinotecan

4.2.13 Chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis)

4.2.14 Patients receiving treatment with St. John's wort or Phenytoin

4.2.15 Patients who plan to receive yellow fever vaccine during the course of the study treatment

4.2.16 Abnormal glucuronidation of bilirubin, known Gilbert's syndrome

4.2.17 Patients with QTc interval >470 milliseconds

4.2.18 For patients to be treated with a regimen containing bevacizumab:

a. History of cardiac disease: congestive heart failure (CHF) ≥NYHA Class II; active coronary artery disease, myocardial infarction within 6 months prior to study entry; unevaluated new onset angina within 3 months or unstable angina (angina symptoms at rest) or cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted)
b. Current uncontrolled hypertension (systolic blood pressure [BP] >150 mmHg or diastolic pressure >90 mmHg despite optimal medical management) as well as prior history of hypertensive crisis or hypertensive encephalopathy
c. History of arterial thrombotic or embolic events (within 6 months prior to study entry)
d. Significant vascular disease (e.g., aortic aneurysm, aortic dissection, symptomatic peripheral vascular disease)
e. Evidence of bleeding diathesis or clinically significant coagulopathy
f. Major surgical procedure (including open biopsy, significant traumatic injury, etc.) within 28 days, or anticipation of the need for major surgical procedure during the course of the study as well as minor surgical procedure (excluding placement of a vascular access device or bone marrow biopsy) within 7 days prior to study enrollment
g. Proteinuria at screening as demonstrated by urinalysis with proteinuria ≥2+ (patients discovered to have ≥2+ proteinuria on dipstick urinalysis at baseline should undergo a 24-hour urine collection and must demonstrate ≤1g of protein in 24 hours to be eligible)

h. History of abdominal fistula, gastrointestinal perforation, peptic ulcer, or intra-abdominal abscess within 6 months
i. Ongoing serious, non-healing wound, ulcer, or bone fracture
j. Known hypersensitivity to any component of bevacizumab
k. History of reversible posterior leukoencephalopathy syndrome (RPLS)
l. History of hypersensitivity to Chinese hamster ovary (CHO) cells or other human or humanized recombinant antibodies.

4.2.19 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 tumors curatively treated with no evidence of disease for ≥3 years

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

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

5. PRE-TREATMENT EVALUATION

See Appendix 1 and Appendix 2 for detailed schedule of assessments.

Baseline evaluations will be performed for all patients to determine study eligibility. These evaluations must be obtained ≤14 days prior to randomization, with up to 21 days allowed for baseline radiologic evaluation and up to 28 days allowed for baseline electrocardiogram (ECG).

Repeat of screening laboratory tests will be allowed only in the event of a laboratory error or for patients who halted screening previously without having failed any of the screening tests/evaluations or inclusion criteria for this study. Otherwise, re-screening will not be allowed.

Any questions regarding patient eligibility should be directed to Sponsor or other Sponsor-nominated designee for written approval.

All appropriate eCRF pages must be completed for patients prior to obtaining pre-randomization approval.

Investigations		**Timing prior to randomization[8]**
Patient History and Evaluation	Prior medical and therapeutic history, including *RAS* testing[1] Physical examination[9] Vital signs (temperature, blood pressure, heart rate, respiratory rate, O_2 saturation on room air) Height, weight, ECOG performance status Clinical tumor measurements Concurrent medication list	≤14 days
Hematology	CBC + differential Platelet count	≤14 days[8]
Biochemistry	Creatinine[2], Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	≤14 days[8]
Urinalysis	Dipstick (including protein, specific gravity, glucose and blood)	≤14 days[8]
Cardiac Assessment	ECG (12 lead)	≤28 days[8]
Radiology & Imaging	CT/MRI scan of chest/abdomen/pelvis with tumor measurement and evaluation by RECIST 1.1 criteria[3]	≤21 days
Biomarker and Correlative Studies	Submission of representative diagnostic tumor tissue[4]	Before or after randomization
	Blood sample collection[5]	≤14 days
Other Investigations	Serum or urine pregnancy test[6]	≤5 days

Investigations		Timing prior to randomization[8]
Adverse Events[7]	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

1 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *RAS* status of tumor (*RAS* mutant status refers to any known mutation in *KRAS* or *NRAS* mutations in exons 2, 3, and 4 resulting in decrease of response to anti-EGFR treatment), smoking history, prior anticancer therapy, and prior date(s) of disease progression.
2 Baseline creatinine or creatinine clearance may be used to demonstrate eligibility as per Section 4.1.
3 Standard tumor 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. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed ≤ 21 days prior to randomization. Baseline imaging should be repeated to obtain an accurate assessment of baseline tumor load prior to randomization in the event of significant change in patient's clinical status as per Investigator Assessment.
4 Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory procedure manual.
5 Details for collection, processing, storing and shipping these samples will be provided in a separate laboratory procedure manual.
6 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG.
7 Adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix 4).
8 Laboratory testing performed as part of standard of care prior to patient signature of the study consent will be acceptable as baseline lab work as long as testing is performed ≤ 14 days prior to randomization. If required laboratory tests cannot be performed within indicated timelines due to technical reasons, lab retest and prolongation of the screening period for 3 working days is allowed. ECGs performed as part of standard of care prior to patient signature of the study consent will be acceptable as baseline ECG as long as it is performed ≤28 days prior to randomization.
9 A physical exam should include general appearance, HEENT (head, eyes, ears, nose), dermatological, respiratory, cardiovascular/circulatory, abdomen, lymphatic, genitourinary, musculoskeletal, and neurological assessments.

6. ENTRY/RANDOMIZATION PROCEDURES

6.1. Entry Procedures

All randomizations will be done through the CanStem303C randomization and trial supply management (RTSM) system. Complete details regarding obtaining a password, accessing the system, and registering/randomizing patients will be provided at the time of study activation.

All eligible patients enrolled on the study by the participating treatment center will be assigned a subject identification number which must be used on all documentation and correspondence.

The following information will be required:

- Patient's date of birth (as allowed by local regulations) and age
- Patient's initials (as allowed by local regulations)
- Confirmation of the requirements listed in Section 4.1 and Section 4.2
- Stratification factors

6.2. Stratification

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

- Geographical region (North America/Western Europe/Australia, Japan/Korea, *vs* rest of the world)
- Time to progression from start of first line therapy (<6 months *vs* ≥6 months)
- *RAS* mutation status (mutant *vs* wild type)
- Bevacizumab as part of study protocol treatment (yes *vs* no)
- Location of primary tumor (left colon *vs* right colon)

6.3. Randomization

Patients will be randomized 1:1 between the 2 treatment arms and the randomization will be provided electronically (via RTSM).

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 randomized 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 the study sponsor that further follow-up is no longer required.

7. TREATMENT PLAN

Protocol treatment is to begin within 2 calendar days of patient randomization for patients randomized to Arm 1. Patients randomized to Arm 2 must begin protocol treatment within 7 calendar days of randomization.

7.1. Treatment Plan

Palliative and supportive care for other disease-related symptoms and for toxicity associated with treatment is permitted for 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 electronic case report forms (eCRFs).

Addition of bevacizumab at the standard dose (5 mg/kg) to the FOLFIRI regimen, per Investigator choice, will be permissible.

7.1.1. Drug Administration

One treatment cycle is defined as 14 days (2 weeks) with BBI-608 administered orally twice daily (with doses separated by approximately 12 hours), and standard FOLFIRI administered every other week (ie, once per cycle). BBI-608 administration will begin 2 days prior to the irinotecan infusion on Day 1 of Cycle 1 (Table 4). These 2 days are referred to as *Run-in Day 1* and *Run-in Day 2*. The *run-in day* period may be extended by up to 3 additional calendar days. Addition of bevacizumab at the standard dose (5 mg/kg) to the FOLFIRI regimen, per Investigator choice, will be permissible.

Table 4: Study Drug Administration

Arm	Agent(s)	Dose and Route	Duration
1	BBI-608	240 mg orally 2 times daily[1,2]	Patients may continue to receive protocol therapy as long as they have not experienced any adverse events requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST 1.1 criteria. [4,5]
	FOLFIRI	Standard FOLFIRI IV, once every 2 weeks[3]	
2	FOLFIRI	Standard FOLFIRI IV, once every 2 weeks[3]	

[1] BBI-608 should be taken one hour before or 2 hours after a meal, 2 times daily, with approximately 12 hours between doses BBI-608 administration will begin 2 days prior to the irinotecan infusion on Day 1 of Cycle 1 (*run-in day* period may be extended by up to 3 additional calendar days). These days are referred to as *Run-in Day 1, Run-in Day 2, etc*. Run-in Day 1 should occur within 2 calendar days of patient randomization on study Arm 1.

[2] Patients should be encouraged to maintain sufficient fluid intake while on protocol treatment, such as taking BBI-608 with approximately 250 mL of fluid over the course of 30 minutes after the dose.

[3] Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. FOLFIRI chemotherapy infusion will start at least 2 hours following the first daily dose of BBI-608 and will be administered every 2 weeks. If bevacizumab is added to the FOLFIRI regimen, bevacizumab infusion should start at least 2 hours following the first dose of BBI-608 starting on Cycle 1 Day 1 and will be administered every 2 weeks. Irinotecan/leucovorin infusion will follow bevacizumab infusion in patients selected by the Investigator to receive standard dose of bevacizumab (5 mg/kg). Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will be administered intravenously, over approximately 90 minutes and 2 hours, respectively, starting on Day 1 of Cycle 1, following bevacizumab infusion or at least 2 hours following the first daily dose of BBI-608 if bevacizumab is not administered. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion. This regimen will be repeated on Day 1 of every 14-day cycle.

[4] If any component of FOLFIRI is discontinued due to toxicity or any other reason deemed appropriate by clinical investigators, BBI-608 should be continued until another criterion for stopping treatment is met. If BBI-608 is discontinued due to toxicity, FOLFIRI should be continued until another criterion for stopping treatment is met.

[5] If no other standard therapies are available at the time of disease progression based on RECIST 1.1 criteria, and the patient has not experienced any adverse events requiring permanent discontinuation, BBI-608 may be continued in monotherapy.

Patients will receive BBI-608 2 times daily, approximately 1 hour prior to or 2 hours after meals, with the first dose given in the morning and the second dose given approximately 12 hours later.

Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible. Starting on Cycle 1 Day 1, FOLFIRI chemotherapy infusion will start at least 2 hours following the first dose of BBI-608 and will be administered every 2 weeks. If bevacizumab is added to the FOLFIRI regimen, bevacizumab infusion should start at least 2 hours following the first dose of BBI-608 starting on Cycle 1 Day 1 and will be administered every 2 weeks. Irinotecan 180 mg/m^2 together with leucovorin 400 mg/m^2 will follow bevacizumab infusion in patients selected by the Investigator to receive standard dose of bevacizumab (5 mg/kg), and will be administered concurrently via approximately 90-minute and 2-hour infusions, respectively, starting on Day 1 of Cycle 1, following bevacizumab infusion or at least 2 hours following the first daily dose of BBI-608 if bevacizumab is not administered. 5-FU 400 mg/m^2 bolus will be administered intravenously immediately following irinotecan/leucovorin infusion, followed by 5-FU 1200 mg/m^2/day (total 2400 mg/m^2) continuous infusion for approximately 46 hours. This regimen will be repeated every 14 days thereafter. FOLFIRI administration should proceed

according to the manufacturer's instructions and local standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after the infusion). If site-specific FOLFIRI administration procedures with respect to timing diverge from the above administration instructions, prior Sponsor approval may be granted, as long as the total dose administered remains per protocol.

For sites in Australia, Belgium, Japan, and the United States, it is permissible to replace leucovorin with levoleucovorin for the FOLFIRI regimen. In these countries only, levoleucovorin should be administered in accordance with local procedures in the event such replacement is used, and at the recommended dose of 200 mg/m^2.

If any component of the FOLFIRI regimen is permanently discontinued due to toxicity or any other reasons deemed appropriate by clinical investigators, BBI-608 and the residual components of medical therapy should be continued until another criterion for stopping treatment is met. If BBI-608 is permanently discontinued due to toxicity, FOLFIRI should be continued until another criterion for stopping treatment is met.

As BBI-608 may target cancer stem cells, it is possible that continued therapy after progressive disease per RECIST 1.1 may provide clinical benefit. If no other standard therapies are available at the time of disease progression based on RECIST 1.1 criteria, and the patient has not experienced any AEs requiring permanent discontinuation, BBI-608 may be continued in monotherapy.

Handling instructions for BBI-608 will be provided to all sites. Investigators may refer to the current IB for detailed instructions.

7.1.1.1. BBI-608 Diarrhea Prophylaxis:

It is strongly recommended that all patients hold their bowel regimen (fiber supplementation may be continued) starting 1 day prior to the first dose of BBI-608. Bowel regimen may be resumed as needed if constipation develops.

Additionally, it is strongly recommended that all patients without constipation at screening/randomization start prophylactic anti-diarrheals, such as Loperamide (Imodium®) 2 mg orally (PO) twice daily or Diphenoxylate/Atropine (Lomotil®) 2.5 to 5 mg PO twice daily, starting 1 day prior to the first dose of BBI-608 and continue with prophylaxis for the first 4 weeks of study treatment with BBI-608. Anti-diarrheal prophylaxis should be held if constipation develops.

7.1.2. Blinding/Unblinding

This is an open label study. The primary endpoint of this study is overall survival, the assessment of which is unlikely impacted by the open-label nature of the study.

However, to comply with ICH E6 (R2) Guideline for Good Clinical Practice (2016) recommending the blinded review of planned analyses [http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf], and to minimize the risk of potential bias into interim and final analyses, a blinding plan was implemented by the Sponsor and by the CRO to maintain the integrity of the study data for the decision making at the interim and final analyses.

7.1.3. Patient Monitoring

For the duration that patients are on study therapy, AE monitoring will be done continuously. Patients will be evaluated for AEs at each visit and are to be instructed to call their physician to report any AEs between visits.

7.1.4. BBI-608 Dose Modification

The major AEs associated with the use of BBI-608 are gastrointestinal events (nausea, diarrhea, and abdominal cramping) and fatigue. Fatigue is often secondary to gastrointestinal events. There is no hematologic toxicity associated with BBI-608. We recommend that pre-exiting laxative bowel regimens, such as stool softeners, be held starting the day prior to first dose of study treatment and may be resumed in cases of no bowel movement during the first 2 days of protocol treatment. Fiber supplementation may be continued. Additionally, prophylactic anti-diarrheal medications, such as Imodium and/or Lomotil, starting 1 day prior to start of BBI-608 are strongly recommended for all patients.

The guidelines which follow outline dosing modifications and recommended interventions should the above AEs occur.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (see Appendix 4). If a patient experiences several AEs and there are conflicting recommendations, please use the recommended dose adjustment that reduces the dose to the lowest level.

Table 5: BBI-608 Dose Modification Recommendations for Gastrointestinal Adverse Events:

Suspected BBI-608 -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 interruption of ½ to 3 days prior to reduction can also be considered. Dosing should be reduced to the next Modification Level as in Table 6. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be increased in 80 mg increments every 3-7 days as tolerated. *, **
Grade 3 or 4 Symptoms	A dose interruption of ½ to 3 days is recommended until symptoms are reduced to ≤ tolerable Grade 2. Dosing should be reduced to the next Modification Level as in Table 6. Pharmacologic symptom support and/or prophylaxis should be maintained. After a dose reduction, AM and PM doses may be increased 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. 160 mg AM/240 mg PM).

Table 6: BBI-608 Dose Modification Table:

Dose Level	Dose
Full dose	240 mg twice daily (q12h)
Modification Level-1	80 mg twice daily (q12h), up-titrate as tolerated**
Modification Level-2	80 mg once daily*, up-titrate as tolerated**

* If 80 mg once daily is not tolerated, a dose interruption of 1-3 days followed by re-challenge at 80 mg once daily is recommended.
** Morning and evening doses can be increased in 80 mg increments every 3-7 days or slower as tolerated, up to 240 mg 2 times daily.

Recommended symptom-specific supportive treatment for common BBI-608-related AEs is presented in Table 7 (unless contraindicated). Prophylactic anti-diarrheal medications, such as Imodium and/or Lomotil, starting 1 day prior to start of BBI-608 are strongly recommended for all patients without constipation at screening:

Table 7: Symptom-Specific Supportive Treatment*

<table>
<tr><th>Diarrhea & Abdominal Cramping</th><th>Nausea, Vomiting, or Anorexia[1]</th></tr>
<tr><td>Dicyclomine (e.g., Bentyl): Recommended when the predominant issue is cramping or abdominal pain</td><td rowspan="2">1st line: 5HT3-inhibitorsJD (Ondansetron, Palonosetron, Granisetron)</td></tr>
<tr><td>Diphenoxylate/atropine (Lomotil)
Loperamide (Imodium)
(These agents may be useful in combination)</td><td>2nd line: Dexamethasone (Decadron), ideally in combination with a 5HT3-inhibitor. Short term use can be very effective</td></tr>
<tr><td>Hyoscine (Buscopan, Scopolamine, Levsin): Anti-spasmodic agents helpful for abdominal cramping</td><td rowspan="2">Other agents: NK1 antagonist (e.g. Aprepitant), atypical antipsychotic (e.g., olanzapine), benzodiazepines (e.g. lorazepam), phenothiazines (e.g. prochlorperazine), cannabinoids (e.g., dronabinol), and other agents such as metoclopromide or scopolamine.</td></tr>
<tr><td>Steroid with limited systemic absorption[2]</td></tr>
<tr><td colspan="2">[1]Adapted from NCCN anti-emetic guideline 2017
[2]Alimentary tract mucositis reflects mucosal injury across the continuum of oral and gastrointestinal mucosal. Expert opinion (2016 ESMO clinical practice guideline recommendations include systemic steroid treatment for the management of adverse event observed with use of targeted agents.
*Decisions on ADR management are at the discretion of the investigator and must adhere with local regulatory guidelines</td></tr>
</table>

Details regarding the use of supporting medication for the management of common BBI-608-related AEs are specified in the supplementary Adverse Event Management document as well as in the Pharmacy Manual.

7.1.4.1. Hematologic Adverse Events

No hematologic toxicity related to BBI-608 treatment has been observed. Should a study subject experience a Grade 1 or 2 hematologic AE, dosing may continue while an alternate explanation is sought, and/or a therapeutic intervention is undertaken.

Should a patient experience a Grade 3 or 4 hematologic AE, continued dosing will be at the discretion of the study Investigator while an alternate explanation is sought, and/or a therapeutic intervention is undertaken.

7.1.4.2. Non-Hematologic Adverse Events

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Appendix 4).

7.1.4.3. Other Situations

Change in Urine Color and Odor:

Occasionally, subjects have reported an orange-brown color change to their urine. Rarely, subjects also report a new odor to their urine. All subjects should be made aware of the possibility of these effects. For the reported AEs of chromaturia in patients receiving BBI-608 + paclitaxel, the majority were recovered/resolved. Dosing can be continued in the presence of these events.

7.1.5. FOLFIRI Dose Modification

Dose modifications for hematologic and non-hematologic toxicities (using NCI CTCAE Version 4.0) expected from FOLFIRI should be performed according to the recommendations outlined in Table 8. Dose modifications for non-gastrointestinal toxicities expected from FOLFIRI may also follow institutional guidelines. Any toxicity requiring dose level modification beyond the second dose modification for fluorouracil or irinotecan may require treatment discontinuation or further modification at the discretion of the Investigator. When a dose reduction is required, no dose re-escalation will be permitted for the duration of study treatment.

Table 8: FOLFIRI Dose Modification Table:

Dose Level*	Irinotecan**	5-Fluorouracil Bolus	5-Fluorouracil Infusion
Full dose	180 (mg/m^2)	400 (mg/m^2)	1200 (mg/m^2/day) (total 2400 mg/m^2)
Modification Level-1	150 (mg/m^2)	200 (mg/m^2)	900 (mg/m^2/day) (total 1800 mg/m^2)
Modification Level-2	120 (mg/m^2)	N/A	600 (mg/m^2/day) (total 1200 mg/m^2)
Modification Level-3	100 (mg/m^2)	N/A	N/A

* If the dose of any component of FOLFIRI is reduced because of potentially-related AEs, subsequent dose increases are not permitted.
** If irinotecan dose is required to be reduced below 100 mg/m^2, lower doses may be used at the discretion of the Investigator.

7.1.5.1. Hematologic Toxicity:

Neupogen/G-CSF may be used at the discretion of the Investigator prior to each dose of FOLFIRI and administration should proceed according to standard guidelines (NCCN/ASCO). Patients not experiencing resolution of neutropenia within 4 weeks at any time during the cycle, may discontinue FOLFIRI treatment.

Prior to each dose of FOLFIRI, the absolute neutrophil count (ANC) and platelet count should be evaluated. If abnormalities are observed, and in the opinion of the Investigator the myelosuppression is most likely a result of FOLFIRI therapy, dose modification is recommended as in Table 9.

Table 9: FOLFIRI Dose Modification for Hematologic Toxicity

Adverse Hematologic Event[1,2,4]	**Treatment Delay**	**Dose Reduction**		
		Irinotecan	**Fluorouracil Bolus**	**Fluorouracil Infusion**
Neutrophils[3] < 1.5 x 10^9/L	Hold treatment until ≥1.5 x 10^9/L	1st Occurrence: Reduce dose to 150 mg/m^2	1st Occurrence: Discontinue 5-FU bolus	1st Occurrence: Continue treatment at full (current) dose
		2nd Occurrence: Reduce dose to 120 mg/m^2		
		3rd Occurrence: Reduce dose to 100 mg/m^2		
Platelets <75 x 10^9/L or Thrombocytopenic bleeding	Hold treatment until ≥75 x 10^9/L	1st Occurrence: Reduce dose to 150 mg/m^2	1st Occurrence: Reduce to 200 mg/m^2	1st Occurrence: Reduce to 900 (mg/m^2/day) (total 1800 mg/m^2) 2nd Occurrence: Reduce to 600 (mg/m^2/day) (total 1200 mg/m^2)
		2nd Occurrence: Reduce dose to 120 mg/m^2		
	If no recovery within 4 weeks, discontinue treatment	3rd Occurrence: Reduce dose to 100 mg/m^2		

[1]Once a dose of any drug is decreased for toxicity re-escalation is not permitted.
[2]May discontinue the regimen if toxicity recurs after 2 dose reductions or if cycle is delayed for >4 weeks.
[3]The above dose modification schedule is applicable for cases of febrile neutropenia (defined as temperature ≥101°F or 38.3°C with a neutrophil count of ≤1000 cells/ml) as well as for cases of Grade 3-4 neutropenia with concomitant infection.
[4]Neupogen/G-CSF may be used at the discretion of the Investigator prior to each dose of FOLFIRI and administration should proceed according to standard guidelines (NCCN/ASCO).

7.1.5.2. Gastrointestinal Toxicity:

Dose modifications for gastrointestinal toxicities expected from FOLFIRI regimen must be performed according to the recommendations in Table 10.

Table 10: FOLFIRI Dose Modification for Gastrointestinal Toxicity

Adverse Gastrointestinal Event[1,2,3]	**Dose Reduction**		
	Irinotecan[4]	**5-Fluorouracil Bolus**	**5-Fluorouracil Infusion**
Grade 1 Diarrhea	Continue treatment at full (current) dose	Continue treatment at full (current) dose	Continue treatment at full (current) dose
Grade 2 Diarrhea	Reduce dose to 150 mg/m^2	Discontinue 5-FU bolus	Continue treatment at full (current) dose
Grade 3 Diarrhea	Reduce dose to 120 mg/m^2	Discontinue 5-FU bolus	Reduce to 900 (mg/m^2/day) (total 1800 mg/m^2)
Grade 4 Diarrhea	Reduce dose to 100 mg/m^2	Discontinue 5-FU bolus	Reduce to 600 (mg/m^2/day) (total 1200 mg/m^2)
Elevation of Total Bilirubin > 1.5 × ULN	Exclude biliary obstruction and consider holding chemotherapy until biliary obstruction is resolved.		

[1]Once a dose of any drug is decreased for toxicity re-escalation is not permitted.
[2]Do not change dose unless diarrhea is intolerable Grade 2. Do not treat until diarrhea is ≤ tolerable Grade 2.
[3]Consideration should be given to the use of an oral antibiotic in patients with persistent diarrhea despite maximal loperamide (up to 16 mg/day) and/or Lomotil (up to 20 mg/day) or if a fever develops in the setting of diarrhea without neutropenia.
[4]Patients with Grade 1-3 diarrhea should be receiving standing anti-diarrheal symptom medications as described in Section 7.1.4 and resumption of irinotecan at modified dose should occur when the diarrhea is reduced to ≤ tolerable Grade 2 while on standing anti-diarrheal symptom medications.

7.1.5.3. Non-Hematologic and Non-Gastrointestinal Toxicity:

Dose modification for other toxicities specified below expected from FOLFIRI regimen should be performed according to the recommendations in Table 11.

Table 11: FOLFIRI Dose Modification for Other Toxicity

Other Adverse Events[1]	Dose Reduction		
	Irinotecan	5-Fluorouracil Bolus	5-Fluorouracil Infusion
Grade 3-4 mucositis or "hand-foot" syndrome	Continue treatment at full (current) dose	Discontinue 5-FU bolus	Continue treatment at full (current) dose
Myocardial infarction or angina pectoris	Continue treatment at full (current) dose	Discontinue 5-FU bolus	Discontinue 5-FU infusion
Grade 2 persistent neurotoxicity or Grade 3 neurotoxicity which recovers prior to next cycle	Continue treatment at full (current) dose	Continue treatment at full (current) dose	Continue treatment at full (current) dose
Grade 3 persistent neurotoxicity, Grade 4 neurotoxicity or Grade 4 other non-hematological toxicity	Dose reduction or treatment discontinuation at the discretion of the Investigator	Dose reduction or treatment discontinuation at the discretion of the Investigator	Dose reduction or treatment discontinuation at the discretion of the Investigator
Other toxicity ≥Grade 2[2,3]	Dose reduction by 1 or more dose levels at the discretion of the Investigator	Dose reduction by 1 or more dose levels at the discretion of the Investigator	Dose reduction by 1 or more dose levels at the discretion of the Investigator

[1]Once a dose of any drug is decreased for toxicity re-escalation is not permitted.
[2]Except anemia, gastrointestinal toxicity, Grade 2 persistent neurotoxicity, Grade 3 neurotoxicity, Grade 4 neurotoxicity, Grade 3-4 mucositis or "hand-foot" syndrome, Grade 4 other non-hematological toxicity and alopecia.
[3]Doses of all 3 drugs or none of the drugs may be reduced depending upon type of event and decision of the Investigator.

When laboratory parameters or AEs indicate that all of the components of the FOLFIRI infusion should be delayed, the FOLFIRI infusion scheduled for that day is not given. Laboratory parameters should be evaluated the following week and repeated weekly until toxicity is resolved to an acceptable level at which time the next FOLFIRI infusion may be administered, marking Day 1 of the subsequent study cycle.

If a toxicity is thought by the Investigator to be related to both BBI-608 and FOLFIRI, then the dose modification rules for both treatment regimens should be followed.

If any or all components of FOLFIRI is/are held or discontinued for toxicities solely related to FOLFIRI, BBI-608 therapy should be continued.

If BBI-608 is permanently discontinued due to toxicity, FOLFIRI therapy should be continued.

7.1.6. Concomitant Medications/Procedures

7.1.6.1. Permitted Treatments

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

Palliative and supportive care is permitted for disease-related symptoms for 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.

Overall, CYP isoenzymes have an insignificant role in the biotransformation of napabucasin. The CYP P450 isoform 1A2 is the predominant isoform involved in the drug's metabolism. Although the following drugs are permitted while on study treatment, all reasonable measures should be done to avoid use of drugs that are strong inhibitors or sensitive substrates of CYP1A2 unless there is medical necessity for their use.

Strong CYP1A2 inhibitors include:

- Ciprofloxacin and other fluoroquinolones
- Fluvoxamine
- Enoxacin
- Zafirlukast

Investigators may refer to the current BBI-608 IB for additional information.

Patients who require use of concomitant medications metabolized by the CYP1A2, 2D6, 2C19, 3A4, and 2C9 enzymes should be monitored, as per drug product label, as use of BBI-608 can inhibit the abovementioned CYP enzymes leading to increased drug concentrations of the enzyme metabolites.

Patients who develop surgically resectable disease with curative intent during study treatment, must hold BBI-608 midnight prior to morning of surgery. FOLFIRI (with or without bevacizumab) components should be held according to the product labels and institutional standards. Following surgical recovery, patients should resume BBI-608 with resumption of oral intake. The decision to resume FOLFIRI following surgery and the timing of FOLFIRI resumption will be made by the Investigator depending on surgical and clinical factors. Patients randomized to either study arm, who discontinue FOLFIRI following surgical resection, will continue study visits once per month (an extended 28-day cycle) for safety assessments.

Although intravenous bisphosphonate use is permitted for patients receiving bevacizumab, per Investigator choice, while on study treatment, all reasonable measures should be done to avoid the use of intravenous bisphosphonates simultaneously or sequentially with bevacizumab in order to mitigate the risk of osteonecrosis of the jaw (ONJ). Patients who have received intravenous bisphosphonates prior to treatment with bevacizumab are also at increased risk of ONJ and should be specifically counseled regarding this risk. Additionally, invasive dental procedures while the patient is receiving bevacizumab treatment also increases the risk of ONJ. As such, it is advised that patients receiving bevacizumab undergo a dental examination and appropriate preventive dentistry prior to start of treatment with bevacizumab.

7.1.6.2. Non-Permitted Treatments

Concurrent chemotherapy, hormonal therapy (except corticosteroids), immunotherapy, biologic therapy, or any other experimental agents should not be given to study patients while on protocol treatment.

7.1.7. Duration of Therapy

Patients may continue to receive protocol therapy as long as they have not experienced any AEs requiring permanent discontinuation of protocol treatment and have not demonstrated disease progression based on RECIST 1.1 criteria. For details concerning toxicity, please consult Section 7.1.4 and Section 7.1.5 . For a complete list of general criteria for stopping study treatment, please see Section 11.

7.1.8. Patient Compliance

Treatment compliance for BBI-608 is defined as the ratio, expressed as a percentage, of the number of capsules (BBI-608) 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 for FOLFIRI is defined as the ratio, expressed as a percentage, of the amount of each of the component drugs administered to a patient (milligrams/m^2) over the course of a time interval to amount of the component IV drug intended to be administered 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.

8. EVALUATION DURING AND AFTER PROTOCOL TREATMENT

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.

8.1. Evaluation During Protocol Treatment

Investigations		Timing
Patient history and Evaluation	Physical examination Vital signs (temperature, blood pressure, heart rate, respiratory rate, O_2 saturation on room air) ECOG Performance status Concurrent medication list Weight	Day 1 of every 14-day study cycle, starting with Cycle 1[1] (+/-3 days) or within 3 days prior to each FOLFIRI infusion
Hematology	CBC + differential, Platelet count	Day 1 of every 14-day study cycle starting with Cycle 1 (+/-3 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 (hematology investigations should be performed within 3 days prior to Day 1 of each study cycle, or within 3 days prior to each FOLFIRI infusion)
Biochemistry	Creatinine, Total Bilirubin, AST, ALT, Alkaline Phosphatase, LDH, Albumin, Potassium, Magnesium, Phosphate	Day 1 of every 14-day study cycle, starting with Cycle 1[1] (±3 days) or within 3 days prior to each FOLFIRI infusion
Urinalysis	Dipstick (including protein, specific gravity, glucose and blood)	
Other Investigations	Serum or urine pregnancy test[2]	Every 28 days starting with Day 1 of Cycle 2 (±3 days)
Adverse Events [3]	Adverse Event evaluation must be done at each study visit[3]	Day 1 of every 14-day study cycle *OR* On each FOLFIRI infusion day
	Adverse Event evaluation by phone[3]	On *Run-in Day 2*
Serious Adverse Events[4]	Serious Adverse Event evaluation will be done from the time of informed consent and for 30 days following the last dose of protocol therapy.	
Cardiology Assessment	ECG	Within 2 hours of completion of 5-fluoropyrimidine bolus infusion on first day of FOLFIRI treatment and as clinically indicated thereafter

Investigations		Timing
Radiology & Imaging	CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria[5,9]	Every 8 weeks (every 56 days) after randomization[5] (±5 days) until 6 months of treatment and every 12 weeks (every 84 days) thereafter until objective disease progression, withdrawal of consent or death
Correlative Studies	Submission of blood samples[6, 8]	At Day 1 of Cycle 3 (±3 days)
Sparse PK Collection	Submission of blood plasma samples to central lab[6, 8]	At Day 1 of Cycle 2 and Day 1 of Cycle 3 (corresponding to the 2nd and 3rd FOLFIRI infusion days)
Quality of Life (Appendix 5)	EORTC QLQ-C30[7, 8]	At Day 1 of Cycle 3, Day 1 of Cycle 5, Day 1 of Cycle 7, Day 1 of Cycle 9 and Day 1 of Cycle 13 (±3 days)
FOLFIRI Administration	IV FOLFIRI infusion	Day 1 of every 2-week (14 day) study cycle (±3 days)

1 Patients are to be assessed every 2 weeks (14 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 version 4.0 (see Appendix 4). Adverse event assessment by phone on *Run-in Day 2* is only applicable to patients receiving BBI-608.
4 Serious adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix 4).
5 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. Tumor evaluations will continue until progressive disease is documented (as described in Section 9). 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, tumor measurements and assessment must be reported.
6 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual.
7 To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence.
8 If these assessments were performed at a planned Cycle Day 1, but laboratory parameters delayed the administration of FOLFIRI and therefore delayed the Cycle Day 1, these assessments do not need to be repeated at the next visit and the original assessments can be used.
9 Copies of imaging assessments may be requested.

8.2. Evaluation After Protocol Treatment Discontinuation

Investigations		Timing
Patient History and Evaluation	Physical examination Vital signs (temperature, blood pressure, heart rate, respiratory rate, O_2 saturation on room air) Weight + ECOG Performance status Subsequent cancer therapy[1] Concurrent medication list	At the first regularly scheduled 4-week assessment at which the patient has been off study therapy for a minimum of 28 days. (±3 days)
Adverse Events [2]	Adverse Event evaluation must be done at each study visit[2]	
Serious Adverse Events [3]	Serious Adverse Event evaluation will be done from the time of informed consent and for 30 days following the last dose of protocol therapy.	
Overall Survival	Assess for survival of patient[4]	At 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. (±7 days)
Other Investigations	Serum or urine pregnancy test[5]	At the first regularly scheduled 4-week assessment at which the patient has been off study therapy for a minimum of 28 days (±3 days)
Hematology	CBC + differential, Platelet count	
Biochemistry	Creatinine, Total Bilirubin, AST, 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 (±3 days)
Radiology & Imaging	CT/MRI scan as per baseline assessment with tumor measurement and evaluation by RECIST 1.1 criteria[6]	Every 8 weeks (56 days) after randomization until 6 months of treatment and every 12 weeks (every 84 days) thereafter until objective disease progression is documented, withdrawal of consent or death.[6] (±5 days)
Correlative Studies	Submission of blood samples[7]	At first regularly scheduled 4-week assessment at which the patient has been off study therapy for a minimum of 28 days (±3 days)
Quality of Life (Appendix 5)	EORTIC QLQ-C30[8]	At first regularly scheduled 4-week assessment at which the patient has been off study therapy for a minimum of 28 days (±3 days)

Investigations	Timing
1 After protocol treatment discontinuation. 2 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix 4). Adverse events relevant only to cancer or current/previous cancer treatments will be captured. Attribution of adverse events will continue to be recorded following treatment discontinuation. 3 Serious adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix 4). 4 In the event that patient is unable to attend clinic, post-progression follow-up may be by means of telephone contact. 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 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. Tumor evaluations will continue until progressive disease is documented (as described in Section 9). If a patient discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain this assessment on the same schedule until progression is observed. 7 Details for collection, processing, storing and shipping these samples will be provided in a separate procedure manual. The sample will be collected only if the patient discontinues protocol treatment prior to 4 weeks of therapy. 8 To be completed in clinic. Questionnaires should be completed prior to any interactions with clinical team to avoid any influence. Questionnaire will be collected in the post-treatment discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.	

9. CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

9.1. Definitions

9.1.1. Evaluable for Adverse Events

All patients who have received at least 1 dose of study drug (BBI-608 or FOLFIRI) will be evaluable for AEs from the time of their first dose of BBI-608.

9.1.2. Evaluable for Overall Survival

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.

9.1.3. Evaluable for Progression Free Survival

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 tumor 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 tumor 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.

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

9.1.4. Evaluable for Objective Response Rate

Patients with measurable disease by RECIST 1.1 at randomization will be included in the analysis of ORR which is defined as a composite of PR and CR as classified according to the definitions set out in Section 9.2.5 *[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.

9.1.5. Evaluable for Disease Control Rate

Patients who have measurable disease by RECIST 1.1 at randomization will be included in the analysis of DCR which is defined as a composite of SD, PR, and CR as classified according to the definitions set out in Section 9.2.5 *[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.

9.1.6. Evaluable for Quality of Life Assessment

All patients who have completed the baseline quality of life questionnaire and at least 1 other QoL questionnaire are evaluable (Appendix 5).

9.1.7. pSTAT3(+) Subpopulation, the pSTAT3(-) Subpopulation and pSTAT3(Unknown) Subpopulation

The pSTAT3 subpopulations will be defined by the results of a Clinical Trial Assay (CTA) for a specimen with an age within a defined cut-section stability (CSS) window (6 months at interim analysis or the final CSS window at final analysis). Specimen age is defined as the time interval between the sectioning and staining of the specimen.

A patient with positive pSTAT3 status within a defined CSS window is the one with pSTAT3 positive designated by CTA with specimen age up to 6 months at interim analysis or up to the final CSS window at final analysis.

A patient with negative pSTAT3 status within a defined CSS window is the one with pSTAT3 negative designated by CTA with specimen age up to 6 months at interim analysis or up to final CSS window at final analysis.

A patient with pSTAT3 status unknown within a defined CSS window will include patients with specimen was not submitted for testing, if the specimen is identified as non-evaluable upon pathology evaluation, if the specimen age is out of the defined CSS window, or if missing due to any other reasons.

Evolving knowledge of Cut-Section Stability (CSS) for pSTAT3 Biomarker Assay

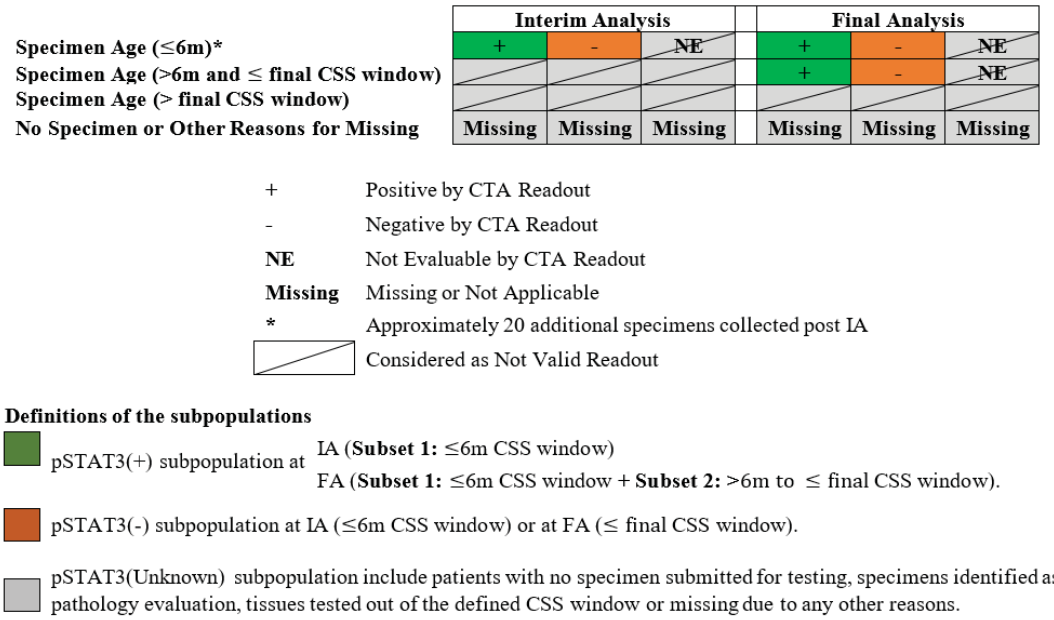
The pSTAT3 IHC D3A7 CTA was used for this study to identify the pSTAT3(+) patient population. This biomarker assay is an immunohistochemistry-based method intended for use in detection of pSTAT3 protein in cut tissue sections. A cut-section stability (CSS) study is ongoing to establish the final pSTAT3 CSS window which is expected to be completed prior to the final analysis.

At the time of the interim analysis in the CanStem303C study, preliminary assessments from the ongoing CSS study were indicative of a stability of at least 6 months for slides stored at -20 degrees Celsius, the same manner in which CanStem303C specimens have been stored. The interim analysis, therefore, included pSTAT3 biomarker status results for only those patients with specimens age up to a CSS of 6 months.

However, after the interim analysis in the CanStem303C study, the biomarker data monitoring from the ongoing CSS study indicates that samples will likely remain stable at -20 degrees Celsius for greater than 6 months. This indicates that the final CSS window could be longer than 6 months and up to 15 months. As a result of evolving knowledge of CSS window, a patient with unknown pSTAT3 status that was due to a specimen out of the 6-month CSS window may have a pSTAT3 positive or negative status at the final analysis. Therefore, it is expected that will be fewer patients with unknown pSTAT3 status within the final CSS window at the final analysis compared to the interim analysis with 6 month CSS window.

Figure 1 below shows the pSTAT3 subpopulations components at the interim and final analysis.

Figure 1: pSTAT3 Subpopulations Components at Interim Analysis and Final Analysis



Note: All specimens will be tested only one time regardless of final stability window.

9.2. 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 Tumors) committee.

9.2.1. Measurable Disease

Measurable tumor lesions are defined as those that can be accurately measured in at least 1 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 tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

9.2.2. 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.

9.2.3. Target Lesions

When more than 1 measurable tumor 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 Section 9.2.4). At baseline, the sum of the target lesions (longest diameter of tumor 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.

9.2.4. 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”.

9.2.5. 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 tumor 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 ≥5mm. Appearance of new lesions will also constitute PD (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 tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor 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 12: 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	tumor 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 ≥6 weeks 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	tumor 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.

9.3. 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).

9.4. 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).

9.5. 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."

Additionally, for optimal tumor assessment scanning options are listed below in the decreasing order of preference:

Order of Preference	Scanning Option
1	Chest-Abdomen-Pelvis CT with oral and IV contrast
2	Chest CT without IV contrast PLUS MRI Abdomen-Pelvis with oral and IV contrast[1]
3	Chest-Abdomen-Pelvis CT with oral contrast[2]

[1]If Iodine contrast media is medically contraindicated.
[2]If Iodine contrast media is medically contraindicated and MRI cannot be performed.

9.5.1. Clinical Lesions

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

9.5.2. 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 >20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

9.5.3. 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).

9.5.4. 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.

9.5.5. Endoscopy/Laparoscopy

The utilization of these techniques for objective tumor 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.

9.5.6. Cytology/Histology.

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

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

10. 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) and serious adverse event (SAE) reporting (version can be found in Appendix 4).

All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program (CTEP) web site:

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All SAEs defined per ICH guidelines (Section 10.1) and other AEs must be recorded on the eCRFs. All SAEs must be reported to the Sponsor within 24 hours (Section 10.2).

10.1. Definition of a Protocol Reportable Serious Adverse Event

All SAEs must be reported in an expedited manner (see Section 10.2 for reporting instructions). These include events occurring from the time the patient signs consent until 30 days after last protocol treatment administration. Determination of relationship between the event and study drug should be made by a qualified physician investigator.

An SAE is an AE 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)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

Note: clinically significant test results should be recorded on the AE CRF using the appropriate CTCAE description and grading scale.

10.2. Serious Adverse Event Reporting Instructions

SAE reporting will commence following the signature of the informed consent and continue for 30 days following the last dose of protocol treatment. Any SAE occurring following patient signature of informed consent and prior to patient randomization must be submitted to the Sponsor for review and response prior to patient randomization and/or study drug administration, even if the patient completely recovered from the SAE. Additionally, any SAE occurring at any time following administration of the final dose of protocol treatment that is suspected to be related to study treatment must be reported.

All SAEs (Section 10.1) must be reported using the SAE Report Form for this trial.

Within 24 hours:	Submit Initial Serious Adverse Event Report
Within 7 days:	Submit Follow-up Serious Adverse Event Report updated with as much detail as possible.

Detailed instructions for the submission of SAE Reports will be provided separately.

10.3. Procedures in Case of an Overdose

Use of BBI-608 in doses in excess of that specified in the protocol should be reported in the following manner:

If an AE(s) is associated with ("results from") the overdose of BBI-608, the overdose and AE are reported on the SAE Report Form, even if no other criteria for seriousness are met. The SAE Report Form should be submitted within 24 hours. The overdose should also be recorded on the relevant AE form in the eCRF using the term "accidental or intentional overdose with adverse effect."

If the overdose of BBI-608 is not associated with an AE, the overdose is reported as a non-serious AE, on the relevant AE form in the eCRF within 24 hours, using the event term "accidental or intentional overdose without adverse effect." The clinical research associate responsible for the investigational center should also be notified of the event within 24 hours.

Investigators/site personnel are to consult the local, approved product labels for each of the components of the FOLFIRI treatment regimen for guidance on the definition of an overdose of components of this regimen as well as for guidance on reporting of any AE or SAE associated with overdose of any of the FOLFIRI components. Overdose of FOLFIRI should also be reported to the Sponsor in accordance with overdose reporting guidelines in Section 10.3).

10.4. Other Protocol Reportable Events – Pregnancy/Exposure Reporting

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.

10.4.1. Pregnancy Prevention

WOCBP and males who are enrolled in the trial must be informed of the requirement to use contraception as outlined in the eligibility criteria (Section 4.1). 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.

10.4.2. 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 BBI-608 and FOLFIRI. Monitoring should continue until conclusion of the pregnancy. The same should occur for female partners of a male participant, or any female exposed to BBI-608 when appropriate and compliant with local policy.

10.4.3. Pregnancy/Exposure Reporting

The Investigator is required to report to the Sponsor any pregnancy where the embryo/fetus could have been exposed to BBI-608. This includes 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 until 30 days in female patients and until 90 days in partners of male patients, after the completion of BBI-608 must also be reported as well as pregnancies occurring until 180 days of the final FOLFIRI dose for female and male patients.

The Investigator is required to inform the Sponsor 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 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.

10.5. Responsibility for Reporting Serious Adverse Events to Regulatory Agencies

Boston Biomedical, or the delegated CRO, will provide expedited reports of SAEs to FDA and other 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 BBI-608 (suspected unexpected serious adverse reaction [SUSAR]):

- **Unexpected** AEs are those which are not consistent in either nature or severity with the reference safety information contained in the Investigator’s Brochure
- AEs considered **related to protocol treatment** are those events which have a reasonable possibility of being related to BBI-608.

Boston Biomedical will determine which SAEs meet the criteria for regulatory reporting.

10.6. Reporting Safety Reports to Investigators

Boston Biomedical, or the delegated CRO, will notify Investigators of all Safety Reports (SAEs) from this trial and Safety Updates from other clinical trials that are reportable to regulatory authorities. This includes all SAEs that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment.

11. PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

11.1. Criteria for Discontinuing Protocol Treatment

Patients should stop protocol treatment in the following instances:

- Progressive Disease (see Section 9.2.5).
- 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
- Request by the patient

If a patient discontinues protocol treatment for a reason other than objective progression, every effort should be made to obtain tumor evaluations on the same schedule until progression is observed.

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.

11.2. Duration of Protocol Treatment

Patients may continue to receive protocol therapy as long as they have not experienced any AEs requiring permanent discontinuation of study medication and have not demonstrated disease progression based on RECIST criteria.

As BBI-608 targets cancer stem cells, it is possible that continued therapy after PD per RECIST 1.1 may provide clinical benefit. If no other standard therapies are available at the time of disease progression based on RECIST 1.1 criteria, and the patient has not experienced any AEs requiring permanent discontinuation, BBI-608 may be continued in monotherapy.

11.3. Therapy After Protocol Treatment is Stopped

Treatment after all protocol therapy has been discontinued is at the discretion of the Investigator. Information on post-study anti-cancer treatment will be collected in this study.

11.4. Follow-up Off Protocol Treatment

Follow-up will continue after treatment completion according to the plan described in the protocol (see Section 8.2). 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. CENTRAL REVIEW PROCEDURES, TISSUE COLLECTION, AND CORRELATIVE STUDIES

12.1. Central Radiology Review

There will be no central radiology review for this study.

12.2. Central Pathology Review

Archival tumor tissue samples will be sent a central pathology laboratory for testing for pSTAT3 status. Tissue Collection

12.2.1. Protocol-Mandated Biomarker Analyses

The submission of a representative diagnostic tumor tissue for the biomarker and a blood sample for correlative studies is mandatory for participation in this trial. Where local center regulations prohibit submission of blocks of tumor tissue, two 2 mm cores of tumor from the block and 10 to 30 unstained slides of representative tumor tissue are requested. Where two 2 mm cores of tumor from the block are not available, 10 to 30 unstained slides of whole sections of representative tumor tissue are requested. The biomarker tissue samples will be analyzed with the pSTAT3 IHC prototype assay as an investigational use only (IUO). Once the market-ready assay (MRA) is available, all patient samples will be re-analyzed to confirm the results using the prototype assay. Where no previously resected or biopsied tumor tissue exists, on the approval of the Sponsor/designated CRO, the patient may still be considered eligible for the study.

After patient consent, blood sample and paraffin tumor blocks will be the preferred tissue material to collect. If tumor blocks are unavailable, then two 2 mm cores of tumor from the block and 10 to 30 specimen slides are preferred. If two 2 mm cores of tumor from the block are not available, 10 to 30 unstained slides of whole sections of representative tumor tissue are acceptable. 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.

Samples may also be used for research purposes but will not be sold. Patients will not be identified by name. Patient samples will be blinded, and the only identification of tissue will be by a patient study number assigned at the time of randomization to the trial.

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

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

12.3. Sparse Pharmacokinetic Plasma Sample Collection (Arm 1 Only)

Plasma samples for sparse pharmacokinetics (PK) analysis will be obtained from all patients randomized to Arm 1 (BBI-608 with FOLFIRI) at the study visits occurring on Day 1 of Cycle 2 and Day 1 of Cycle 3 (corresponding to FOLFIRI infusion days). Patients randomized to Arm 2 (FOLFIRI) will not undergo plasma collection for PK analysis.

Day 1 (Cycle 2) Study Visit:

The Day 1 (Cycle 2) visit should be scheduled prior to 10 AM. On the day of this visit, patients should be instructed to wait to take their first daily dose of BBI-608 until they arrive in clinic. After arrival in the clinic, but approximately 5 minutes prior to administration of the first daily dose of BBI-608, a plasma sample will be obtained. Irinotecan infusion will be started immediately following bevacizumab infusion (for patients who will receive bevacizumab together with FOLFIRI per investigator decision) or approximately 2 hours after BBI-608 administration if bevacizumab is not administered. A second plasma sample will be obtained within 1 to 4 hours after administration of the first daily dose of BBI-608.

Day 1 (Cycle 3) Study Visit:

The Day 1 (Cycle 3) visit should be scheduled prior to 10 AM. On the day of this visit, patients should be instructed to wait to take their first daily dose of BBI-608 until they arrive in clinic. After arrival in the clinic, but at least 60 minutes prior to administration of the first daily dose of BBI-608, a plasma sample will be obtained. Irinotecan infusion will be started immediately following bevacizumab infusion (for patients who will receive bevacizumab together with FOLFIRI per investigator decision) or approximately 2 hours after BBI-608 administration if bevacizumab is not administered. A second plasma sample will be obtained within 5 to 8 hours after administration of the first daily dose of BBI-608.

For all days during which a plasma sample is obtained for PK analysis, the precise time of all doses of BBI-608 (on the day of sampling and the day prior), the precise time of the initiation of irinotecan administration, 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 separate Sparse PK sampling laboratory manual for this study.

13. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

13.1. Objectives and Design

The primary objectives of this study are to compare OS of patients with metastatic pretreated CRC treated with BBI-608 plus biweekly FOLFIRI (Arm 1) versus biweekly FOLFIRI (Arm 2) in the General Population and in the pSTAT3(+) Subpopulation.

Secondary objectives for this study include comparisons of PFS in the General Population and in the pSTAT3(+) Subpopulation, Objective Response Rate in the General Population and in the pSTAT3(+) Subpopulation, Disease Control Rate in the General Population and in the pSTAT3(+) Subpopulation, Quality of Life Assessment in the General Population and in the pSTAT3(+) Subpopulation, and adverse events in the 2 treatment arms.

This is a multi-center, prospective, open-label, randomized, adaptive design Phase 3 trial of the cancer stem cell pathway inhibitor BBI-608 plus standard bi-weekly FOLFIRI (Arm 1) versus standard bi-weekly FOLFIRI (Arm 2) in patients with previously treated mCRC. Patients will be randomized to receive either BBI-608 plus standard bi-weekly FOLFIRI, (Arm 1) or standard bi-weekly FOLFIRI (Arm 2) in a 1:1 ratio and will be stratified by geographical region (North America/Western Europe/Australia, Japan/Korea, *versus* rest of the world), time to progression from start of first line therapy (<6 months *versus* ≥6 months), *RAS* mutation status (mutant *versus* wild type), bevacizumab as part of protocol treatment (yes *versus* no), and location of the primary tumor (left colon *versus* right colon). Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible.

13.2. Study Endpoints and Analysis

13.2.1. Primary Endpoint for the Study

Overall Survival in the General Population and pSTAT3(+) Subpopulation

Overall survival in the General Population and the pSTAT3(+) Subpopulation, the primary endpoints of this study, are defined as the time from randomization to death from any cause. Patients who are alive at the time of the interim or the final analyses or who have become lost to follow-up will be censored on the date the patient was last 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 (listed in Section 3.1) for the General Population and unstratified log-rank test for the pSTAT3(+) Subpopulation.

Sensitivity analyses based on stratified Cox proportional hazards model will also be performed for the General Population or/and in the pSTAT3(+) Subpopulation depending on the decision from interim analysis. Geographical region (North America/Western Europe/Australia, Japan/Korea, *versus* rest of the world), time to progression on first line therapy from start of first

line therapy (<6 months *versus* ≥6 months), *RAS* status (mutant *versus* wild type), bevacizumab as part of protocol treatment (yes *versus* no), and location of the primary tumor (left colon *versus* right colon) will be the stratification factors to define the stratified Cox proportional hazards model.

Subgroup analysis and the corresponding forest plot analysis may be performed using the stratification factors mentioned above as well as the following factors:

- Age (<65 *versus* ≥65)
- Sex (male *versus* female)
- Presence of liver metastases (yes *versus* no)
- Primary tumor site (colon *versus* rectum)
- ECOG Performance Status (0 *vs* 1)
- Race (White, Black, Asian, other)
- Country (Canada, USA, Western Europe, Australia, Japan, Korea, China, others)
- Microsatellite Instability (MSS *vs* MSI-L *vs* MSI-H *vs* MSI-V)
- Prior Bevacizumab: Yes / No

13.2.2. Key Secondary Endpoints

The following key secondary outcomes will be assessed:

Progression-Free Survival in the General Population and the pSTAT3(+) Subpopulation

Progression-free survival is defined as the time from randomization to the first objective documentation of disease progression or death, whichever comes first. If a patient has not progressed or died at the time of the interim or final analysis, PFS will be censored on the date of the last tumor assessment. This includes patients who are lost to follow-up or have withdrawn consent. The progression free survival 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 for the General Population and unstratified log-rank test for the pSTAT3(+) Subpopulation.

Disease Control Rate in the General Population and the pSTAT3(+) Subpopulation

Disease control rate 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 patients with measurable disease by RECIST 1.1 at randomization. For the General Population, differences of DCR between the two arms will be compared using a 1-sided Cochran-Mantel-Haenszel test stratified for stratification factors. Treatment difference of DCR and its 95% confidence interval based on harmonic mean method adjusting stratification factors will be provided. For the pSTAT3(+) Subpopulation, differences of DCR between the two arms will be compared using a 1-sided Z-test via normal approximation. Treatment difference of DCR and its 95% confidence interval based on normal approximation (unstratified) will be provided.

Objective Response Rate in the General Population and the pSTAT3(+) Subpopulation

Objective response rate is defined as the proportion of patients with a documented complete response and partial response (CR + PR) based on RECIST 1.1. The primary estimate for ORR will be based on patients with measurable disease by RECIST 1.1 at randomization. Differences of ORR between the two arms will be analyzed the same as DCR for the General Population and for the pSTAT3(+) subpopulation.

13.2.3. Other Secondary Endpoints

Quality of Life Analysis in the General Population and the pSTAT3(+) Subpopulation

The QoL of patients will be assessed using EORTC QLQ-30 while the patient remains on study treatment (FOLFIRI with or without BBI-608) as per Section 8.1. The EORTC QLQ-30 is a self-administered cancer specific questionnaire with multi-dimensional scales (Appendix 5). It consists of both multi-item scales and single item measures, including 5 functional domains, a global quality of life domain, 3 symptom domains, and 6 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 BBI-608 plus FOLFIRI versus FOLFIRI 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 (Appendix 5). 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 endpoints in QoL analysis are the mean EORTC QLQ-C30 QoL change scores from baseline at Time 2 (Cycle 5 Day 1) and Time 4 (Cycle 9 Day 1) for the physical function and global health status/quality of life subscale scores. Wilcoxon tests will be used to compare the difference at each of these 2 timepoints between 2 treatment arms for each of these 2 subscales. The proportion of patients in either arm with at least a minimum of 10-unit(s) deterioration in change scores at both Cycle 5 Day 1 and Cycle 9 Day 1 will be summarized.

Safety Analysis

All patients who have received at least 1 dose of study treatment (BBI-608 or FOLFIRI) will be included in the safety analysis. The incidence of AEs will be summarized by type of AE and severity using the NCI Common Terminology Criteria for Adverse Events Version 4.0. The Exact test (*Chan 1999*) may be used when comparing AE rate between treatment arms.

13.3. Sample Size and Duration of Study

The primary study endpoints are OS for the General Population and the pSTAT3(+) Subpopulation. The hypotheses (the General Population and the pSTAT3(+) Subpopulation) for the study are as follows:

For the General Population, the null and alternative hypotheses are:

H_{10}: BBI-608 + FOLFIRI ≤ FOLFIRI in the General Population

H_{11}: BBI-608+FOLFIRI > FOLFIRI in the General Population

For the pSTAT3(+) Subpopulation, the null and alternative hypotheses are:

H_{20}: BBI-608 + FOLFIRI ≤ FOLFIRI in the pSTAT3(+) Subpopulation

H_{21}: BBI-608+FOLFIRI > FOLFIRI in the pSTAT3(+) Subpopulation

Sample Size and Power in the General Population

For the General Population, this study is designed to have a power of 90% and a 1-sided α=0.025 to detect a 20% reduction in the risk of death (HR 0.80 which corresponds to an increase of median survival from 12.54 to 15.68 months) The above design assumptions account for the anticipated varying control hazard rates for the bevacizumab versus no-bevacizumab stratification levels. It is assumed that approximately 30% of subjects will receive bevacizumab with expected mOS for the control arm FOLFIRI+bevacizumab subjects being 13.66 months while 70% of the subjects will not receive bevacizumab and have expected mOS of 12.06 months [Van Cutsem 2012]. Without adjusting for multiplicity, it is estimated that 850 events in the General Population will be required to detect this reduction, which would be observed by randomizing 1250 patients (General Population) over 26 months with patient follow up for an additional 14 months, for a total study duration of 40 months. It is anticipated that up to 5% dropout rate will occur over the entire study.

Sample Size and Power in the pSTAT3(+) Subpopulation

According to the preliminary data from Studies BBI608-101, CO.23, BBI608-201, BBI608-224, and BBI608 246, of the 599 patients with biomarker samples in the pooled analysis, 241 patients were pSTAT3(+), the pSTAT3(+) prevalence was estimated to be around 40% (95% CI: 36%, 44%). If considering a lower boundary of 36% as the biomarker positive prevalence in the current study, and proportional to the total deaths events in the General Population, there would be 310 (approximately 36% of 850) events in the pSTAT3(+) Subpopulation.

For the pSTAT3(+) Subpopulation, without adjusting for multiplicity, and assuming 310 events, there will be approximately 88% nominal power at 1-sided α=0.025 to detect a 30% reduction (HR [BBI-608+FOLFIRI vs FOLFIRI] = 0.70) in the risk of death in the pSTAT3(+) Subpopulation.

Overall Power of the Study

Assuming at the final analysis there are 850 events in the General Population and 310 events in the pSTAT3(+) Subpopulation, considering multiplicity adjustment (Section 13.6), the overall power for the entire study which succeeds either in terms of OS in the General Population or in the pSTAT3(+) Subpopulation or both, is approximately 90%, assuming that the true OS hazard ratio in the General Population is 0.80 and that in the pSTAT3(+) Subpopulation is 0.70.

13.4. Safety Monitoring

Adverse events will be monitored on an on-going basis by central review.

13.5. Interim Analysis

An interim analysis will be conducted when 425 deaths occur (50% of total number of 850 deaths) in the General Population for the purpose of decision rules of futility, population and hypothesis selection, and event count adjustment (Figure 2). The OS results will be evaluated by the Data Safety and Monitoring Board (DSMB). Additionally, the DSMB will review safety

during conduct of the study. The role and responsibility of the DSMB will be defined in a separate Charter. The recommendations from DSMB on the study design and conduct will be based on the following decisions:

- Futility stopping: terminate the trial due to lack of efficacy (futility) or terminate pSTAT3(-) and pSTAT3 status unknown subpopulation
- Patient population and hypothesis selection: select the most appropriate patient population and hypothesis (hypothesis in General Population, and/or hypothesis in pSTAT3(+) Subpopulation) for evaluating the significance of the treatment effect at the final analysis
- Event count adjustment: remain the current events size or increase the target number of events in 1 of or both pre-defined patient populations

The details decision rules are described as following:

Futility stopping rule: Perform an early assessment of the efficacy profile of BBI-608+FOLFIRI *vs* FOLFIRI in the 2 pre-defined patient populations and terminate the trial due to lack of efficacy (futility) if there is no evidence of treatment benefit in either population.

The decision rules will be applied simultaneously based on the observed hazard ratios at interim analysis:

- HR_0: Hazard Ratio (BBI-608+FOLFIRI vs FOLFIRI) in the General Population.
- HR_+: Hazard Ratio (BBI-608+FOLFIRI vs FOLFIRI) in the pSTAT3(+) Subpopulation.
- $HR\_$: Hazard Ratio (BBI-608+FOLFIRI vs FOLFIRI) in the pSTAT3(-) Subpopulation.

If HR_+: > c_1 and HR_0: > c_2, then the trial may be stopped due to lack of efficacy.

If HR_+: ≤ c_1 and $HR\_$> c_3, then continue the trial for pSTAT3(+) Subpopulation only and perform the final analysis in the pSTAT3(+) Subpopulation. Here c_1= c_2= c_3=1 are futility boundaries for the pSTAT3(+) Subpopulation, the General Population and the pSTAT3(-) Subpopulation respectively.

Patient population and hypothesis selection rule: Select the most appropriate patient population and hypothesis for evaluating the significance of the treatment effect at the final analysis.

The patient population selection rules are based on futility analysis and the interaction condition introduced in [*Millen 2012*]. In this trial, if the General Population continues after interim analysis, the interaction condition will be evaluated by comparing the ratio of $HR_+/HR\_$ with pre-specified threshold of c_4 where c_4 will be set to 0.9. If $HR_+/HR\_ > c_4$ which indicates the treatment effect in the pSTAT3(+) Subpopulation is comparable to pSTAT3(-) Subpopulation, the hypothesis for the General Population only (the broad indication) would be appropriate. On the other hand, if $HR_+/HR\_ \leq c_4$, which indicate the pSTAT3(+) Subpopulation has substantial improvement compared to the pSTAT3(-) Subpopulation, both hypotheses of the pSTAT3(+) subpopulation and the General Population would be considered.

If only the pSTAT3(+) Subpopulation is continued, only the hypothesis of the pSTAT3(+) Subpopulation will be tested, and no interaction check will be performed.

Event count adjustment rule: Increase the target number of events in 1 of or both pre-defined patient populations to improve the probability of success in the trial.

Within each patient population (General Population or pSTAT3(+) Subpopulation), conditional power is defined as the probability of establishing a significant OS effect at the final analysis conditional upon the interim analysis data at a 1-sided α=0.025. Conditional power is computed within each patient population using the population-specific hazard ratio observed at the interim analysis before an event count adjustment. A closed-form expression for conditional power is provided in Appendix 6. The event count adjustment rule will be defined by identifying an optimal balance between the competing goals of increasing conditional power and reducing the number of events. The event count adjustment may also consider other factors including potential clinical benefits and operational feasibility. The details of the event count adjustment rule will be provided in a separate document and be available to DSMB and other unblinded staff as appropriate for recommendation and/or decision for the interim analysis results. In the event that the event count for pSTAT3(+) Subpopulation is to be increased, the protocol may be amended to reflect this change.

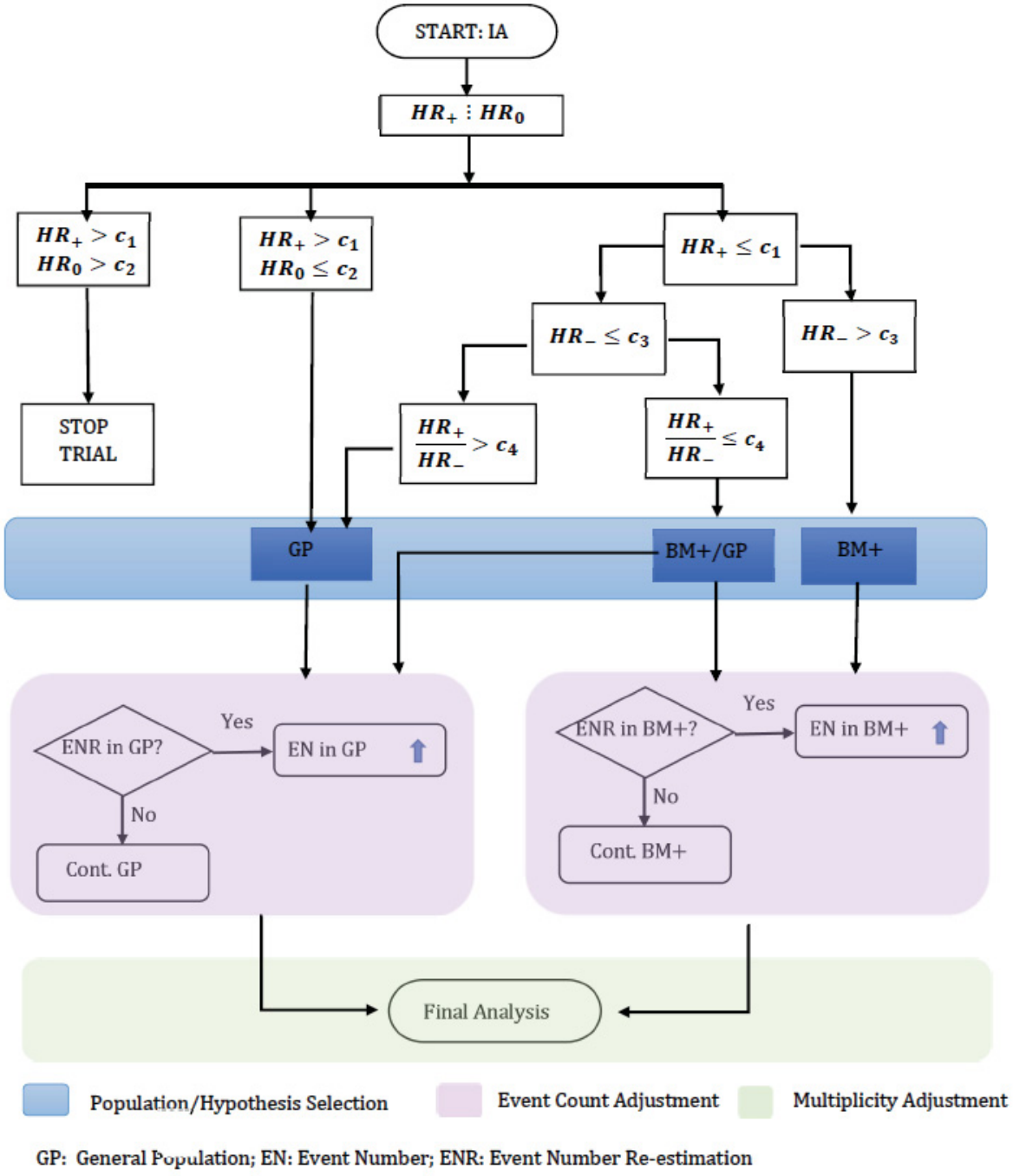
If the final analysis is performed in both the General Population and the pSTAT3(+) Subpopulation, the number of events in the trial will be driven by that in the General Population or in the pSTAT3(+) Subpopulation, whichever comes last.

13.6. Multiplicity Adjustment

To address multiplicity introduced by the analysis of several endpoints (primary endpoint and key secondary endpoints), analysis of the 2 patient populations (General Population and pSTAT3(+) Subpopulation), and data-driven design changes, a Hochberg-based gatekeeping procedure will be implemented [*Dmitrienko (2011, 2013)* and *Kordzakhia (2018b)*]. The hypothesis testing for the key secondary endpoints will follow the order of PFS, DCR, and ORR in both the General Population and the pSTAT3(+) Subpopulation.

The gatekeeping procedure will be applied in conjunction with the combination function approach at the final analyses to ensure strong Type I error rate control. A description of the multiplicity adjustment procedure is provided in Appendix 6.

Figure 2: Adaptive Study Design Schema



GP: General Population; EN: Event Number; ENR: Event Number Re-estimation

13.7. Pharmacokinetic Analyses

13.7.1. Sparse Pharmacokinetic Analysis

Plasma BBI-608 concentrations determined from sparse PK samples will be listed by day within cycle, nominal time, and dose in the case of dose reduction, if appropriate. The listing will include actual sampling time relative to the BBI-608 dose administered on the day of the PK sample collection. If necessary, BBI-608 concentration data may also be included in a population PK analysis that will be subsequently used to conduct exposure-response modeling. The results of population PK analysis and exposure response modeling will be reported in a separate document.

14. PUBLICATION

Boston Biomedical Inc. acknowledges that the Investigator(s) have certain professional responsibilities to report to the scientific community on findings in clinical investigations they conduct. A Principal Investigator shall have the right to publish the results of research performed under this protocol, provided such publication does not disclose any Confidential Information or trade secrets of Boston Biomedical (other than the clinical results).

If the Study is conducted as part of a multi-center protocol, Principal Investigator agrees not to independently publish their findings except as part of an overall multi-center publication. No other publication is allowed before the primary peer-reviewed scientific publication

The primary author agrees to, prior to submitting a manuscript, abstract, or any other written or oral presentation describing the Results for publication or presentation, forward to Boston Biomedical a copy of the item to be submitted for publication or presentation no less than 45 days prior to their submission. Upon request by Boston Biomedical, the primary author agrees to withhold such publication an additional 30 days to permit the preparation and filing of related patent applications. In addition, Boston Biomedical shall have the right to require the primary author to delete from any publication or presentation any Confidential Information (other than the Clinical Data) of Boston Biomedical and to require that any publication or presentation concerning the Study acknowledge the Sponsor's support.

14.1. Research Outside the Terms of this Protocol

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

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

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

15. ETHICAL, REGULATORY, AND ADMINISTRATIVE ISSUES

15.1. Regulatory Considerations

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

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

Any changes to the protocol, including any amendments to the patient information, informed consent, quality of life forms, and any other patient study-related documents, will require the Sponsor to submit to the Regulatory Authorities as well as to the Ethics Committees. Further, changes outlined in such an amendment will not be implemented prior to receiving approval from the Regulatory Authority and Ethics Committee.

15.2. 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, color, 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), 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 Institutional Review Board (IRB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and IRB 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.

Centers are expected to ensure compliance with local IRB or institutional policy regarding participation of vulnerable persons/groups. It is the center's responsibility to ensure compliance with all local SOPs.

Persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited to this study. 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 IRB (if applicable).

Subjects who were competent at the time of enrollment 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. The Sponsor 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.

15.3. Obtaining Informed Consent

Informed consent will be obtained for each participant/potential participant in this trial, in accordance with ICH-GCP Section 4.8. The center is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, the Sponsor 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. The Sponsor recognizes that in many centers 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.

The Sponsor requires that each participant sign a consent form prior to their enrolment in the study to document his/her willingness to take part. The Sponsor 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.

The Sponsor allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local center. Centers 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.

15.3.1. 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.

15.4. Discontinuation of the Trial

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

If this trial is discontinued at any time by the center (prior to closure of the trial by the Sponsor), it is the responsibility of the Principal Investigator to notify the Sponsor of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the Sponsor or locally by the center, it is the responsibility of the Principal Investigator to notify the local Institutional Review Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

Following trial closure after demonstrating overall survival benefit, and until the time that BBI-608 is commercially available, all patients randomized on the trial may have an opportunity to receive treatment with BBI-608; provided, that the Principal Investigator has determined that such continued treatment would be in the best interest of the patient, and subject to approval by the applicable regulatory authorities. This may be done via a new, open label extension study, requiring additional regulatory approval, or in another manner as determined by the Sponsor.

15.5. Retention of Patient Records and Study Files

All essential documents and study data must be maintained in accordance with ICH-GCP.

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

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

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

The Sponsor will inform the Investigator/Institution as to when the essential documents no longer need to be retained.

15.6. On-Site Monitoring/Auditing

In addition to the routine review of case report forms and supporting documents sent to the central office, site monitoring will be conducted at participating centers in the course of the study as part of the overall quality assurance program. 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 the Sponsor.

15.7. Case Report Forms

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection. Details for accessing the EDC system and completing the on-line Case Report Forms will be provided separately.

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APPENDIX 1. PATIENT EVALUATION FLOW SHEET FOR ARM 1 (BBI-608 IN COMBINATION WITH FOLFIRI)

Tests & Procedures	**Pre-Treatment**	**During Protocol Treatment**				**After Protocol Treatment Discontinuation (+/- 3 days)**	
		Run-in [1]		**Cycle 1**	**Additional Cycles (+/- 3 days)**		
Day		**1**	**2**	**1**	**1**		
Timing	≤14 days prior to randomization					4 weeks post protocol treatment	Every 8 weeks thereafter[15]
History[2] and Physical Exam	X			X	X	X	
ECOG PS	X			X	X	X	
Weight	X			X	X	X	
Height	X						
Vital signs	X			X	X	X	
FOLFIRI Infusion[3]				X	X		
Begin BBI-608 administration		X					
Hematology[4]	X			X	X	X	
Biochemistry[4]	X			X	X	X	
Urinalysis[4]	X			X	X	X	
ECG (12-lead)	X			X		X	
Radiology and Imaging[5]	X	Every 8 weeks for 6 months and every 12 weeks thereafter until progressive disease is documented.					
Submission of representative block of diagnostic tumor tissue	before or after randomization						
Blood collection for correlative studies[6,7]	X				X		

Tests & Procedures	Pre-Treatment	During Protocol Treatment				After Protocol Treatment Discontinuation (+/- 3 days)	
		Run-in [1]		Cycle 1	Additional Cycles (+/- 3 days)		
Day		1	2	1	1		
Blood collection for sparse PK analysis					X		
Pregnancy test, serum or urine (if applicable)[8,9]	X				X	X	
Adverse Event assessment[10,11]	X	X	X[11]	X	X	X	X[14]
Quality of Life assessment (EORTC QLQ-C30)[12]	X				X	X[13]	
Assessment for survival of patient						X[16]	X[16]

1 BBI-608 administration will begin 2 days prior to the FOLFIRI infusion on day 1 of cycle 1. These two days are referred to as *run-in day 1* and *run-in day 2*. The *run-in day* period may be extended by up to 3 additional calendar days. *Run-in day 1* should occur within 2 calendar days of patient randomization on study Arm 1.

2 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *RAS* status of tumor, prior anticancer therapy and prior date(s) of disease progression.

3 FOLFIRI administration should proceed according to institutional standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after infusion). Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible.

4 Laboratory investigations should be performed within 3 days prior to FOLFIRI administration on Day 1 of every 14-day Cycle of protocol treatment or within 3 days prior to each FOLFIRI infusion. Laboratory testing performed as part of standard of care prior to patient signature of the study consent will be acceptable as baseline lab work as long as testing is performed ≤ 14 days prior to randomization. Laboratory testing performed as part of pre-treatment assessments within 3 days of Cycle 1 Day 1 will be acceptable as Cycle 1 Day 1 lab work and will not need to be repeated.

5 Tumor 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. Tumor evaluations will continue until progressive disease is documented (as described in Section 9). 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, tumor measurements and assessment must be reported. Tumor assessments should be obtained within +/- 5 days of protocol specified schedule. Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed ≤ 21 days prior to randomization.

6 Sample collections should be performed at baseline and at Day 1 of Cycle 3 after randomization.

7 A sample will be collected following protocol treatment discontinuation if discontinuation occurs prior to 4 weeks of therapy.

8 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. Baseline pregnancy test should be done within 5 days of randomization.

9 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.

10 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix 4). Following permanent protocol treatment discontinuation, patients will be assessed for any protocol treatment related adverse events every 8 weeks, starting with the 4-week post-protocol treatment discontinuation visit.

11 Adverse event assessments by phone should be performed on *run-in day 2*.

12 To be completed in clinic. Questionnaires should be completed at baseline and at Day 1 of Cycle 3, Day 1 of Cycle 5, Day 1 of Cycle 7, Day 1 of Cycle 9 and Day 1 of Cycle 13 (+/- 3 days) after randomization for as long as patient remains on Protocol therapy or until deterioration to ECOG PS 4 or hospitalization for end of life care.

13 EORTC QLQ-C30 questionnaires will be collected in the post-protocol discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.

14 These assessments may occur within a ±7-day window, and after the first visit at which the patient has been off protocol treatment for 4 weeks, patients will be assessed every 8 weeks for survival and any protocol treatment related adverse events. Medical history at post-progression follow up must include post-protocol treatment cancer therapies.

15 After the first visit at which the patient has been off protocol treatment for 4 weeks, patients will be assessed for survival every 8 weeks until deterioration to ECOG PS 4 or hospitalization for end of life care

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

APPENDIX 2. PATIENT EVALUATION FLOW SHEET FOR ARM 2 (FOLFIRI)

Tests & Procedures	Pre-Treatment	During Protocol Treatment		After Protocol Treatment Discontinuation (± 3 days)	
		Cycle 1	Additional Cycles (± 3 days)		
Day		1	1		
Timing	≤14 days prior to randomization			4 weeks post protocol treatment	Every 8 weeks thereafter[13]
History[1] and Physical Exam	X	X	X	X	
ECOG PS	X	X	X	X	
Weight	X	X	X	X	
Height	X				
Vital signs	X	X	X	X	
FOLFIRI Infusion[2]		X	X		
Hematology[3]	X	X	X	X	
Biochemistry[3]	X	X	X	X	
Urinalysis[3]	X	X	X	X	
ECG (12-lead)	X	X		X	
Radiology and Imaging[4]	X	Every 8 weeks for 6 months and every 12 weeks thereafter until progressive disease is documented.			
Submission of representative block of diagnostic tumor tissue	before or after randomization				
Blood collection for correlative studies[5,6]	X		X		
Pregnancy test, serum or urine (if applicable)[7,8]	X		X	X	
Adverse Event assessment[9]	X	X	X	X	X[12]

Tests & Procedures	Pre-Treatment	During Protocol Treatment		After Protocol Treatment Discontinuation (± 3 days)	
		Cycle 1	Additional Cycles (± 3 days)		
Day		**1**	**1**		
Quality of Life assessment (EORTC QLQ-C30)[10]	X		X	X[11]	
Assessment for survival of patient				X[14]	X[14]

1 Medical history must include date of diagnosis including histological documentation of malignancy, documentation of *RAS* status of tumor, prior anticancer therapy and prior date(s) of disease progression.

2 FOLFIRI administration should begin within 7 calendar days of randomization and proceed according to institutional standard practice (with respect to pre-treatment laboratory evaluation, clinical assessment, pre-medication, and monitoring during and after infusion). Addition of bevacizumab to the FOLFIRI regimen, per Investigator choice, will be permissible.

3 Laboratory investigations should be performed within 3 days prior to FOLFIRI administration on Day 1 of every 14-day study Cycle of protocol treatment or within 3 days prior to each FOLFIRI infusion. Laboratory testing performed as part of standard of care prior to patient signature of the study consent will be acceptable as baseline lab work as long as testing is performed ≤ 14 days prior to randomization. Laboratory testing performed as part of pre-treatment assessments within 3 days of Cycle 1 Day 1 will be acceptable as Cycle 1 Day 1 lab work and will not need to be repeated.

4 Tumor 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. Tumor evaluations will continue until progressive disease is documented (as described in Section 9). Qualifying scans performed as part of standard of care prior to patient signature of the study informed consent will be acceptable as baseline scanning as long as scanning is performed ≤ 21 days prior to randomization.

5 Sample collections should be performed at baseline and at Day 1 of Cycle 3 after randomization.

6 A sample will be collected following protocol treatment discontinuation if discontinuation occurs prior to 4 weeks of therapy.

7 In women of childbearing potential only. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. Baseline pregnancy test should be done within 5 days of randomization.

8 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.

9 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events version 4.0 (see Appendix 4). Following permanent protocol treatment discontinuation, patients will be assessed for any protocol treatment related adverse events every 8 weeks, starting with the 4-week post-protocol treatment discontinuation visit.

10 To be completed in clinic. Questionnaires should be completed at baseline and At Day 1 of Cycle 3, Day 1 of Cycle 5, Day 1 of Cycle 7, Day 1 of Cycle 9 and Day 1 of Cycle 13 (+/- 3 days) after randomization for as long as patient remains on Protocol therapy or until deterioration to ECOG PS 4 or hospitalization for end of life care.

11 EORTC QLQ-C30 questionnaires will be collected in the post-protocol discontinuation period only if the patient discontinues protocol treatment prior to 24 weeks of therapy and has an ECOG PS of less than 4 and has not been hospitalized for end of life care.

12 After the first visit at which the patient has been off protocol treatment for 4 weeks, patients will be assessed every 8 weeks for survival and any protocol treatment related adverse events. Medical history at post-progression follow up must include post-protocol treatment cancer therapies.

13 These assessments may occur within a ±7-day window, and after the first visit at which the patient has been off protocol treatment for 4 weeks, patients will be assessed for survival every 8 weeks until deterioration to ECOG PS 4 or hospitalization for end of life care.
14 In the event that the patient is unable to attend clinic, post-progression follow-up for survival may be by means of telephone contact

APPENDIX 3. 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 4. 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 5. 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; 2 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.

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 appropriate case report form. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

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, side-effects, et cetera.

Study staff 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 by the patient. If a specific reason is not given, this also should be noted on the questionnaire by the patient.

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.

Assessments During Follow-up

The quality of life questionnaire should be given to the patient before being seen by the doctor, for as long as the patient continues on Protocol therapy, as required by the schedule at approximately:

- 4, 8, 12, 16 and 24 weeks or until deterioration to ECOG PS 4 or hospitalization for end of life care
- the first regularly scheduled 4-week assessment at which the patient has been off study therapy for a minimum of 28 days (±3 days) if study therapy discontinuation occurred prior to 24 weeks and until deterioration to ECOG PS 4 or hospitalization for end of life care

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!

- 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.

  - 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.
- 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.
- 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.

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

During the Last Week:	**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
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
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

During the Last Week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
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
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

During the Last Week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
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 Very Poor	2	3	4	5	6	7 Excellent

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

1 Very Poor	2	3	4	5	6	7 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 6. DECISION RULES AND MULTIPLICITY CONTROL PROCEDURE FOR ADAPTIVE DESIGN

To address multiplicity induced by the analysis of several endpoints (primary and key secondary endpoints) at several decision points (interim and final analyses) in several patient populations (General Population and STAT3(+) Subpopulation), a multiplicity adjustment will be utilized to control the overall Type I error rate (familywise error rate) in this trial in the strong sense at a 1-sided α=0.025. This multiplicity adjustment is constructed by applying the closed testing principle in conjunction with the combination function approach. The key components of the multiplicity adjustment are defined below and a detailed description of this multiplicity adjustment will be provided in the SAP.

Hochberg-based Gatekeeping Procedure

The first component of the multiplicity adjustment that accounts for the first 2 sources of multiplicity (analysis of several endpoints in several patient populations) relies on a Hochberg-based gatekeeping procedure. This procedure is defined using the mixture-based approach developed in Dmitrienko and Tamhane [*2011, 2013*] and later enhanced in Kordzakhia et al. [*2018b*]. This gatekeeping procedure will be applied to the 8 null hypotheses of no effect based on the 4 endpoints that are evaluated in the 2 patient populations:

- Family 1: Hypothesis H_{10} (null hypothesis of no OS effect in the General Population) and Hypothesis H_{20} (null hypothesis of no OS effect in the pSTAT3(+) Subpopulation).
- Family 2: Hypothesis H_{30} (null hypothesis of no PFS effect in the General Population) and Hypothesis H_{40} (null hypothesis of no PFS effect in the pSTAT3(+) Subpopulation).
- Family 3: Hypothesis H_{50} (null hypothesis of no DCR effect in the General Population) and Hypothesis H_{60} (null hypothesis of no DCR effect in the pSTAT3(+) Subpopulation).
- Family 4: Hypothesis H_{70} (null hypothesis of no ORR effect in the General Population) and Hypothesis H_{80} (null hypothesis of no ORR effect in the pSTAT3(+) Subpopulation).

The hypotheses will be organized into 2 branches (i.e. the null hypotheses in the General Population [H_{10}, H_{30}, H_{50} and H_{70}] and the null hypotheses in the pSTAT3(+) Subpopulation [H_{20}, H_{40}, H_{60} and H_{80}]), and tested sequentially within each branch.

Key features of the Hochberg-based gatekeeping procedure include:

- The gatekeeping procedure accounts for the clinically relevant logical restrictions (i.e. for the fact that the null hypotheses are organized into branches and tested sequentially within each branch).
- The gatekeeping procedure utilizes powerful Hochberg-type tests (regular and truncated Hochberg tests) for testing the hypotheses within each family. These tests account for positive correlations between the test statistics within each family, which is induced by the fact that the pSTAT3(+) Subpopulation is nested within the General Population. The regular and truncated Hochberg tests control the Type I error rate within each family since if the test statistics within each family follow a bivariate normal distribution with a non-negative pairwise correlation (Sarkar [*2008*]).

- The gatekeeping procedure uses truncated Hochberg tests in the first 3 families because they serve as gatekeepers for other families. The regular Hochberg test is applied in Family 4 since it is the last family in the sequence. The truncated Hochberg tests used in Families 1, 2, and 3 will be defined using a pre-specified truncation parameter γ=0.8.

To define the regular and truncated Hochberg tests, consider, for example, Family 1 which includes the hypotheses H_{10} and H_{20}. Let p_1 and p_2 denote the corresponding 1-sided p-values and let $p_{(1)} < p_{(2)}$ denote the ordered p-values. Finally, let α_1 denote the 1-sided significance level applied within this family (α_1 may not be equal to α=0.025). The regular Hochberg test relies on the following 2-step testing algorithm:

- Step 1: The test rejects both H_{10} and H_{20} if $p_{(2)} \leq \alpha_1$.
- Step 2: If $p_{(2)} > \alpha_1$, the test rejects the hypothesis corresponding to the smaller p-value if $p_{(1)} \leq \alpha_1/2$.

The truncated Hochberg test utilizes the following 2-step testing algorithm:

- Step 1: The test rejects both H_{10} and H_{20} if $p_{(2)} \leq (\gamma+(1-\gamma)/2)\alpha_1$.
- Step 2: If $p_{(2)} > (\gamma+(1-\gamma)/2)\alpha_1$, the test rejects the hypothesis corresponding to the smaller p-value if $p_{(1)} \leq \alpha_1/2$.

Interim Analysis Decision Rules

This section defines the decision rules that will be applied at the interim analysis.

Futility Stopping and Patient Population Selection Rules

The 2 decision rules will be applied simultaneously based on the observed hazard ratios:

- HR_0: Hazard ratio in the General Population
- HR_+: Hazard ratio in the pSTAT3(+) Subpopulation
- HR_-: Hazard ratio in the pSTAT3(-) Subpopulation

The resulting decision rules are defined as follows using appropriate values of the thresholds denoted by c_1 through c_4:

- Case 1: If Condition 1 ($HR_+ > c_1$) is met and Condition 2 ($HR_0 > c_2$) is met, terminate the trial at the interim analysis due to lack of efficacy
- Case 2: If Condition 1 ($HR_+ > c_1$) is met and Condition 2 ($HR_0 > c_2$) is not met, continue the trial and perform the final analysis in the General Population only
- Case 3: If Condition 1 ($HR_+ > c_1$) is not met and Condition 3 ($HR_- > c_3$) is met: Continue the trial and perform the final analysis in the pSTAT3+ Subpopulation only
- Case 4: If Condition 1 ($HR_+ > c_1$) is not met, Condition 3 ($HR_- > c_3$) is not met and Condition 4 ($HR_+/HR_- > c_4$) is met: Continue the trial and perform the final analysis in the General Population only

- Case 5: If Condition 1 ($HR_+ > c_1$) is not met, Condition 3 ($HR\_ > c_3$) is not met and Condition 4 ($HR_+/HR\_ > c_4$) is not met: Continue the trial and perform the final analysis in the General Population as well as the pSTAT3(+) Subpopulation.

Here $c_1 = c_2 = c_3 = 1$ in the Conditions 1 to 3 and $c_4 = 0.9$ for the Condition 4.

These patient population selection rules are based on the influence and interaction conditions introduced in *Millen 2012*.

Event Count Adjustment Rule

Within each patient population (the General Population or the pSTAT3(+) Subpopulation), conditional power (CP) is defined as the probability of establishing a significant OS effect at the final analysis conditional upon the interim analysis data at a 1-sided α=0.025. Conditional power is computed within each patient population using the population-specific hazard ratio observed at the interim analysis before an event count adjustment. A closed-form expression for conditional power [*Dmitrienko 2017*] is given below:

$$\mathrm{CP} = \Phi\left(\sqrt{\frac{v_1}{v_2}}Z + \theta\sqrt{\frac{m_2 - m_1}{4}} - \frac{c}{\sqrt{v_2}}\right)$$

where

$$v_1 = \frac{m_1}{m_2},\ v_2 = \frac{m_2 - m_1}{m_2},$$

Z is the 1-sided log-rank test statistic [*Jennison and Turnbull, 2000*] computed at the interim analysis within the selected patient population and c = 1.96 is the significance level to be applied at the final analysis. m_1 and m_2 denote the number of OS events at the interim analysis and at the original final analysis. θ is the observed effect size (log-hazard ratio) at the interim analysis.

The event count adjustment rule will be defined by identifying an optimal balance between the competing goals of increasing conditional power and reducing the number of events. The resulting approach leads to an event count adjustment rule that minimizes the average number of events within each patient population. The event count adjustment may also consider other factors including potential clinical benefits and operational feasibility.

If the final analysis is performed in the General Population as well as the pSTAT3(+) Subpopulation, the target number of events in the trial will be determined by the number of events in the General Population or the pSTAT3(+) Subpopulation whichever comes last.

Adaptive Design

A multi-stage adaptive design will be utilized in this Phase 3 trial. The decision rules employed in the adaptive design will be applied along with the gatekeeping procedure defined earlier in this section using the combination function approach [*Cui 1999* and *Brannath 2002*]. The combination function approach will be applied using the weighted inverse-normal combination function to address the third source of multiplicity (evaluation of the treatment effect at several decision points). The joint application of the combination function approach and gatekeeping

procedure relies on ideas presented in Sugitani, Bretz and Maurer [*2016*], Kordzakhia et al [*2018a*], and Sugitani et al. [*2018*].

Combination Function Approach for General Population

For the General Population, the combination function approach remains the same as previous version of protocol. The test statistics for evaluating the significance of the treatment effect or p-values will be computed from the data collected up to the interim analysis (Stage 1) and after the interim analysis (Stage 2). The stage-wise p-values for the primary endpoint (OS) will be obtained from the increments of the log-rank test statistics using the general approach developed in Shen and Cai [*2003*] and Wassmer [*2006*]. The increments of the log-rank test statistics that correspond to the 2 trial stages are defined as follows:

$$Z_{11}^{*} = Z_{11}, Z_{21}^{*} = \frac{\sqrt{k_{21}}\, Z_{21} - \sqrt{k_{11}}\, Z_{11}}{\sqrt{k_{21} - k_{11}}} \quad (1)$$

- Z_{11} and Z_{21}, the 1-sided log-rank test statistic [*Jennison and Turnbull, 2000*] at the interim analysis and final analysis for the General Population.
- k_{11} and k_{21}: the number of events at the interim analysis and final analysis for the General Population.

The 1-sided stage-wise p-values referred as the Stage 1 and Stage 2 p-values for testing the null hypothesis H_{10}, will be computed from these log-rank test statistics as

$$p_1 = 1 - \Phi(Z_{11}^{*}), q_1 = 1 - \Phi(Z_{21}^{*}) \quad (2)$$

where $\Phi(x)$ denotes the cumulative distribution function of the standard normal distribution.

The two stage-wise test statistics are independent of each other under the null hypothesis of no treatment effect of H_{10} and thus the final treatment effect p-value can be found by combining the stage-wise p-values, i.e.,

$$s_1 = c_2(p_1, q_1) = 1 - \Phi\left(\sqrt{w_1}\Phi^{-1}(1 - p_1) + \sqrt{1 - w_1}\Phi^{-1}(1 - q_1)\right) \quad (3)$$

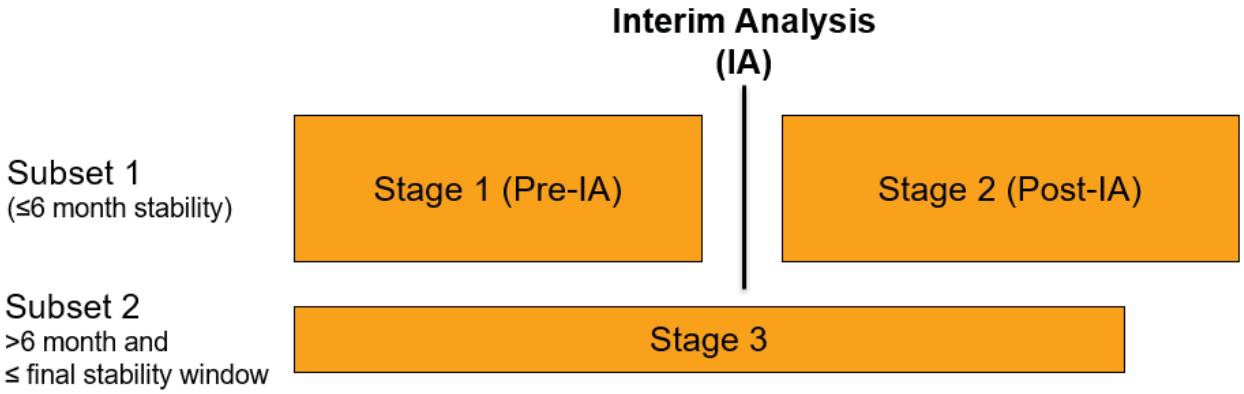
where w_1 and $1 - w_1$ are the pre-defined stage weights assigned to Stages 1 and 2 for the null hypothesis H_{10}.

Combination Function Approach for pSTAT3(+) Subpopulation

At the interim analysis, based on preliminary assessments of the ongoing CSS study, patients with specimens that were within the stability window of 6 months are included for pSTAT3 subpopulations designations. Due to the availability of additional patients with pSTAT3 results within the final CSS window [See Section 9.1.7 for detailed explanations], the test statistics at the final analysis for the primary and the key secondary endpoints in the pSTAT3(+) subpopulation will be computed across two subsets of patients data, i.e., Subset 1 of the patients

with pSTAT3 positive status within specimen age up to 6-months (including both Stage 1 pre-interim analysis data and Stage 2 post- interim analysis data), and Subset 2 (Stage 3) of patients with pSTAT3 positive status with specimen age for longer than 6 months and but within the final CSS window. Figure 3 presents the data that will be used for the primary and the key secondary endpoints in the pSTAT3(+) Subpopulation at the final analysis.

Figure 3: Data in Final Analysis of the pSTAT3(+) Subpopulation



Subset 2 data may also be treated as Stage 3 data for the pSTAT3(+) subpopulation

For the pSTAT3(+) subpopulation, the statistics test for evaluating the significance of the treatment effect or the corresponding p-values in terms of overall survival (OS) at the final analysis will be computed from the following three stages of data from the two subsets of patients defined above. The three stages of data are:

- Stage 1 (Subset 1 Stage 1) Data: OS data collected up to the interim analysis from Subset 1.
- Stage 2 (Subset 1 Stage 2) Data: OS data collected after the interim analysis from Subset 1.
- Stage 3 (Subset 2) Data: OS event data from Subset 2.

The final treatment effect p-value for the null hypothesis of OS in the pSTAT3(+) subpopulation can be computed by combining the stage-wise p-values from the three parts of the data.

Since Subset 1 and Subset 2 are two mutually exclusive sets of patients, Subset 2 data may also be treated as Stage 3 data for the pSTAT3(+) subpopulation to describe multi-stage combination function approach.

Subset 1 Stage 1 and Stage 2 p-values for the primary endpoint (OS) in the pSTAT3(+) subpopulation will be obtained from the increments of the log-rank test statistics in a similar fashion as conducted for the General Population:

$$Z_{12}^{*} = Z_{12}\,, Z_{22}^{*} = \frac{\sqrt{k_{22}}\,Z_{22} - \sqrt{k_{12}}\,Z_{12}}{\sqrt{k_{22} - k_{12}}} \tag{4}$$

- Z_{12} and Z_{22} are the 1-sided log-rank test statistic at the interim analysis and final analysis for the pSTAT3(+) subpopulation with specimen age up to the 6-month stability window (Subset 1).

- k_{12} and k_{22}: the number of events at the interim analysis and final analysis for the pSTAT3(+) subpopulation with specimen age up to the 6-month stability window (Subset 1).

Furthermore, let Z_{32}^* denote the 1-sided log-rank test statistic for the pSTAT3(+) subpopulation in Subset 2. To ensure the test statistic Z_{32}^* be independent of the stage wise test statistics Z_{12}^* and Z_{22}^* under the null hypothesis of no treatment effect (Magirr et al., 2016), the test statistic Z_{32}^* needs to be computed based on the data available by the analysis cutoff date (a pre-determined calendar date) for Subset 2 (See Section 9.1.7 for details of the analysis cut dates).

The stage-wise p-values for the pSTAT3(+) subpopulation are defined as follows:

$$p_2 = 1 - \Phi(Z_{12}^*), q_2 = 1 - \Phi(Z_{22}^*), r_2 = 1 - \Phi(Z_{32}^*). \quad (5)$$

As stated above, since the length of the patient follow-up period is pre-defined in Subset 2, the test statistic Z_{32}^* is independent of the stage wise test statistics Z_{12}^* and Z_{22}^* under the null hypothesis of no treatment effect. As a result, the final treatment effect p-value for the null hypothesis H_{20} can be computed by combining the stage-wise p-values, i.e.,

$$\begin{aligned} s_2 &= c_3(p_2, q_2, r_2) \\ &= 1 - \Phi\left(\sqrt{v_2}\sqrt{w_2}\Phi^{-1}(1-p_2) + \sqrt{v_2}\sqrt{1-w_2}\Phi^{-1}(1-q_2) + \sqrt{1-v_2}\Phi^{-1}(1-r_2)\right) \end{aligned} \quad (6)$$

where w_2 and $1 - w_2$ are the pre-defined weights assigned to Stages 1 and 2 and, in addition, v_2 and $1 - v_2$ are the pre-defined weights assigned to Stages 1+2 and 3 for the null hypothesis H_{20}.

Combination Function Approach for Key Secondary Endpoints

The stage-wise test statistics for PFS are defined in the same manner. To define the stage-wise test statistics for DCR and ORR, the log-rank test needs to be replaced by the Z test for proportions and the number of events need to be replaced by the numbers of patients. The 1-sided stage-wise p-values for PFS, DCR, and ORR are defined as follows:

- Hypothesis H_{30}: Let p_3 and q_3 denote the 1-sided p-values computed from the null distributions of the stage-wise test statistics (Stage 1 and 2) for PFS in the General Population.
- Hypothesis H_{40}: Let p_4 and q_4 and r_4 denote the 1-sided p-values computed from the null distributions of the stage-wise test statistics (Subset 1 Stage 1, 2 and Subset 2) for PFS in the pSTAT3(+) Subpopulation.
- Hypothesis H_{50}: Let p_5 and q_5 denote the 1-sided p-values computed from the null distributions of the stage-wise test statistics (Stage 1 and 2) for DCR in the General Population.
- Hypothesis H_{60}: Let p_6 and q_6 and $r_6$denote the 1-sided p-values computed from the null distributions of the stage-wise test statistics (Subset Stage 1, 2 and Subset 2) for DCR in the pSTAT3(+) Subpopulation.
- Hypothesis H_{70}: Let p_7 and q_7 denote the 1-sided p-values computed from the null distributions of the stage-wise test statistics (Stage 1 and 2) for ORR in the General Population.

Hypothesis H_{80}: Let p_8 and q_8 and r_8 denote the 1-sided p-values computed from the null distributions of the stage-wise test statistics (Subset Stage 1, 2 and Subset 2) for ORR in the pSTAT3(+) Subpopulation.To apply the combination function principle, the stage-wise p-values for OS, PFS, DCR, and ORR will be combined using an appropriately defined weighted inverse-normal combination function.

The inferences for the 8 hypotheses corresponding to OS, PFS, DCR, and ORR will be performed at the final analysis using the composite *p*-values that are defined as follows:

- Hypothesis H_{10}: The composite *p*-value is defined as $s_1 = c_2(p_1, q_1)$.
- Hypothesis H_{20}: The composite *p*-value is defined as $s_2 = c_3(p_2, q_2, r_2)$.
- Hypothesis H_{30}: The composite *p*-value is defined as $s_3 = c_2(p_3, q_3)$.
- Hypothesis H_{40}: The composite *p*-value is defined as $s_4 = c_3(p_4, q_4, r_4)$.
- Hypothesis H_{50}: The composite *p*-value is defined as $s_5 = c_2(p_5, q_5)$.
- Hypothesis H_{60}: The composite *p*-value is defined as $s_6 = c_3(p_6, q_6, r_6)$.
- Hypothesis H_{70}: The composite *p*-value is defined as $s_7 = c_2(p_7, q_7)$.
- Hypothesis H_{80}: The composite *p*-value is defined as $s_8 = c_3(p_8, q_8, r_8)$

If the interim analysis outcome will be the treatment effect is evaluated only in the General Population at the final analysis and thus the hypotheses H_{20}, H_{40}, H_{60} and H_{80} are dropped after the interim analysis, the corresponding Stage 2 and Stage 3 (Subset 2) p-values (i.e. q_2, q_4, q_6, q_8, r_2, r_4, r_6 and r_8) , will be set to 1. Similarly, if the treatment effect is evaluated only in the pSTAT3(+) subpopulation at the final analysis and thus the hypotheses H_{10}, H_{30}, H_{50} and H_{70} are dropped after the interim analysis, the corresponding Stage 2 p-values (i.e., q_1, q_3, q_5 and q_7), will be set to 1.

Finally, to compute the multiplicity adjusted *p*-values for the hypotheses of interest at the final analysis, a closed family associated with these null hypotheses needs to be introduced. The closed family contains 2^8 - 1= 255 intersections. Let $H(I)$ denote an arbitrary intersection hypothesis from the closed family, which is associated with the index set I. A local *p*-value, also known as the intersection p-value, will be computed for the intersection hypothesis $H(I)$ as shown below using the composite p-values defined above (i.e. s_1 through s_8).

To ensure that the final gatekeeping procedure is consistent with the logical relationships among the null hypotheses, the corresponding restrictions need to be imposed on the hypotheses within each intersection. These restrictions ensure, for example, that the hypothesis H_{30} cannot be rejected if the hypothesis H_{10} is not rejected. Let I^* denote the restricted index set which accounts for the logical relationships among the null hypotheses for the intersection hypothesis $H(I)$. It is easy to show that, for any intersection hypothesis $H(I)$ in the closed family, there can be at most two indices left in the restricted index set I^* and therefore it is sufficient to consider the following 2 cases:

Case 1. Suppose that there are 2 indices in the restricted index set I^* that are denoted by i and j, i.e., $I^* = \{i, j\}$. If the corresponding hypotheses are included in the same family, the local *p*-value for this intersection hypothesis is given by:

$$p(I) = \min\,(2s_{(i)}, s_{(j)}) \tag{7}$$

where $s_{(i)}$ and $s_{(j)}$ denote the ordered p-values, i.e., $s_{(i)} < s_{(j)}$. If the corresponding hypotheses are included in 2 different families and the index i corresponds to the more important family, the local p-value for this intersection hypothesis is given by:

$$p(I) = 2\min\,(s_i/(1+\gamma), s_j/(1-\gamma)). \tag{8}$$

Case 2. Suppose that there is only 1 index in the restricted index set I^*, denoted by i, i.e., $I^* = \{i\}$. In this case, the local p-value for the intersection hypothesis is simply given by:

$$p(I) = s_i \tag{9}$$

The resulting intersection p-values will be utilized for computing the multiplicity-adjusted p-values for the 8 null hypotheses at the final analysis. Per communication from FDA on July 23, 2019 , it was suggested to sponsor to introduce a small penalty for the interim analysis because of the unblinded analysis of the efficacy data even though the interim analysis were not to stop for efficacy. Therefore, a small penalty for the interim analysis (1-sided alpha of 0.0001) is introduced here and a null hypothesis will be rejected if the intersection p-values for all intersection hypotheses containing this particular null hypothesis are less than or equal to a 1-sided α=0.0249.

A detailed description of the computation of the intersection p-values will be provided in the SAP.

The proposed decision rules in the adaptive design ensure overall Type I error rate control with respect to the primary and key secondary endpoints. The Type I error rate control is maintained even if the target number of events is increased or a decision to restrict the patient enrollment to the subpopulation of pSTAT3(+) patients is made at the interim analysis.