BOSTON BIOMEDICAL
Sumitomo Dainippon Pharma Global Oncology

TITLE:	**A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma**
PROTOCOL NUMBER:	**BBI608-503-103HCC**
STUDY DRUGS:	**BBI503** **BBI608**
SPONSOR:	[redacted]
MEDICAL MONITOR:	[redacted]
SAFETY FAX:	[redacted]
SAFETY CONTACT:	[redacted]
DATE OF PROTOCOL:	**September 12, 2014**
DATE OF AMENDMENT:	**April 3, 2018**
AMENDMENT:	**4**

SYNOPSIS

Study Title:	**A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib, or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma**
Study Number:	BBI608-503-103HCC
Study Phase:	Phase Ib/II
Study Drugs:	BBI608 and BBI503, investigational, small molecule, anticancer drugs that are hypothesized to affect multiple oncogenic pathways, including pathways implicated in cancer stem cell viability.
Primary Objectives:	Phase Ib: To determine the safety, tolerability, and recommended Phase II dose (RP2D) of BBI608 administered in combination with sorafenib and of BBI503 administered in combination with sorafenib in adult patients with advanced hepatocellular carcinoma who have not received prior systemic chemotherapy. Phase II: To evaluate the tolerability, safety. and preliminary anti-tumor activity in patients with advanced hepatocellular carcinoma randomized to receive treatment with sorafenib in combination with BBI608, sorafenib in combination with BBI503, or sorafenib alone; BBI608 and BBI503 would be administered at their respective RP2D dose levels for combination administration with sorafenib, which were determined during phase Ib.
Secondary Objectives:	To determine the pharmacokinetic profile of BBI608 administered in combination with sorafenib and of BBI503 administered in combination with sorafenib. To perform biomarker studies for BBI608 administered in combination with sorafenib and for BBI503 administered in combination with sorafenib.
Study Design:	This is an open label, phase Ib/II study. The study population is adult patients with advanced hepatocellular carcinoma who have not received systemic chemotherapy. The phase Ib portion will involve dose-escalation of BBI608 administered in combination with a fixed starting dose of sorafenib (Arm 1), and dose escalation of BBI503 administered in combination with a fixed starting dose of sorafenib (Arm 2). The fixed starting dose-level of sorafenib for both arms will be 400 mg twice daily (800 mg total daily dose). Eligible patients will be randomized to either Arm 1 or Arm 2. In Arm 1, escalating doses of BBI608 will be administered to cohorts of three to six patients until RP2D is determined according to the criteria for determining dose-limiting toxicity (DLT) and the criteria for dose-escalation. In Arm 2, escalating doses of BBI503 will be administered to cohorts of three to six patients until RP2D is determined according to the criteria for determining dose-limiting toxicity (DLT) and the criteria for dose-escalation. Prior to initiation of combination therapy in each arm, sorafenib will be administered as monotherapy starting on Cycle 1, Day 1 for 14 days. Dose-adjustment of sorafenib according to the approved product label is allowed. Following the sorafenib run-in period, the combination regimen will begin on Cycle 1, Day 15. Protocol therapy will continue in repeating 28-day cycles until disease progression, unacceptable toxicity, or another discontinuation criterion

	is met. For both arms, pharmacokinetic (PK) studies will be performed on Cycle 1, Day 15 and Cycle 2, Day 15. An additional pharmacokinetic study may be performed to confirm exposure following dose-modification. Once RP2D is determined for both study arms, the phase II portion will begin. The phase II portion will be an open-label, 3-arm, randomized phase II trial of patients with advanced HCC who have not received prior systemic treatment. Patients will be randomized to receive either, Arm 1: sorafenib administered in combination with BBI608 (at the RP2D determined for BBI608 plus sorafenib during the phase Ib portion); Arm 2: sorafenib in combination with BBI503 (at the RP2D determined for BBI503 plus sorafenib during the phase Ib portion), or Arm 3: sorafenib alone at a starting dose of 400 mg twice daily. The starting dose for sorafenib is the same for all study arms. **Note:** Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment due to BBI503 portfolio priorities and to increase efforts in enrolling patients on to Arms 1 and 3. At the time of the amendment 3 being in effect, there were approximately 10 subjects already enrolled in Arm 2. Therefore, the actual sample size in Phase II in the end is projected to be approximately 70 patients after the amendment 3 Pharmacodynamic assessments will be performed in patients with readily accessible tumors through an optional on-study tumor biopsy. Archival tissue, if available, will be collected from all patients. Throughout the study, safety and tolerability of BBI608 in combination with sorafenib and of BBI503 in combination with sorafenib will be assessed for the duration of study treatment and up to 30 days after discontinuation of study drug (either BBI608 or BBI503). Evaluation of anti-tumor activity will be performed at regular 8–week intervals, with the first assessment 8 weeks (56-days) after Cycle 1, Day 1. The radiologic assessments will be evaluated according to RECIST 1.1 and modified RECIST (mRECIST) for patients with HCC. Alpha-feto protein (AFP) measurement will be performed at baseline, at the end of the 2-week sorafenib monotherapy Run-In, and at the start of each subsequent study cycle. A patient may continue protocol therapy beyond progression that is determined by RECIST criteria (either RECIST 1.1 or mRECIST for patients with HCC), provided that the patient is obtaining potential clinical benefit in the opinion of the investigator. If sorafenib is discontinued due to sorafenib-related toxicities, study drug (either BBI608 or BBI503) may be continued.
Study Population:	This study will enroll patients with advanced hepatocellular carcinoma (HCC) arising from any setting who have not received prior systemic chemotherapy for their disease, and for which sorafenib is an appropriate treatment option in the judgment of the treating investigator. Prior surgical or loco-regional therapy is allowed, including trans-catheter arterial embolization, trans-catheter arterial chemoembolization, percutaneous ethanol injection, or radiofrequency ablation, provided that the procedure was performed at least 4 weeks prior to Cycle 1, Day 1, and provided that there has been documented disease progression per RECIST (either RECIST 1.1 or mRECIST for patients with HCC) since the surgical procedure.

<table>
<tr><td></td><td>Additional key inclusion criteria include: ECOG performance status ≤ 1, Child-Pugh class A and B7 albumin, adequate renal function, and a life expectancy of greater than 3 months. Patient accrual will occur over a period of time dependent upon the enrollment rate of the study. Patients with HIV infection are excluded.</td></tr>
<tr><td>Test Product, Dose, and Mode of Administration:</td><td>Phase Ib:

Patients in this trial will receive study drug in combination with a fixed dose of sorafenib according to the arm they are randomly assigned to and according to the dose-level cohort that is currently open.

Sorafenib will be administered at a fixed dose of 400 mg twice daily (800 mg total daily dose). This dose of sorafenib will be the same for each arm and for each dose-level cohort. Sorafenib should be taken on an empty stomach, one hour prior to or two hours after meals. Sorafenib should not be taken with study drug, and at least 2 hours should separate a dose of sorafenib from a dose of study drug.

The starting dose of study drug (BBI608 or BBI503) and dosing instructions for each arm during the phase are as follows.

Arm 1:

BBI608 will be administered orally, twice daily, with approximately 12 hours between doses. The first dose of BBI608 should be administered shortly after waking in the morning. The second dose of BBI608 should be taken in the evening. BBI608 should be taken with fluids, either 1 hour before a meal or 2 hours after. The first dose of BBI608 should be taken prior to the first dose of sorafenib.

The dose of BBI608 to be administered will depend on the assigned dose-level cohort as follows in the table below:

<table>
<tr><th>BBI608 Dose Level</th><th>BBI608 Dose & Schedule</th></tr>
<tr><td>BBI608 Dose-Level I</td><td>160 mg Twice Daily</td></tr>
<tr><td>BBI608 Dose-Level II</td><td>240 mg Twice Daily</td></tr>
</table>

Initially, 3 patients will be enrolled at BBI608 Dose-Level 1. Dose-escalation will proceed according to the Criteria for Dose Escalation and Criteria for Determination of Dose-Limiting Toxicity (DLT).

Alternate and/or intermediate dose-levels are permitted upon agreement with the Principal Investigator and medical monitor for the Sponsor.

Arm 2:

BBI503 will be administered orally, daily. The daily dose of BBI503 will be administered before bed. The dose of BBI503 to be administered will depend on the assigned dose-level cohort as follows in the table below:

<table>
<tr><th>BBI503 Dose Level</th><th>BBI503 Dose & Schedule</th></tr>
<tr><td>BBI503 Dose-Level I</td><td>100 mg Once Daily</td></tr>
<tr><td>BBI503 Dose-Level II</td><td>200 mg Once Daily</td></tr>
</table>

Initially, 3 patients will be enrolled at BBI503 Dose-Level 1. Dose-escalation will proceed according to the Criteria for Dose Escalation and Criteria for Determination of Dose-Limiting Toxicity (DLT).

Intermediate dose-levels are permitted upon agreement with the Principal Investigator and medical monitor for the Sponsor. The total daily dose of BBI503 may be divided into sub-doses.</td></tr>
</table>

	Phase II Portion: The dose of BBI608 or BBI503 *to be administered in combination with sorafenib during the phase II portion will be the RP2D determined during the phase Ib dose-escalation portion of study. Sorafenib administration will be as described for the phase Ib portion. * Once the amendment 3 is in effect, Arm 2 in Phase II portion will be closed for enrollment
Criteria for Dose Escalation – Phase Ib Portion Only	Enrollment at the next dose level and/or additional patients into the ongoing cohort will occur according to the following criteria: • If zero treated patients experience a DLT (defined below) by Day 28 of continuous daily dosing, then dose escalation will occur. • If one treated patient experiences a DLT (defined below) by Day 28 of continuous daily dosing, then an additional three patients will be enrolled for a total of six patients treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (one of six patients). • If two or more treated patients at a dose level experience a DLT by Day 28 of continuous daily dosing, this will be the maximally administered dose. • A total of six patients will be treated at the previous dose level, and subsequent escalation will not exceed the maximally administered dose. The maximally tolerated dose (MTD) is defined as the dose level at which no more than one out of six patients have an observable DLT. RP2D will be determined according to safety, tolerability, and pharmacokinetics. The criteria for dose-escalation will apply to a given administration schedule independently.
Criteria for Determination of Dose-Limiting Toxicity:	Dose-Limiting Toxicity (DLT) is defined as the occurrence of any of the following toxicities possibly, probably, or definitely related to study drug (either BBI608 or BBI503) or to study drug in combination with sorafenib during the first 28 days of combination therapy, unless there is a clear alternative explanation: • CTCAE (Common Terminology Criteria for Adverse Events) Grade 4 hematological toxicity. • Grade 3 thrombocytopenia in the presence of active bleeding will be considered a DLT. • Grade 3 or 4 non-hematological toxicity, except for Grade 3 nausea/vomiting/anorexia, diarrhea, or fatigue, symptoms that will be considered DLTs only if they persist more than seven (7) days despite optimal medical management. Grade 4 toxicity will be considered DLT. Alopecia will not be considered DLT. Assessment for DLT will occur during the first 28 days of BBI608 or BBI503 therapy in combination with sorafenib. DLT will be determined from adverse events, as well as changes from baseline in physical examination findings and laboratory parameters. The criteria for determination of DLT will apply to a given administration schedule independently. Patients who discontinue protocol therapy for a reason other than DLT may be replaced in order to fully evaluate a given dose-level.
Duration of Treatment:	For an individual patient, treatment with study drug (either BBI608 or BBI503) and sorafenib will continue in 28-day cycles or until the investigator determines the patient is no longer deriving potential clinical benefit due to unacceptable toxicity, disease progression, or another discontinuation criterion. A patient may continue protocol therapy beyond progression that is determined

	solely by RECIST 1.1 criteria or mRECIST criteria for patients with HCC, provided that the patient is obtaining potential clinical benefit in the opinion of the investigator. It is expected that most patients will receive between 4 and 24 weeks of treatment.
Pharmacokinetic and Pharmacodynamic Variables:	Pharmacokinetic variables to be determined include maximum plasma drug concentration (Cmax), time to reach Cmax (Tmax), area under the time-concentration curve (AUC), and terminal half-life. Blood samples for PK analyses will be performed on Cycle 1, Days 15-16 and on Cycle 2, Day 15 of the phase Ib portion. During the phase II portion, approximately six patients will collect PK as Phase I schedule, then a single pharmacokinetic blood draw may be obtained on Cycle 2, Day 15. Paraffin embedded tumor tissue is requested from all patients prior to initiation of protocol therapy. Patients may enroll if they do not have archival tissue. Patients may enroll if they are not aware if they have archival tissue. Pharmacodynamic studies as well as the concentration of study drug (either BBI608 or BBI503) in tumors will be examined following study drug administration in patients with accessible tumors who consent to an optional on-study biopsy. This optional biopsy will be obtained on Cycle 2, Day 15.
Statistical Methods:	Statistics will be descriptive in nature, and formal sample size calculations were not performed. Phase Ib: Central randomization will be performed whereby patients will be assigned to Arm 1 (BBI608 plus sorafenib) or Arm 2 (BBI503 plus sorafenib) using block randomization. Each block will be considered a cohort with 3 subjects on Arm 1 and 3 subjects on Arm 2. After the first cohort for an Arm is complete, the dose level for the next cohort will be determined by the dose escalation rules. Safety will be summarized according to study arm. All patients receiving at least one dose of study drug (either BBI608 or BBI503) will be considered evaluable for safety analyses. Adverse events will be assessed according to CTCAE and will be evaluated by grade and organ class. Adverse event listings and tabulated summaries of categorized adverse events will be generated for all patients. Vital signs, laboratory data, and ECG data will be summarized for changes over time on study. The pharmacokinetic population will be all treated patients in a given arm with sufficient data to determine pharmacokinetic parameters. Phase II: Approximately 90 patients (30/arm) were planned to be randomized in 1:1:1 ratio into three treatment arms: Arm 1 (sorafenib plus BBI608), Arm 2 (sorafenib plus BBI503), and Arm 3 (sorafenib alone) before Amendment 3 was in effect. After amendment 3 was in effect, Arm 2 in the Phase II portion was closed for enrollment and randomization is conducted in a 1:1 ratio to the two remaining arms: Arm 1 and Arm 3. The targeted sample size remains 30 for Arm 1 and 30 Arm 3 after the amendment 3. There were approximately 10 subjects already enrolled in Arm 2 by the time amendment 3 was put into effect. Therefore, the total sample size of Phase II at the end of the trial is projected to be approximately 70 patients. Baseline characteristics as well as the observed safety, tolerability, and preliminary signs of anti-tumor activity will be summarized for each arm.

	The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics. Patient response will be assessed based on standard RECIST 1.1, as well as mRECIST for patients with HCC. Data listings and summaries of tumor markers, imaging results, and similar data may be generated. Kaplan-Meier estimates of overall survival and progression-free survival will be generated. Phase Ib and Phase II: Anti-tumor activity will be summarized by arm. Patients in a given study arm who have received at least one cycle of study drug (either BBI608 or BBI503) and who have had at least one disease assessment following the initiation of therapy will be considered evaluable for response. The anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics. Patient response will be assessed based on standard RECIST 1.1, as well as mRECIST for patients with HCC. Data listings and summaries of tumor markers, imaging results, and similar data may be generated. Kaplan-Meier estimates of overall survival and progression-free survival will be generated. Phase II There is no statistical hypothesis testing in the Phase 2 part and the sample size of Phase 2 part is considered to be clinically adequate to assess tolerability, safety, and preliminary anti-cancer activity of the study drugs of interest. Estimation and 95% confidence intervals will be provided for the proportion of patients with grade 3 adverse events by treatment, as well as for the proportion of patients that are alive and progression free 4 months (PFS-4) after randomization for each arm.

DOSE ESCALATION SCHEME BBI608-503-103HCC: A PHASE IB/II CLINICAL TRIAL

Arm 1: BBI608 in Combination with Sorafenib

Cohort	No. Subjects	Dose Level	Dose & Schedule of BBI608
I	3*	Level 1	160 mg Twice Daily
II	3*	Level 2	240 mg Twice Daily

*Group may be expanded to six subjects, as provided for in the protocol.

Arm 2: BBI503 in Combination with Sorafenib

Cohort	No. Subjects	Dose Level	Dose & Schedule of BBI503
I	3*	Level 1	100 mg Daily
II	3*	Level 2	200 mg Daily

*Group may be expanded to six subjects, as provided for in the protocol.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

GCS-F	Granulocyte Colony Stimulating Factor
GGT	Gamma Glutamyl Transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hct	Hematocrit
HED	Human Equivalent Dose
Hgb	Hemoglobin
HGF	Hepatocyte Growth Factor
HIPAA	Health Information Portability and Accountability Act
IC_{50}	Inhibitory Concentration, 50%
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
LD	Longest Diameter
LDH	Lactic Dehydrogenase
MR	Minor Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NOAEL	No Observable Adverse Effect Level
NOEL	No Observable Effect Level
ORR	Overall Response Rate
PD	Progressive Disease
PK	Pharmacokinetic

PR	Partial Response
QD	Once Daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RBC	Red Blood Cell (count)
SAE	Serious Adverse Event
SD	Stable Disease
SE	Standard Error
SGOT	Serum Glutamic Oxaloacetic Transaminase (AST)
SGPT	Serum Glutamic Pyruvic Transaminase (ALT)
T_{max}	Time to Maximum Plasma Concentration
TNM Scale	Tumor Node Metastases Scale
ULN	Upper Limit of Normal
WBC	White Blood Cell (count)

1 PRECLINICAL SUMMARY AND STUDY RATIONALE

1.1 Brief Scientific Background

Recent studies have uncovered the presence of cancer stem cells (CSCs, also called tumor initiating cells, or cancer stem-like cells) which have self-renewal capability and are considered to be fundamentally responsible for malignant growth, relapse, and metastasis. Importantly, CSCs are inherently resistant to conventional therapies. Therefore, a targeted agent with activity against cancer stem cells for cancer patients is being explored (Clevers, 2011: Singh and Settleman, 2010; Lobo, Shimono et al. 2007; Boman and Wicha, 2008; please also find a list of reviews on CSCs in all major cancer types in the special issue of Journal of Clinical Oncology on cancer stem cells (J Clin Oncol. 2008 Jun 10; 26(17)).

This study will evaluate the safety, tolerability, and preliminary signs of activity of two different investigational agents designed as cancer stem cell inhibitors, BBI608 and BBI503, each administered in combination with sorafenib in patients with advanced hepatocellular carcinoma (HCC). Sorafenib is an oral agent currently approved for the treatment of advanced HCC. A combination regimen which targets the cancer stem cell population in addition to the bulk tumor cells (non-stem cancer cells) may be an approach for this disease.

The study agents, BBI608 and BBI503, are discussed subsequently. Brief introductions to both agents are followed by pre-clinical efficacy data and updates from clinical development to date. Additional information is available in the Investigator Brochures (IB) for both compounds.

1.1.1 BBI608

BBI608 is a small molecule that is hypothesized to affect multiple oncogenic cellular pathways, including inhibition of the STAT3 pathway, which has been implicated in cancer stem cell viability.

1.1.2 BBI503

BBI503 is the product candidate selected from our BBI5600 program designed by BBI to target CSCs. BBI503 may target cancer through inhibition of kinases that may be responsible for cancer stemness properties.

1.2 Preclinical Efficacy

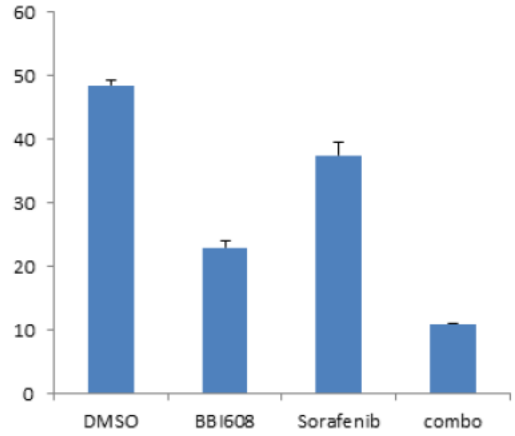
1.2.1 BBI608

Cancer stem cells are intrinsically resistant (more than 5 to 10-fold than other tumor cells) to chemotherapeutic drugs. BBI608 has activity (~100 to 500 nM) against cancer stem cells in vitro. At the same time, BBI608 spares normal hematopoietic stem cells (IC50 not reached at 30 μM) in vitro.

BBI608 has demonstrated in-vitro activity in a broad spectrum of human cancer cell lines derived from both solid tumors and hematologic malignancies (IC50 ~100 nM to 500 nM).

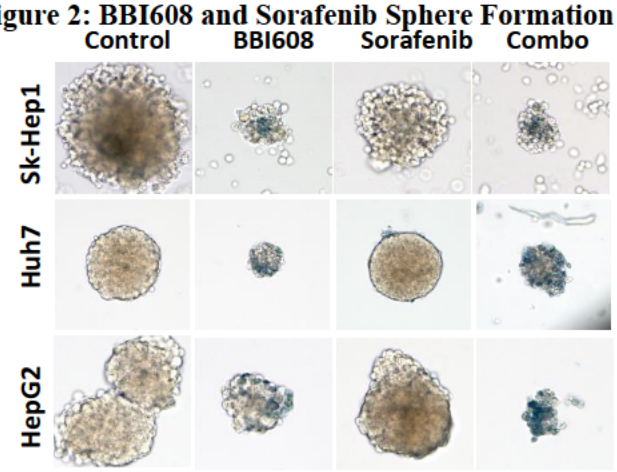
Further pre-clinical work in HCC cell lines has shown that BBI608 is active in vitro against both bulk tumor cells and cancer stem cells (CSCs) derived from HCC cell lines. Moreover, there is evidence that BBI608 may act synergistically with sorafenib in vitro. **Figure 1** below demonstrates in vitro activity of BBI608 and BBI608 with sorafenib against bulk tumor cells, whereas **Figure 2** shows that BBI608 and BBI608 with sorafenib reduces the ability of CSCs to form characteristic spheres in non-adherent stem cell media in vitro.

Figure 1: BBI608 and Sorafenib Colony Formation



Using HepG2 cell lines, 1000 cells per well were seeded in 6-well plates. 24 hrs later, the cells were treated with either 0.15 μM BBI608, 2 μM sorafenib, , or both 0.15 μM BBI608 and 2 μM sorafenib for 24 hours. After 24 hours, the remaining cells were cultured in fresh medium for 7-10 days until visible colonies formed.

Figure 2: BBI608 and Sorafenib Sphere Formation



Single cells were grown in suspension for 48 h before adding either BBI608 alone (1.6 μM), sorafenib alone (2 μM), or a combination of BBI608 and sorafenib at concentrations of 1.6 μM and 2 μM, respectively. Drugs were applied for 24 hr, after which drugs were washed out and cells were allowed to recover for another 24 h. DIC images were then taken. Blue coloration of cells is due to Tryphan Blue and indicates dead cells.

1.2.2 BBI503

BBI503 has potent activity (~200 to 500 nM) against CSCs derived from multiple cell lines in vitro. BBI503 also has potent activity in various non-stem cancer cells. BBI503 has shown in vitro activity in a broad spectrum of human cancer cell lines (IC50 ~200 nM to 600 nM).

Further pre-clinical evaluation has shown the activity of BBI503 against CSCs derived from HCC cell lines, both alone and in combination with sorafenib, BBI503 both kills cancer stem cells, and reduces the ability of CSCs to form characteristic spheres in non-adherent stem cell media (see **Figure 3**: BBI503 & Sorafenib Sphere Formation). Equivalent treatment with sorafenib does not affect the CSC sphere-forming ability,

and the cells remain viable. Cancer stem cell markers such as CD133 and CD44 are reduced after treatment with BBI503. Treatment with the combination of BBI503 + Sorafenib has also shown in vitro activity against CSC derived from HCC cell lines.

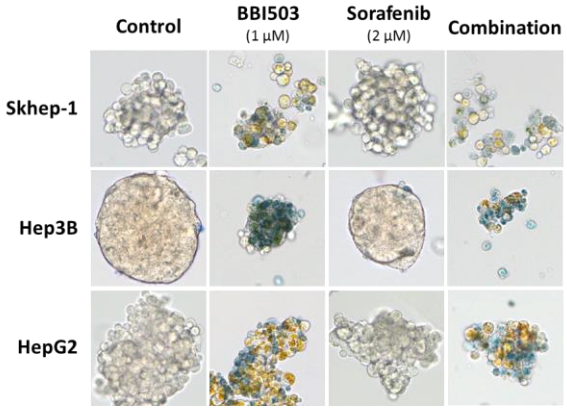
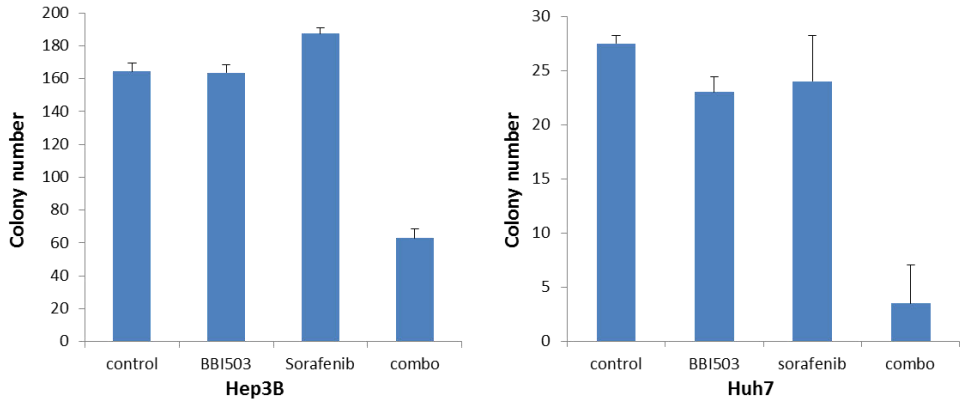


Figure 3: BBI503 & Sorafenib Sphere Formation

Single CSC cells were grown in suspension for 48 hrs. 1μM BBI503 and 2 μM Sorafenib were added for 24 hrs. Drug was removed, and cells were cultured another 24 hours. DIC images were taken for the CSC sphere. Note: BBI503 compound is bright yellow, and is accumulated in CSC cells; blue is from Trypan Blue indicating dead cells.

Additional studies were performed on bulk cancer cells derived from HCC cell lines. Compared with the CSC-enriched sphere culture, bulk cells contain mainly (~ 98%) non-CSCs. In **Figure 4** below, the combination of BBI503 and sorafenib may be synergistic in-vitro.

Figure 4: BBI503 & Sorafenib Colony Formation



Using Hep3B and Huh7 cell lines, 1000 cells per well were seeded in 6-well plates. The next day, the cells were treated with BBI503 0.3 μM, sorafenib 2 μM, or the combination of both for 24 hours. After 24 hours, the remaining cells were cultured in fresh medium for 7-10 days until visible colonies formed.

1.3 Safety and Antitumor Activity in Phase I

1.3.1 BBI608

A phase 1 dose escalation study (BBI608-101) in adult patients with advanced cancer was initiated to evaluate the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics and preliminary anti-tumor activity of napabucasin. A modified Simon accelerated titration scheme was used for dose escalation, with a cycle consisting of twice-daily oral administration of napabucasin for 4 weeks, and was repeated every 4 weeks (28 days) until progression of disease, unacceptable toxicity, or other discontinuation criteria were met.

The dose of napabucasin was escalated from 20 mg to 2000 mg/day, and MTD was not reached according to the protocol definition. However, further dose escalation beyond 1000 mg/day was limited by pill burden and gastrointestinal adverse events. In the 87 patients the most common adverse events (regardless of reported causality) included diarrhea (83%), fatigue (62%), abdominal pain (59%), nausea (56%), vomiting (52%), and anorexia (51%). Grade 3 events included diarrhea (16%), fatigue (14%), abdominal pain (6%), dehydration (6%), and anemia (6%). The recommended phase II dose (RP2D) was determined to be 500 mg twice daily (1000 mg total daily dose). The plasma concentration of napabucasin reached a mean maximal concentration of 843 ng/mL.

BBI608 has also been combined with several chemotherapeutic agents to date. The current safety and efficacy data are available in the IB (version 6.3).

1.3.2 BBI503

A phase 1 dose escalation study (BBI503-101) in adult patients with advanced cancer has been initiated to determine the safety, tolerability, recommended phase 2 dose (RP2D), pharmacokinetics, and preliminary anti-tumor activity of BBI503. A modified Simon accelerated titration scheme was used for dose escalation, in which BBI503 was administered orally, once daily, twice daily, or three times daily in continuous 28-day cycles. Cycles were repeated until progression of disease, unacceptable adverse events, or anther discontinuation criterion was met.

The dose of BBI503 has been escalated from 10 mg to 600 mg total daily, and a MTD has not been reached according to the protocol definition. However, further dose-escalation was limited by pill burden or gastrointestinal adverse events (nausea, diarrhea). BBI503 plasma concentration reached the in-vitro IC_{50} and pharmacokinetic parameters maximized at 300 mg to 400 mg total daily. The putative recommended phase II dose for once daily dosing is 300 mg once daily and the putative recommended phase II dose for twice daily dosing is 200 mg twice daily (400 mg total daily).

BBI503 observed adverse events have been predominantly mild to moderate gastrointestinal disturbances. The most common events have been CTCAE grade 1 or grade 2 abdominal cramping, diarrhea, and nausea. Non-gastrointestinal events have included fatigue. Grade 3 events considered possibly, probably, or definitely related to protocol therapy have included diarrhea, fatigue, vomiting, and abdominal cramping. Adverse events can be managed with supportive care such as intravenous fluids and pharmacologic measures targeting the specific symptom. Dose-modification or holding of dosing until symptoms improve and/or resolve is recommended for moderate to severe symptoms.

Please refer to the Investigator Brochure for additional clinical data.

In summary, BBI503 has shown an manageable safety profile, favorable pharmacokinetics, and preliminary signs of antitumor activity.

1.4 Combination Therapy for Hepatocellular Carcinoma

Advanced HCC remains a clinical challenge. This is due to several factors, including the chemoresistant nature of the disease, the toxicity profile of currently available systemic chemotherapeutic agents, and the general poor health and underlying liver dysfunction of HCC patients (Kelley, R 2013). The Sorafenib Hepatocellular Carcinoma Assessment Protocol (SHARP) trial remains the only randomized controlled trial of a systemic chemotherapeutic agent to demonstrate a statistically significant survival benefit in patients with advanced, unresectable HCC (Bruix, J 2012; Llovet, JM 2008). In that study, 602 patients were randomly assigned to receive sorafenib (400 mg twice daily) or placebo. A median Overall Survival (OS) of 10.7 months was observed in the treatment arm compared to 7.9 months for placebo. Time to Tumor Progression (TTP) for the sorafenib and placebo arms was 5.5 months and 2.8 months, respectively.

The benefits achieved with sorafenib monotherapy are important, but modest in magnitude (2.8 months increase in median survival). Many patients do not experience disease control, and disease control can be short-lived in those that do achieve it with therapy. Unfortunately, however, no other agent has proven more effective. Recent phase III trials with other regimens (FOLFOX, brivanib, sunitinib and linifanib; Qin, S et al, 2012; Johnson, PJ et al, 2013, Cheng, A et al 2011; Cianap, C et al, 2012) have all failed to demonstrate a statistically significant improvement in OS when compared to treatment with sorafenib.

There have also been multiple studies of combination therapy using sorafenib plus an additional agent or regimen. Few combinations, however, have progressed for further evaluation in the phase III, pivotal setting. Those that have been evaluated in phase III trials, such as Brivanib, FOLFOX, and Erlotinib, have failed to demonstrate superiority to sorafenib alone. Increased toxicity and poor quality of life were observed in the BRISK-FL study, and an increased incidence of hand-foot syndrome has been observed in combination studies with 5-FU or 5-FU derivative therapies [Dig Dis Sci. 2012 May; 57(5): 1122–1129]. An unmet medical need exists for active systemic therapies in HCC.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objectives for the phase Ib and phase II portions of this study are:

Phase Ib:

- To determine the safety, tolerability, and recommended phase II dose (RP2D) of BBI608 in combination with sorafenib and the safety, tolerability, and recommended phase II dose (RP2D) of BBI503 in combination with sorafenib when administered to adult patients with advanced hepatocellular carcinoma who have not received previous systemic chemotherapy.

Phase II:

- To evaluate the tolerability, safety, and preliminary anti-tumor activity in patients with advanced hepatocellular carcinoma randomized to receive treatment with sorafenib in combination with BBI608, sorafenib in combination with BBI503*, or sorafenib alone; BBI608 and BBI503 will be administered at their respective RP2D dose levels for combination administration with sorafenib, which were determined during the phase Ib portion of the study.

  * Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

2.2 Secondary Objectives

The secondary objectives for this study are:

- To determine the pharmacokinetic profile of BBI608 administered in combination with sorafenib and of BBI503 administered in combination with sorafenib.
- To perform biomarker studies for BBI608 administered in combination with sorafenib and for BBI503 administered in combination with sorafenib.

3 SELECTION OF STUDY POPULATION

This study will be conducted in patients with advanced, metastatic, unresectable and incurable hepatocellular carcinoma who have not received previous systemic chemotherapy and who are candidates for sorafenib. The study population and inclusion criteria for phase Ib and phase II are the same.

The study will initially be conducted at selected sites in North America, and may be expanded to sites globally.

3.1 Inclusion Criteria

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

1. Signed written informed consent must be obtained and documented according to International Conference on Harmonisation (ICH) and local regulatory requirements
2. Histologically or cytologically confirmed hepatocellular carcinoma that is metastatic, unresectable, or recurrent.
    a. Patients must not be candidates for curative resection
    b. Patients who have recurrent disease after having had one or more prior resections may be eligible, provided that they are not candidates for further curative resection.
    c. Patients who have recurrent hepatocellular carcinoma following hepatic transplantation are excluded unless the following criteria are met:
        i. Transplantation was performed at least 6 months prior to the relapse of HCC.
        ii. Patients are on stable immune suppressive therapy with no clinical evidence of rejection.
        iii. Are receiving ≤ 2.5 mg everolimus daily.
    d. Patients with known HIV infection are excluded.
    e. Patients with Hepatitis B are eligible provided there is no active viral replication*. Patients with Hepatitis C who are not on interferon are eligible.
3. Patients who have a diagnosis of HCC made through radiologic imaging may be eligible, provided they meet the following criteria according to the American Association for the Study of Liver Disease, AASLD (Bruix and Sherman, 2005; Bruix and Sherman, 2011):
    a. *Two* dynamic imaging techniques (such as 4-phase multi-detector CT or dynamic contrast-enhanced MRI) must be used for lesions < 2 cm in diameter
    b. Typical vascularity pattern (arterial hypervascularity AND venous or delayed phase washout) must be present on dynamic imaging
    c. If these criteria are not met, biopsy must be performed to confirm diagnosis
4. Patients must be candidates for sorafenib
5. Must have had no previous systemic anti-cancer treatment, though previous loco-regional therapy is allowed:
    a. Prior treatment with any of the following is allowed: trans-arterial embolization, trans-arterial chemo-embolization, percutaneous ethanol injection, radio-embolization, radio-frequency ablation, or other ablation techniques.
6. Must be Child-Pugh class A or class B7 albumin (no more than a score of two in albumin)
    a. Patients with uncontrolled massive ascites or presence of hepatic encephalopathy are excluded

b. Patients who are on therapeutic anticoagulation, their PT/INR will be assigned a score of one. c

7. Must have total serum bilirubin ≤ 3 mg/dl
8. ≥ 18 years of age
9. Measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Section 16)
11. Male or female patients of child-producing potential must agree to use contraception or avoidance of pregnancy measures during the study and for 30 days after the last BBI608 or BBI503 dose
12. Females of childbearing potential must have a negative serum pregnancy test
13. Aspartate Aminotransferase (AST) and Alanine transaminase (ALT) < 5.0x the upper limit of normal (ULN)
14. GFR > 35 mL/min/1.73m^2 according to the Cockroft-Gault estimation.
15. Hemoglobin ≥ 8.5 mg/dl
16. Absolute neutrophil count ≥ 1.5 x 10^9/L
17. Platelets ≥ 60 x 10^9/L
18. Life expectancy ≥ 3 months

*2015 ASCO guidelines for monitoring and use of antiviral therapy and prophylaxis for Hepatitis B should be followed

3.2 Exclusion Criteria

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

1. Previous treatment with sorafenib
2. Patients with known hypersensitivity to sorafenib or any other component of sorafenib.
3. Previous systemic anti-VEGF or any prior systemic anti-cancer therapy, including prior treatment with systemic agents such as regorafenib, ramucirumab, pazopanib, or experimental agents such as brivanib.
4. Have had a surgical procedure requiring general anesthesia or inpatient hospitalization for recovery less than 4 weeks prior to beginning protocol therapy.
5. Have had a loco-regional procedure for the treatment of hepatocellular carcinoma (such as a percutaneous, trans-arterial, or radio-ablative procedure) less than 4 weeks prior to beginning protocol therapy. Protocol therapy may begin a minimum of 4 weeks after such a procedure provided the following criteria are met:
    a. There is progression of disease documented by RECIST 1.1
    b. All adverse events from the procedure have resolved or have been deemed irreversible and the patient meets inclusion criteria.
6. Any known symptomatic or untreated brain metastases requiring increase of steroid dose within 2 weeks prior to starting on study. Patients with treated brain metastases must be stable for 4 weeks after completion of that treatment. Patients must have no clinical symptoms from brain metastases and must be either off steroids or on a stable dose of steroids for at least 2 weeks prior to protocol enrollment. Patients with known leptomeningeal metastases are excluded, even if treated.

7. Pregnant or breastfeeding
8. Significant gastrointestinal disorder(s) (e.g., Crohn's disease, ulcerative colitis, extensive gastric and small intestine resection) such that, in the opinion of the treating investigator, absorption of oral medications may be impaired.
9. Unable or unwilling to swallow BBI608, BBI503, or sorafenib capsules or tablets
10. Uncontrolled inter-current illness including, but not limited to: ongoing or active infection, clinically significant non-healing or healing wounds, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, significant pulmonary disease (shortness of breath at rest or mild exertion), or uncontrolled infection or psychiatric illness/social situations that would limit compliance with study requirements (e.g. no reliable transportation).
11. Subjects with a history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid tumor with no known active disease present that, in the opinion of the investigator, will not affect patient outcome in the setting of current hepatocellular carcinoma diagnosis.
12. Abnormal ECGs which are clinically significant such as QT prolongation (QTc > 480 msec), clinically significant cardiac enlargement or hypertrophy, new bundle branch block, or signs of active ischemia. Patients with evidence of prior infarction who are NYHA functional classes II, III, or IV are excluded, as are patients with marked arrhythmias such as Wolff Parkinson White pattern or complete AV dissociation*.

    *Patients with complete or incomplete AV dissociation who have a pacemaker may be eligible for enrollment provided they are NYHA functional class I: "No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)."

3.3 Number of Patients

The number of patients enrolled on this study depends on the number of cohorts enrolled in phase Ib and the adverse events observed. It is expected that approximately 6 to 12 patients will be enrolled in each arm during phase Ib dose-escalation, for 12 to 24 patients total in phase Ib. After RP2D is determined for BBI608 in combination with sorafenib and for BBI503* in combination with sorafenib, enrollment to a randomized phase II portion of the study will begin. A total of approximately 90 patients will be randomized to one of three study arms: sorafenib in combination with BBI608, sorafenib in combination with BBI503, or sorafenib alone, so that approximately 30 patients per arm will be enrolled. Patient accrual will occur over a period of time dependent upon the enrollment rate. *Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment due to BBI503 portfolio priorities and to increase efforts in enrolling patients on to Arms 1 and 3. When amendment 3 was in effect, there were approximately 10 subjects enrolled in each of the three arms, and approximately 30 patients will be enrolled in each of the two open arms (70 total for phase II).

The sample size for the phase II portion provides for an evaluation of tolerability, safety, and preliminary anti-tumor activity (see Section 10 and Section 10.5 for details). Briefly, enrollment will support an evaluation of the proportion of patients treated with combination therapy or with sorafenib alone who experience a grade 3 adverse event. Enrollment also supports an evaluation of the proportion of patients treated with combination therapy or with sorafenib alone who are alive and without progression at 4 months (16 weeks) after randomization.

Non-evaluable patients for reasons unrelated to the treatment will be replaced, such as subjects with exclusion criteria inadvertently randomized or subjects who withdraw for personal reasons.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label Phase Ib/II study of oral study drug (BBI608 or BBI503) administered in combination with sorafenib to adult patients with advanced hepatocellular carcinoma (HCC). The study will proceed initially as a phase Ib dose-escalation study, in which patients will be randomized to receive escalating doses of either BBI608 in combination with sorafenib [phase Ib Arm 1], or escalating doses of BBI503 in combination with sorafenib [phase Ib Arm 2]. The phase Ib portion of the study is designed to determine the safety, tolerability, pharmacokinetics, and recommended phase II dose (RP2D) for BBI608 plus sorafenib and of BBI503 plus sorafenib.

When putative RP2D is determined for each study drug in combination with standard sorafenib dosing according to the criteria for determination of dose-escalation and dose limiting toxicity per-protocol, the phase II portion of the study will begin.

The phase II portion is a randomized, 3-arm, open-label controlled study designed to compare the safety, tolerability, and preliminary anti-tumor activity in patients with advanced hepatocellular carcinoma randomized to receive treatment with either sorafenib plus BBI608 [phase II Arm 1], sorafenib plus BBI503 [phase II Arm 2], or sorafenib alone [phase II Arm 3]. In the phase II portion, BBI608 and BBI503 will be administered at their respective RP2D dose levels for administration with standard sorafenib dosing which were determined during the phase Ib portion of the study. Sorafenib will be administered at standard dose for both the phase Ib and phase II portions of this study.

Note:

Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment due to BBI503 portfolio priorities and to increase efforts in enrolling patients on to Arm 1 and 3.

When amendment 3 being in effect, there were approximately 10 subjects enrolled in Arm 2. Approximately 30 patients will be enrolled in each of the two open remaining arms (70 total for phase II).

During both the Phase Ib and Phase II portions of this study, objective (i.e. radiologic) disease assessments are required. A baseline objective disease assessment is required within 14 days of starting protocol therapy. Per-protocol objective disease assessments will be performed every eight weeks (56 days), as calculated according to the date of the first dose of protocol therapy on study. A window of ±7 days is allowed when scheduling radiologic disease assessments (applies to each scan individually). Clinically indicated radiologic evaluations outside of this schedule are allowed (see Section 5.7, Tumor Evaluation Visits)

4.2 Design - Phase Ib

Patients will be randomized into available enrollment slots in either Arm 1, *BBI608 in combination with sorafenib*, or in Arm 2, *BBI503 in combination with sorafenib*. Protocol therapy for each arm will consist of daily oral administration of either BBI608 or BBI503 in combination with a fixed dose of sorafenib.

Prior to initiation of combination therapy for an individual patient, sorafenib will be administered as monotherapy for 14 days. Dose-adjustment of sorafenib is allowed according to the approved product label. The combination regimen of study drug (either BBI608 or BBI503) plus sorafenib will be administered in continuous 28-day cycles until disease progression, unacceptable toxicity, or another discontinuation criterion is met.

Sorafenib will be administered at a fixed dose of 400 mg twice daily (800 mg total daily dose). This dose of sorafenib will be the same for each arm and for each dose-level cohort. Sorafenib should be taken on an empty stomach, one hour prior to or two hours after meals. Sorafenib should not be taken with study drug, and at least 2 hours should separate a dose of sorafenib from a dose of study drug.

Dose-escalation, determination of dose-limiting toxicity, and determination of RP2D will occur independently in each study arm.

Arm 1:

BBI608 will be administered orally, twice daily. The first dose of BBI608 should be administered shortly after waking in the morning. The second dose of BBI608 should be taken before bed, and approximately 12 hours should separate the two BBI608 doses. BBI608 should not be taken with sorafenib.

BBI608 should be administered before the first dose of sorafenib. A dose of BBI608 should be separated from a dose of sorafenib by at least 2 hours. It is recommended to take both BBI608 and sorafenib around the same time every day.

Examples of dosing schedules consistent with these instructions can be found in the accompanying study manual. The dose of BBI608 to be administered will depend on the assigned dose-level cohort as follows in the table below:

BBI608 Dose Level	**BBI608 Dose & Schedule**
BBI608 Dose-Level I	160 mg Twice Daily
BBI608 Dose-Level II	240 mg Twice Daily

Initially, 3 patients will be enrolled at BBI608 Dose-Level 1. Dose-escalation will proceed with cohorts of three to six patients according to the Criteria for Dose Escalation and Criteria for Determination of Dose-Limiting Toxicity (DLT).

Intermediate or additional dose-levels are permitted upon agreement with the Principal Investigator and medical monitor for the Sponsor. The RP2D determined for BBI608 in combination with standard sorafenib dosing during the phase Ib portion of the study will be the starting dose for the BBI608 plus standard sorafenib arm of the randomized phase II portion of the study.

Arm 2:

BBI503 will be administered orally, daily. The daily dose of BBI503 will be administered before bed. BBI503 should not be taken with sorafenib.

BBI503 is taken 1 hour prior to meals or 2 hours after. A dose of BBI503 and a dose of sorafenib should be separated by at least 2 hours.

The dose of BBI503 to be administered will depend on the assigned dose-level cohort as follows in the table below:

BBI503 Dose Level	**BBI503 Dose & Schedule**
BBI503 Dose-Level I	100 mg Once Daily
BBI503 Dose-Level II	200 mg Once Daily

Initially, 3 patients will be enrolled at BBI503 Dose-Level 1. Dose-escalation will proceed with cohorts of three to six patients according to the Criteria for Dose Escalation and Criteria for Determination of Dose-Limiting Toxicity (DLT).

Intermediate or additional dose-levels are permitted upon agreement with the Principal Investigator and medical monitor for the Sponsor. The total daily dose of BBI503 may be divided into sub-doses. The RP2D determined for BBI503 in combination with standard sorafenib dosing during the phase Ib portion of the study will be the starting dose for the BBI503 plus standard sorafenib arm of the randomized phase II portion of the study.

RP2D Determination

In both Arm 1 and Arm 2, dose escalation will proceed with the purpose of determining a recommended Phase 2 dose (RP2D). Dose escalation will proceed in each arm independent of the other arm. The goal of dose escalation in Arm 1 is to determine RP2D of BBI608 in combination with sorafenib. The goal of dose-escalation in Arm 2 is to determine RP2D of BBI503 in combination with sorafenib. In both arms, if a patient discontinues study participation for reasons other than DLT, that patient may be replaced so that the safety of the dose-cohort can be fully evaluated.

For both arms, the decision to escalate the dose of study drug in combination with sorafenib is based on the adverse events observed and the criteria for determination of dose-escalation (dose-escalation decision rules) in **Table 1** below. The criteria for determination of dose-escalation will be applied independently to each arm.

Table 1: Criteria for Determination of Dose Escalation

Number of Subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 subjects at the next dose level
$\geq$ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
1 out of 3	Enter at least 3 more subjects at this dose level. • If 0 of these 3 subjects experience DLT, proceed to the next dose level • If 1 or more of this group experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional subjects will be entered at the next lower dose level if only 3 subjects were treated previously at that dose.
$\leq$1 out of 6 at highest dose level below the maximally administered dose	This is the maximally tolerated dose. RP2D will not exceed MTD.

For each arm, the DLT and Escalation Decision Rules outlined in **Table 1** apply to a given administration schedule independently. The recommended phase II dose will be determined based on the clinical safety and tolerability observed, as well as on pharmacokinetics and pharmacodynamics of the dosing cohort.

The determination of RP2D in each study arm will not be based solely on DLT observed during the DLT observation period. The determination of RP2D will include an assessment of Grade 2 adverse events of long duration as well as toxicities beyond the first cycle.

Once a putative recommended phase 2 dose (RP2D) has been determined, up to 6 additional patients evaluable for determination of dose-escalation may be enrolled to confirm safety and tolerability. A putative RP2D determination may be updated.

The phase Ib portion of the study will be declared to be completed once RP2D for BBI608 in combination with sorafenib and RP2D for BBI503 in combination with sorafenib are both determined.

The principal investigator and study staff at all study sites will be notified when the phase Ib portion of the study has ended. Receipt of this notification must be confirmed. Once the phase Ib portion has ended, further enrollment will be in the randomized phase II portion. As such, during the informed consent process for the phase II portion of the study, potential study patients must be made aware of the possibility of being randomized to receive standard of care (sorafenib) alone.

4.3 Design – Phase II

The phase II portion of the study will begin when RP2D is determined for each agent in combination with sorafenib. Patients enrolled into the phase Ib portion will not be eligible for enrollment into the phase II portion.

The primary aim of the phase II portion is to evaluate the tolerability, safety, and preliminary anti-tumor activity in patients randomized to each arm above. Sorafenib is the current standard of care for patients with advanced HCC. The evaluation of safety and activity planned for the phase II portion of this study will inform the design of further trials. (see Section 10.5 in Section 10 for further details).

The phase II portion of the study will require patients to meet the same inclusion and exclusion requirements as the phase Ib portion, which are outlined in Section 0 and in Section 3.2. After completing all screening tests and ensuring all criteria are met, study sites will submit a randomization request for those patients who are eligible for enrollment. Patients will be centrally randomized in an open label fashion in a 1:1:1 ratio to one of the following three arms outlined in **Table 2** below:

Note:

Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment due to BBI503 portfolio priorities and to increase efforts in enrolling patients on to Arm 1 and 3.

At the time of the amendment 3 there were approximately 10 subjects enrolled in Arm 2, therefore a total of approximately 70 patients will be enrolled in the phase II portion of the study, or approximately 30 patients will be enrolled in each of the two open remaining arms.

Table 2: Phase II Study Arms

Study Arm	**Backbone Chemotherapy**		**Investigational Agent**	
	Agent	*Starting Dose*	*Agent*	*Starting Dose*
Phase II Arm 1	Sorafenib	400 mg Twice Daily	BBI608	Phase Ib RP2D
Phase II Arm 2	Sorafenib	400 mg Twice Daily	BBI503	Phase Ib RP2D
Phase II Arm 3	Sorafenib	400 mg Twice Daily	-	-

Once randomized, patients are to begin protocol therapy within 72 hours of randomization. There are only slight differences in the patient visit schedule and schedule of assessment for patients enrolled onto the phase II portion of the study. The study visit schedules are outlined in section 5.

The schedule of administration for protocol therapy is the same in both the phase Ib and phase II portions of the study. In addition, for both phase Ib and phase II, the backbone chemotherapy is the standard dosing of sorafenib.

For patients enrolled to the phase II portion of the study, per-protocol objective (radiologic) disease assessments (see Section 5.7.2) should occur every 8 weeks (56 days) until disease progression is documented according to RECIST 1.1 and mRECIST for HCC. Protocol therapy may be continued in an open-label fashion until the investigator determines that the patient is no longer deriving clinical benefit.

If sorafenib is discontinued for any reason, study drug (BBI608 or BBI503) may be continued. If a patient is randomized to Phase II Arm 1 or Phase II Arm 2, and study drug is permanently discontinued, patients will begin the follow-up portion of the protocol assessment schedule (see Section 5.10), and may receive any further treatment as determined by the treating investigator, including sorafenib. Objective (radiologic) disease assessments should continue to be obtained every 8 weeks in these patients until progression is documented according to RECIST 1.1 and mRECIST for HCC.

If RP2D for either BBI608 or BBI503 in combination with sorafenib is updated during the course of the phase II portion of the study, then patients randomized to that study arm will be administered study drug at the updated RP2D. If needed, up to 30 patients total may be enrolled in a study arm at a given dose of study drug during the phase II portion of the study.

4.4 Rationale for Study Design

HCC is a global disease with a marked unmet medical need for effective systemic therapy. The scientific literature suggests that cancer stem cells may play a role in resistance to effective chemotherapies. Thus, there is a strong rationale to clinically evaluate the addition of an agent which targets cancer stem cells to a therapy such as sorafenib which has proven effectiveness in HCC.

In addition to clinical safety and tolerability, pharmacokinetic and pharmacodynamic data will be collected on this trial in order to establish the optimal dosing regimen for both BBI608 and BBI503 in combination with sorafenib. The phase II portion will establish a body of evidence on which to base further clinical development.

4.5 Selection of Dose

The starting doses of study drug (either BBI608 or BBI503) for phase Ib are based on clinical experience during the monotherapy phase I evaluation of both agents. Doses were selected which were well tolerated as monotherapy, and which were well below the maximally administered dose for each agent.

For the phase Ib portion, the starting dose of BBI608 in combination with sorafenib is 160 of BBI608 taken twice daily. This is 33% of the BBI608 monotherapy RP2D (480 mg twice daily, 960 mg total daily dose), and 16.7% of the maximally administered dose during the monotherapy phase I trial (1000 mg twice daily, 2000 mg total daily dose). Of note, MTD was not determined in the BBI608 monotherapy phase I dose-escalation trial.

The starting dose of BBI503 in combination with sorafenib is 100 mg once daily. This is 33% of the BBI503 monotherapy once daily RP2D (300 mg once daily), and 16.7% of the maximally administered dose during the monotherapy phase I trial (200 mg three times daily and 300 mg twice daily, or 600 mg total daily dose). Of note, MTD was not determined in the BBI503 monotherapy phase I dose-escalation trial.

The dose of BBI608 and of BBI503* for the phase II portion of the study will be determined during the phase Ib portion of the study. The starting dose for phase II Arm 1 (sorafenib plus BBI608) will be the RP2D of BBI608 in combination with sorafenib as determined during dose-escalation of phase Ib Arm 1. The starting dose for phase II Arm 2 (sorafenib plus BBI503) will be the RP2D of BBI503 in combination with sorafenib as determined during dose-escalation of phase Ib Arm 2.

* Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

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

Patients are considered evaluable for determination of DLT and for determination of dose-escalation if they have been exposed to at least 28 days of continuous daily administration of study drug (BBI608 or BBI503) in combination with sorafenib at a compliance level of at least 80% for the combination regimen.

Compliance for study drug (either BBI608 or BBI503) and sorafenib is calculated by dividing the number of pills ingested by the total number of pills assigned to be ingested (see Section 7.4). The assigned dose of BBI608 or BBI503 is that determined by the dose-level cohort into which the patient is enrolled. The assigned dose of sorafenib is the dose administered at the start of combination therapy, as determined during the 2-week run-in period. The starting dose of sorafenib is 400 mg twice daily, and dose-reductions according to standard of care are allowed. Events meeting DLT definition that occur during the sorafenib run-in period will not be considered DLTs. Events occurring at any time that are determined to be due solely to sorafenib will not be considered DLTs.

Enrollment at the next dose level of study drug (either BBI608 or BBI03) and/or enrollment of additional patients into the ongoing cohort will be based on the tolerability and safety observed in evaluable patients, according to criteria described below:

- If zero treated patients experience a DLT (defined below) by Day 28 of continuous daily dosing, then dose escalation will occur.
- If one treated patient experiences a DLT (defined below) by Day 28 of continuous daily dosing, then an additional three patients will be enrolled for a total of six patients treated at the same dose level. Escalation will occur if no additional DLTs are seen in that cohort (one of six patients).
- If two or more treated patients at a dose level experience a DLT (defined below) by Day 28 of continuous daily dosing, this will be the maximally administered dose.

Once the maximally administered dose is determined, a total of six patients will be treated at the previous dose level.

The BBI medical Monitor and Principal Investigator will review all significant combination therapy related toxicities to determine if the dose escalation schedule requires modification. Intermediate or additional dose levels or an alternate administration schedule may be assigned to a cohort after agreement between the BBI Medical Monitor and the Principal Investigator.

4.7 Dose-Limiting Toxicity

Dose-Limiting Toxicity (DLT) is defined as the occurrence of any of the following toxicities possibly, probably, or definitely related to study drug (either BBI608 or BBI503) or to study drug in combination with sorafenib during the first 28 days of combination therapy, unless there is a clear alternative explanation:

- CTCAE (Common Terminology Criteria for Adverse Events) Grade 4 hematological toxicity.
- Grade 3 thrombocytopenia in the presence of active bleeding.
- Grade 3 or 4 non-hematological toxicity, except for Grade 3 nausea/vomiting/anorexia, diarrhea, or fatigue, symptoms that will be considered DLTs only if they persist more than seven (7) days despite optimal medical management. Grade 4 toxicity will be considered DLT.

Alopecia will not be considered a DLT. Assessment of DLTs will occur during the first 28 days of BBI608 or BBI503 therapy in combination with sorafenib. DLTs will be determined from both adverse events and changes from baseline in physical examination findings and laboratory parameters.

The criteria for determination of DLTs will apply to a given administration schedule independently. Patients who discontinue protocol therapy for a reason other than a DLT may be replaced in order to fully evaluate a given dose-level.

4.8 Study Duration

For both the phase Ib and phase II components of the study, patients will receive treatment with combination therapy (either BBI608 or BBI503* in combination with sorafenib) until the investigator has determined that the patient is no longer likely to receive clinical benefit due to progression of disease, unacceptable toxicity, or another discontinuation criterion (see Section 5.9). It is expected that most patients will receive between one and four cycles of combination therapy for a treatment period of 4 to 16 weeks. It is expected that patient accrual for both the phase Ib and phase II portions of the trial will occur over a period of 12-18 months, with an additional 12 months to complete follow-up.

* Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

5 STUDY VISITS

5.1 Overview

For the phase Ib portion of the study, study visits will consist of a Pre-Study Evaluation, during which the patient will be evaluated to determine eligibility for entry into the study; a Cycle 1, Day 1 Visit at the start of the sorafenib monotherapy run-in period; a phone call to patients on Cycle 1, Day 8, which is the approximate mid-point of the 14-day sorafenib monotherapy run-in period; a Cycle 1, Day 15 Visit, which is the start of combination therapy; a Cycle 1, Day 22 visit; and then regular evaluations every 2-weeks starting on Cycle 2, Day 1.

For the phase II portion of the study, study visits will also involve a Pre-Study Evaluation. Cycle 1 visits will include a brief visit on Cycle 1, Day 1 (the start of the sorafenib monotherapy run-in period); a phone call to patients on Cycle 1, Day 8; a full visit on Cycle 1, Day 15 (the start of combination therapy); and a visit on Cycle 1, Day 22. In Cycle 2, there will be visits on Cycle 2, Day 1 and on Cycle 2, Day 15. Starting in Cycle 3, the only required in-person visit is on the first day of the study cycle (i.e., Cycle 3, Day 1; Cycle 4, Day 1, etc.).

During the phase II portion, an in-person visit on Cycle 3, Day 15 is optional, and is optional on Day 15 of each subsequent cycle, provided patients are stable. If the in person visit is not performed on Cycle 3, Day 15 or on Day 15 of a subsequent cycle, study staff are to reach out to the patient with a phone call.

For both phase Ib and phase II, an End-of-Study Evaluation will also be completed between 14 and 30 days after the last dose of protocol therapy; See Section 14 for a schedule of Assessments).

In general, unless otherwise noted, a window of ± 2 days is allowed when scheduling protocol visits and evaluations. If, due to unforeseen circumstances, frame-shifting of a study cycle or patient visit schedule occurs beyond the allowable window of ± 2 days, the medical monitor for the Sponsor should be notified of the alternate schedule. The protocol window of ± 2 days may then be applied to the frame-shifted schedule.

Unscheduled clinical assessments during a study cycle are allowed, but should not replace a per-protocol study visit unless it is within the ± 2 day window. During the phase II portion of the study, an unscheduled visit during Cycle 3 or beyond will satisfy the requirement for Day 15 patient contact provided it was +/- 7 days from Day 15 of a given cycle, using the date of the start of the cycle as reference.

5.2 Informed Consent

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

Informed consent should be obtained within approximately one month prior to Run-In Day 1. An appropriate informed consent must be completed prior to undergoing any laboratory or radiologic evaluations that are specifically being performed for the purpose of screening for this study. However, assessments or laboratory evaluations that have been performed as a part of standard of care (and not specifically for this study) may be used to qualify for enrollment. All screening procedures should be performed within the time frames indicated in the sections below.

The treating investigator must verify that the patient meets all inclusion/exclusion criteria. The patient is considered enrolled into the study when he or she begins Cycle 1, Day 1.

A log will be kept of all patients who sign informed consent. This “screening log” will indicate whether the consented patient was enrolled; if the patient was not enrolled, then the log will indicate the reason for non-enrollment. Recording of official study data on Case Report Forms (CRFs) is only required for those patients who enroll in the study (who begin Run-In Day 1).

In addition, any adverse events (AEs) that occurred as a result of screening tests that would not have otherwise been performed should be recorded.

5.3 Pre-Study Evaluations (Baseline)

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

The Pre-Study evaluation may be held up to 5 days (±2) prior to the first dose of sorafenib and/or study drug (either BBI608 or BBI503). The following evaluations will be obtained (unless otherwise obtained as a part of standard of care).

- Medical history, including resolved medical/surgical conditions, active concurrent medical conditions/adverse events, concurrent medications, as well as detailed history of current cancer diagnosis, treatment, and response to treatment (see Section 6.1).
- Vital signs (weight, temperature, blood pressure, height, respiration and pulse) and Physical examination, including documentation and measurement of any external or palpable subcutaneous lesions (see Sections 9.1.2 and 9.1.3)
- ECOG performance status (see Section 16)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3);
- Urinalysis (see Section 6.3)
- Serum pregnancy test (if applicable)
- Serum AFP level* (see Section 6.3)
- Electrocardiogram*
- Assess Child Pugh Class
- Optional tumor biopsy, if applicable* (see Section 6.5.2)
- Tumor lesion measurement and staging according to RECIST 1.1 as well as modified RECIST for patients with HCC [computed tomography (CT) of the chest, abdomen, and pelvis with tri-phasic liver scan *or* magnetic resonance imaging (MRI) of the abdomen and pelvis with contrast plus a CT scan of the chest without contrast in case of allergic reaction to CT scan contrast despite appropriate pre-treatment] **

**These do not need to be repeated if they were done within 7 days of this visit*

***Imaging obtained that meets these specifications can be used as the baseline assessment if it was obtained within two weeks ± 7 days of Cycle 1, Day 1.*

Note:

After the amendment 3 was in effect, Arm 2 in the Phase II portion was closed for enrollment due to BBI503 portfolio priorities and to increase efforts in enrolling patients on to Arm 1 and 3.

At the time of the amendment 3 being in effect, there were approximately 10 subjects enrolled in Arm 2 and approximately 30 patients remains to be the targeted sample size in each of the two open remaining arms, therefore, the total actual sample size in Phase II in the end is projected to be approximately 70 patients after the amendment 3.

5.4 On-Study Evaluation & Assessment Schedule │ Cycle 1

The patient will be administered sorafenib monotherapy for the first two weeks of Cycle 1, which can also be termed "sorafenib run-in". The goal of the run-in period is to establish the tolerability of sorafenib prior to initiating combination therapy with study drug (either BBI608 or BBI503).

Sorafenib will be obtained by the patient during this study as a standard-of-care medication; sorafenib will not be provided by study Sponsor.

Time required for the patient to initially obtain sorafenib should be taken into consideration when scheduling screening evaluations. Throughout the study, sorafenib will be supplied as a standard of care medication, guided by institutional and manufacturer policy.

5.4.1 Cycle 1, Day 1 │ Start of Sorafenib Run-In

- Patient begins sorafenib dosing at 400 mg twice daily (800 mg total daily dose).
- Schedule radiologic assessments for 8 weeks (56 days) from the date of Cycle 1, Day 1 (a scheduling window of ± 7 days is allowed for each radiologic assessment) *
- Vital signs (temperature, blood pressure, respiration and pulse) and weight
- AE assessment
- Review concomitant medications

**Radiologic evaluations do not need to correlate with study cycles. The per-protocol assessments should be performed every 8 weeks regardless of study cycle count. As such, per-protocol radiologic assessments should be scheduled in advance once the first dose of sorafenib is administered on Cycle 1, day 1 (Run-In Day 1).*

5.4.2 Cycle 1, Day 8 │ Mid Run-In (Phone Call is allowed)

- Phone call to patient to assess adverse events with sorafenib monotherapy
- Review concomitant medications
- If visit is held in person, assess vital signs

5.4.3 Cycle 1, Day 15 │Start of Combination Therapy

The assessments on Cycle 1, Day 15 may be performed before, after, or both before and after the administration of study drug (either BBI608 or BBI503) as indicated below. Assessments performed before the administration of study drug are to characterize any objective effects of sorafenib monotherapy prior to the initiation of combination therapy.

For the phase Ib portion of the study, both sorafenib and study drug should be administered in clinic to accommodate pharmacokinetic evaluations. The administration schedule is according to study arm and is outlined in the study procedure manual.

For both the phase Ib and phase II portions of the study, the following C1D15 assessments should be performed *prior to the first dose of study drug* for patients randomized to receive either BBI608 or BBI503 in combination with sorafenib. If patients in Phase II have been randomized to receive sorafenib alone [Arm 3], the following labs are still required but may be obtained at any time on C1D15 (either before or after dosing with sorafenib on that day):

- Physical exam (including vital signs, weight)
- ECOG performance status (see Section 16)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Electrocardiogram prior to first dose of study drug
- Serum AFP
- AE assessment
- Concomitant medications

After the above assessments are performed, study drug (either BBI608 or BBI503) may be initiated for those in the phase Ib portion of the study and for those in the Phase II portion who have been randomized to either [Arm 1] or [Arm 2*]. For those patients administered a dose of study drug (either BBI608 or BBI503), the following assessments should be performed *after* receiving the dose:

- *Phase Ib Only:* Blood samples for pharmacokinetics (see Section 6.4).
- *Phase Ib Only:* Electrocardiogram pre dose and approximately 3.5 hours after the first dose of study drug (either BBI608 or BBI503) dispense 14-day supply of study drug (either BBI608 or BBI503)
- Dispense two (2) days of study drug (either BBI608 or BBI503) dosing to be kept as "extra doses" by patient during study in case of loss or issues with visit scheduling (see Pharmacy Manual)

The procedures above do not apply to those in the phase II portion who have been randomized to [Arm 3], sorafenib alone.

* Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

5.4.4 Cycle 1, Day 16 │ Phase Ib Arm 2 Only

- *Phase Ib Arm 2 Only:* Blood samples for pharmacokinetics (see Section 6.4).
- Assess adverse events

5.4.5 Cycle 1, Day 22

- Vital signs, Weight
- Assess adverse events
- Record concomitant medication

5.5 On-Study Evaluation & Assessment Schedule │ Cycle 2

5.5.1 Cycle 2, Day 1

For both Phase Ib and Phase II, patients will have the following assessments:

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- ECOG performance status
- Physical examination
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Serum AFP (see Section 6.3)
- Assess adverse events
- Record concomitant medication
- Dispense 28 day supply study drug (either BBI608 or BBI503)*

*2 days of "extra doses" may be re-dispensed at a monthly visit if it was needed during the preceding cycle

5.5.2 Cycle 2, Day 15

Patients receiving BBI608 should take their dose of protocol therapy in clinic on this day.

- Vital signs, Weight
- Assess adverse events
- Record concomitant medication

- Blood samples for pharmacokinetics (Section 6.4)
- *Phase Ib Only:* Electrocardiogram approximately 3.5 hours after morning dose of BBI608 or approximately 13 hours after previous night dosing of BBI503
- *Phase II:* Electrocardiogram at least 3.5 hours after morning dose of BBI608 if patient has been taking the doses regularly, otherwise this assessment would be moved to C3D1 or subsequent visit. The electrocardiogram is required for patients on all arms. Optional on-treatment tumor biopsy*

*If the optional on-treatment tumor biopsy is scheduled on a day other than when pharmacokinetic blood drawn are obtained, then a single blood draw for determination of plasma study drug levels is required at the time of the biopsy. The on-treatment biopsy can be performed beyond the window for the visit due the complexity of the procedure.

5.6 On-Study Evaluation & Assessment Schedule │ Cycle 3 and Subsequent Cycles

5.6.1 Cycle 3, Day 1 (and Day 1 of all subsequent study cycles)

The following assessments will also be performed:

- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Physical examination
- ECOG performance status
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Serum AFP (see Section 6.3)
- Assess adverse events
- Record concomitant medication
- Dispense study drug (either BBI608 or BBI503) (28 day supply) *

*2 days of "extra doses" may be re-dispensed at a monthly visit if it was needed during the preceding cycle

5.6.2 Cycle 3, Day 15 (and Day 15 of all subsequent cycles) *

- Vital signs, Weight
- Assess adverse events
- Record concomitant medication

*These study visits do not need to be in-person. If a patient is not seen in-person, he or she should be contacted by phone in order to assess adverse events and record concomitant medication. Vital signs and weight need only be obtained if there is an in-person visit.

5.7 Tumor Evaluation Visits

5.7.1 Baseline

Baseline radiologic evaluation of chest, abdomen, and pelvis of sufficient quality to determine presence of disease according to RECIST and mRECIST for HCC is required prior to starting protocol therapy. This is defined as computed tomography (CT) with intravenous contrast of the chest, abdomen, and pelvis with tri-phasic liver scan. For those with an allergic reaction to intravenous CT contrast despite appropriate pre-treatment measures, magnetic resonance imaging (MRI) of the abdomen and pelvis with gadolinium plus a non-contrast CT scan of the chest is required.

Radiologic assessments satisfying the above requirements that are obtained within 14 days of the first dose of sorafenib (Cycle 1, Day 1) may be used as baseline imaging.

5.7.2 Per-Protocol

Per-protocol radiologic assessments will be performed every eight weeks (56 days), as calculated according to the date of the first dose of the sorafenib run-in period. A window of ±7 days is allowed when scheduling radiologic disease assessments (applies to each scan individually). Per-protocol radiologic assessments are defined as a computed tomography (CT) with intravenous contrast of the chest, abdomen, and pelvis with tri-phasic liver scan. For those with an allergic reaction to intravenous CT contrast despite appropriate pre-treatment measures, per-protocol evaluation with magnetic resonance imaging (MRI) of the abdomen and pelvis with gadolinium plus a non-contrast CT scan of the chest is required.

Additional radiologic evaluations when clinically indicated are allowed. However, evaluations obtained for clinical indications cannot be substituted for per-protocol radiologic assessments unless they also satisfy the above per-protocol definition of radiologic assessment.

Per-Protocol radiologic evaluations should be performed every 8 weeks (56 days) until radiologic disease progression is observed according to *both* RECIST 1.1 and modified RECIST for patients with HCC. If protocol therapy is permanently discontinued for any reason without documentation of PD per RECIST 1.1 and mRECIST for HCC, per-protocol imaging evaluations should continue every 8-weeks until criteria for disease progression are satisfied according to both RECIST 1.1 and mRECIST for HCC.

Patients with an imaging assessment which meets criteria for either complete response (CR) or partial response (PR) according to RECIST 1.1 or mRECIST should have a repeat, confirmatory, radiologic assessment approximately 4 weeks after the assessment in which CR or PR criteria were met. After the confirmatory image, radiologic assessments return to the every 8 week schedule.

If, at any time, a determination is made for a study subject to discontinue protocol therapy, the treating investigator should determine the likelihood that the patient will be able to attend the next scheduled radiologic assessment. If the treating investigator feels it is unlikely that a patient will be able to obtain the next scheduled per-protocol radiologic assessment, a per-protocol radiologic assessment should be obtained as soon as possible (a minimum of 4 weeks, however, should elapse between per-protocol assessments).

Tumor response will be evaluated using the guidelines for Response Evaluation Criteria in Solid Tumors (RECIST 1.1) and modified RECIST for patients with HCC. Highlights of these guidelines are contained in Section 9.

In general, for each radiologic imaging assessment obtained during the study, the following information and documentation is required:

- Completed RECIST 1.1 and mRECIST for HCC worksheets (provided by Sponsor) that document lesion measurements and descriptions
- De-identified, dictated, radiology report of the image (see Section 5.7.4)

De-identified digital images and/or complete copies of the digital imaging study may be requested from study sites (see Section 5.7.4).

5.7.3 Patient Disposition & RECIST Criteria

RECIST criteria serve to categorize clinical radiologic images. RECIST categorization alone should not determine continuation or discontinuation of protocol therapy in a patient. Given that both study drugs (BBI608 and BBI503) have a unique mechanism of action that targets cancer stem cells, study drug therapy may be continued in a patient who is clinically well but who meets criteria for "Progressed Disease" per RECIST (either RECIST 1.1 or modified RECIST for patients with HCC). Continuation of study drug (either BBI608 or BBI503) therapy in this context is allowed provided that no further standard, approved

treatment options exist, and provided that the investigator concludes that the potential benefit to the patient outweighs the potential risk.

5.7.4 Documentation and Digital Files

Clinical site staff will be responsible for collection and documentation of those lesion measurements required to complete response assessments according to RECIST 1.1 guidelines and modified RECIST guidelines for patients with HCC. Worksheets will be provided on which measurements for target and non-target lesions using both RECIST 1.1 and mRECIST for HCC can be documented. Please refer to Section 9 for further information on definitions and RECIST guidelines.

Quantitative image measurements and qualitative image characteristics according to RECIST guidelines will be documented in study Case Report Forms (CRFs). For exploratory purposes, the Sponsor may collect additional information from patient radiologic images. Examples of additional information include but are not limited to: de-identified radiology reports or dictations, digital copies of de-identified radiologic images, and/or complete de-identified image files.

5.8 End of Study Evaluation

For both phase Ib and phase II, all patients should be seen 14 to 30 days after discontinuation of protocol therapy. This is the End of Study (EOS) visit. The following assessments will be made during the end of study visit:

- Physical examination
- ECOG performance status
- Vital signs (weight, temperature, blood pressure, respiration and pulse)
- Hematology (see Section 6.3)
- Blood chemistry (see Section 6.3)
- Urinalysis (see Section 6.3)
- Serum AFP (see Section 6.3)
- Assess Child Pugh Class
- Tumor measurements and staging if radiologic progression has not yet been documented on study. That is, if a patient discontinues protocol therapy due to radiologic progression of disease, an End of Study *imaging* assessment is not required.
- Assess adverse events
- Record concomitant medications

Patients who are identified at the EOS visit as having persistent adverse events related to study drug (either BBI608 or BBI503) should continue to be followed on a monthly basis (or more frequently if clinically indicated) until resolution of study drug - related adverse events or until the AEs are deemed irreversible.

Any Serious Adverse Events (SAEs) that occur up to 30 days after the last dose of study drug (either BBI608 or BBI503) will be reported to the Sponsor regardless of assessed causality (also see Section 8.2).

5.9 Discontinuation from Study

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

- Progression of disease*
- Noncompliance with any part of the study, as evaluated by the Principal Investigator and Medical Monitor
- Patient request
- Withdrawal of consent
- Lost to Follow-up despite documented efforts at contact

- Clinically unacceptable adverse events despite optimal treatment or dose reduction.
- Death

*Since study drug (either BBI608 or BBI503) targets cancer stem cells, patients may continue study drug (either BBI608 or BBI503) administration with or without sorafenib beyond progression per RECIST if the investigator concludes that the potential clinical benefits outweigh potential risks.

5.9.1 Dates Associated with Discontinuation from Study

The following clarifies important dates at the end of study treatment:

Date of Last Dose: The date that the last dose of study medication is taken (either BBI608 or BBI503). *The Date of Last Dose* does not necessarily need to be the *Date Off Active Study.*

Date Off Active Study: The date when both the patient and the investigator/study team understand the patient to be off of active protocol treatment. In most cases, this will be the same as the *Date of Last Dose*; however, it does not need to be the case. In addition, the *Date Off Active Study* may not coincide with a formal study visit.

End of Study Visit: A formal study visit held 14 to 30 days after the *Date of Last Dose*.

5.10 Follow Up After Treatment Discontinuation

For both the phase Ib and phase II portions of the study, the follow-up phase of the study will begin after the EOS study visit has been completed. Patients will be followed for specified clinical endpoints (both primary safety and secondary exploratory efficacy endpoint), and other important information such as post-protocol therapy.

As specified in Section 5.7.2, per-protocol imaging (every 8 weeks/56 days) should continue until criteria for disease progression according to both RECIST 1.1 and mRECIST for HCC are met.

There are no further visits required specifically for the study after the EOS visit, with the exception of radiologic assessments every 8 weeks until progression of disease is documented according to both RECIST 1.1 criteria and mRECIST for patients with HCC criteria.

The clinical parameters and endpoints for follow-up after a patient permanently discontinues study drug (either BBI608 or BBI503) administration are specified in table below, as is the recommended follow up frequency. Follow-up and information collection is intended to be accomplished through review of the local medical record system by site study staff and/or study CRAs-Monitors. Contact with the primary oncologist and/or primary care physician for a given patient may also be required.

Table 3: Clinical Parameters for Post-Protocol Therapy Follow-Up

Endpoint	Description	Follow-Up Frequency
Performance Status Decline	First date when ECOG performance status of ≥ 3 is documented, if possible	Evidence for clinical endpoints will be assessed monthly for the first 6 months after discontinuing study drug (either BBI608 or BBI503) Then, Quarterly from 6 months to 18 months after discontinuing study drug (either BBI608 or BBI503) Then, Semi-annually thereafter
Subsequent Therapy	Names and dates of anti-cancer treatment administered after permanent study drug (either BBI608 or BBI503) discontinuation. "Clinical Trial" can also be used if agent name is not publically available	
Objective Disease Progression following subsequent therapy	Date criteria for RECIST 1.1 and/or mRECIST for HCC categorization of "PD" are met after starting any post-protocol therapy, if possible*	
Survival	Date of death due to any cause	

*Passive follow-up only of radiologic imaging obtained following initiation of any post-protocol therapy

6 STUDY PROCEDURES

6.1 Medical History

A complete medical history will be obtained. The components will include, but are not limited to, the following:

- Demography: date of birth, sex, race, ethnicity, height, and weight
- Clinically significant prior non-cancer diagnoses, surgeries, and current medications
- Prior cancer history, current cancer diagnosis, tumor stage at time of diagnosis and at time of study screening
- Prior surgical procedure(s), including date, anatomic site, and specific procedure performed; including loco-regional liver-directed therapy such as embolization, chemoembolization, radiofrequency ablation, etc.
- Current and prior modifiable risk-factors (smoking, alcohol use, including estimated amount and duration of use)
- Prior imaging reports, lesion measurements, and/or image reproductions may be requested from different periods in the cancer-specific history for a given patient.
- The suspected causal setting in which HCC arose is requested (i.e., a history of hepatitis C (HCV), hepatitis B (HBV), or inherited metabolic disorders).
- History of non-alcoholic fatty liver disease (NAFLD), if any
- Smoking and tobacco history
- In addition to AFP levels at baseline, at least one alfa-feto protein (AFP) level from before the baseline visit is requested, in order to establish two AFP levels prior to starting sorafenib on study.

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

6.2 Physical Examination

Complete physical examination including height, weight, blood pressure, heart rate, respiratory rate, temperature (oral, axillary or tympanic) and ECOG performance status (Section 16). In addition, presence of encephalopathy and degree of ascites should be assessed so that Child Pugh score can be calculated.

6.3 Clinical Laboratory Tests

Safety laboratory determinations will include hematology, blood chemistry, and urinalyses. All laboratory tests required during the study must be obtained at a laboratory approved by the sponsor and site Principal Investigator. Please see the Laboratory and Procedure Manual for further details.

- Hematology: CBC including hemoglobin, hematocrit, white blood cell count with 5-part differential (automated differential is acceptable), red blood cell, platelet, INR (for prothrombin time).
- Blood chemistry: CO_2, calcium, phosphorus, magnesium, albumin, glucose, and serum creatinine, AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, total and direct bilirubin, uric acid, total protein and blood urea nitrogen (BUN), sodium, potassium, and chloride
- Routine urinalysis: dipstick and microscopy including protein, specific gravity, glucose and blood
- Serum pregnancy test for female patients of childbearing potential
- Serum alpha fetoprotein levels

6.4 Pharmacokinetic Assessments

6.4.1 Phase Ib

Pharmacokinetic assessments will be performed during the phase Ib portion of the study, and the schedule of assessments is based on the study arm the patient is assigned to.

6.4.1.1 Arm 1: BBI608

Plasma samples for pharmacokinetics will be obtained on Cycle 1, Day 15 and on Cycle 2, Day 15. Patients from selected sites may have overnight pharmacokinetic testing performed. The exact schedule of time-points for all pharmacokinetic sampling can be found in the study Laboratory and Procedure Manual and is found in **Table 4** below.

Table 4: Complete Pharmacokinetic Sampling Schedule for Arm 1 (BBI608)

Cycle	Day	Procedure	Scheduled Time
1	15	ECG	Immediately before pre-dose sample
1	15	Draw blood sample	0 hr (pre-dose)
1	15	Patient is administered AM BBI608 dose	
1	15	Draw blood sample	0.5 hr (30 min)
1	15	Draw blood sample	1 hr
1	15	Draw blood sample	1.5 hr
1	15	Draw blood sample	2 hr
1	15	Draw blood sample	3 hr
1	15	ECG	~ 3.5 hr (± 15 min)
1	15	Draw blood sample	4 hr
1	15	Draw blood sample	6 hr
1	15	Draw blood sample	8 hr
1	15	Draw blood sample	10 hr
1	15	Draw blood sample	12 hr (pre-dose)
1	15	Patient is administered PM BBI608 dose	
2	15	Draw blood sample	0 hr (pre-dose)
2	15	Patient is administered AM BBI608 dose	
2	15	Draw blood sample	0.5 hr (30 min)
2	15	Draw blood sample	1 hr
2	15	Draw blood sample	1.5 hr
2	15	Draw blood sample	2 hr
2	15	Draw blood sample	3 hr
2	15	ECG	~ 3.5 hr
2	15	Draw blood sample	4 hr
2	15	Draw blood sample	6 hr
2	15	Draw blood sample	8 hr
2	15	Draw blood sample	10 hr
2	15	Draw blood sample	12 hr (pre-dose)
2	15	Patient is administered PM BBI608 dose	

6.4.1.2 Arm 2: BBI503

Plasma samples for pharmacokinetics will be obtained on Cycle 1, Day 15; Cycle 1, Day 16; and Cycle 2, Day 15. Patients from selected sites may have overnight pharmacokinetic testing performed. The exact schedule of time-points for all pharmacokinetic sampling can be found in the study Laboratory and Procedure Manual and in **Table 5** below.

Table 5: Complete Pharmacokinetic Sampling Schedule for Arm 2 (BBI503)

Please note that BBI503 will be administered in the morning of Cycle 1 Day 15 only. Subsequent administrations of BBI503 will be at night.

Cycle	Day	Procedure	Scheduled Time
1	15	ECG	Immediately before pre-dose sample
1	15	Draw blood sample	0 hr (predose)
1	15	Patient is administered BBI503 dose*	Morning of Cycle 1 Day 15
1	15	Draw blood sample	1 hr
1	15	Draw blood sample	2 hr
1	15	Draw blood sample	3 hr
1	15	ECG	~ 3.5 hr (± 15 min)
1	15	Draw blood sample	4 hr
1	15	Draw blood sample	6 hr
1	15	Draw blood sample	8 hr
1	15	Draw blood sample	10 hr
1	15	Draw blood sample	12 hr
1	16	Draw blood sample	24 hr
1	16	Patient is administered BBI503 dose	Evening of Cycle 1 Day 16
2	14	Patient is administered BBI503 dose at night**	-
2	15	Draw blood sample	12 hours post dose
2	15	ECG	13 hours post dose
2	15	Draw blood sample	16 hours post dose
2	15	Draw blood sample	20 hours post dose
2	15	Draw blood sample	24 hours post dose

*Following C1D1 AM dose, subsequent doses of BBI503 will be in the evening
**Time of dose administration must be recorded.

6.4.2 Phase II

During the phase II portion, a single blood draw for pharmacokinetics may be performed in patients on the morning of Cycle 2, Day 15; prior to the first dose, as outlined in **Table 6** and **Table 7** for patients randomized to Arm 1 (BBI608) or Arm 2 (BBI503).

Table 6: Single Sample Pharmacokinetic Sampling Schedule for Phase II / Arm 1 (BBI608)

Cycle	Day	Procedure	Scheduled Time
2	15	Draw blood sample	0 hr (predose)
2	15	Patient is administered BBI608 morning dose	

Table 7: Single Sample Pharmacokinetic Sampling Schedule for Phase II / Arm 2 (BBI503)

Cycle	Day	Procedure	Scheduled Time
2	14	Patient is administered BBI503 dose at night	-
2	15	Draw blood sample	Any time on Day 15*

*PK sample can be drawn at any time on Cycle 2 Day 15. Exact time of blood draw and the previous night dosing time must be recorded.

, A total 6 patients for Napabucasin at the RP2D levelwill have a complete PK assessment using the pharmacokinetic draw schedules outlined in Section 6.4.1, Patients assigned to the sorafenib only arm will not have PK blood draws obtained.

Note:

After the amendment 3 was in effect, Arm 2 in the Phase II portion was closed for enrollment due to BBI503 portfolio priorities and to increase efforts in enrolling patients on to Arm 1 and 3.

At the time of the amendment 3 being in effect, there were approximately 10 subjects enrolled in Arm 2 and approximately 30 patients remains to be the targeted sample size in each of the two open remaining arms, therefore, the total actual sample size in Phase II in the end is projected to be approximately 70 patients after the amendment 3.

6.5 Pharmacodynamic Assessments

Pre-clinical studies conducted at BBI have identified several biomarkers in tumor tissues whose levels either increase or decrease upon exposure to BBI608 or BBI503. Tumor biopsy is an optional component of this study. Provided that the patient has an accessible tumor, an optional tumor biopsy consent form will be made available to the patient. In addition to biopsy, archival tissue will also be collected.

The goal of the proposed biomarker study is to examine the response of biomarkers in patients treated with study drug (either BBI608 or BBI503). Subject tumor samples will be processed for determination of pharmacodynamic markers by histopathology and flow cytometry.

Tumor biopsy may be collected from patients who consent to the optional procedure during the phase II portion of the study – including patients who are randomized to the sorafenib only arm.

6.5.1 Archival Tissue

Paraffin-fixed tumor tissue from a previous biopsy or resection is requested of all patients. Release of tissue to BBI for testing is required if tissue is available. However, patients may still enroll on study if they do not have tissue available. For those with tissue available, tumor blocks are preferred. If archival tumor blocks are not available, then archival tumor-tissue cores are requested. If tumor cores cannot be made, 20 glass slides are requested.

Site study staff and Sponsor-CRAs/monitors will aid in the coordination and shipment of archival tissue samples to BBI. Remaining tissue blocks and/or slides will be returned to sites at the conclusion of testing, or at a time requested by the study site.

Specific shipping and processing instructions will be detailed in the study Laboratory and Procedure Manual.

6.5.2 Tumor Biopsy

Biopsy is an optional component of this study. Patients identified by the Principal Investigator as having a lesion amenable to biopsy through a minimal to low-risk procedure may be asked to review a separate biopsy-component consent form. Of note, image-guided biopsy of internal or visceral lesions may qualify as a low-risk procedure. Patients can refuse the optional biopsy-component of this study and still enroll in the main study.

Patients may consent to one biopsy or to two biopsies. If the patient consents to two biopsies, a tumor biopsy will be collected at some point prior to the administration of the first dose of sorafenib on study, and again on Cycle 2, Day 15. Collection, storage, and shipping of tissue samples will be performed as described in the study Laboratory & Procedure Manual. If a patient consents to only one biopsy, then either a baseline/pre-treatment biopsy will be obtained prior to the first dose of sorafenib on study, or an on-treatment biopsy will be obtained on Cycle 2, Day 15.

If the tumor biopsy is scheduled for a day other than when blood draws for pharmacokinetics are being obtained, then a single blood draw within 30 minutes of the time of the biopsy is required.

7 TREATMENT

7.1 Sorafenib

Sorafenib is to be administered at a starting dose of 400 mg twice daily, in accordance with the standard starting dose. Sorafenib will be administered on an empty stomach, either 1 hour prior to a meal or 2 hours after a meal. Sorafenib will be administered according to the product label. Dose modification is allowed according to standard of care. Patients must qualify for treatment with sorafenib and must be able to obtain sorafenib in order to be enrolled on study.

Sorafenib will be dispensed during the study according to standard of care practices and in accordance and local site and manufacturer policies.

During the phase Ib portion of the study, if sorafenib is discontinued for any reason, administration of study drug (either BBI608 or BBI503) may continue per protocol.

During the phase Ib portion of the study, if study drug (BBI608 or BBI503) administration is permanently discontinued for any reason, the patient will be considered to have ended the active treatment component of the protocol. The follow-up phase of the study will begin at that time (see Section 5.10), regardless of further treatment decisions made at the discretion of the investigator.

During the phase II portion of the study, patients may continue to receive BBI608 or BBI503 if they are in [phase II Arm 1] or [phase II Arm 2] and if sorafenib is discontinued for any reason. Patients in [phase II Arm 3] who discontinue sorafenib will end the active treatment part of the protocol, and will begin the follow-up portion of the protocol – including radiologic assessments every 8 weeks (56 days) until disease progression is determined per RECIST 1.1 and mRECIST for HCC.

7.2 Study Drug

7.2.1 BBI608

BBI608 capsules will be supplied to the pharmacy at the clinical sites. BBI608 will be labeled as an investigational agent, limited by federal law. The pharmacist will dispense the appropriate number of BBI608 80 mg capsules according to the assigned dose cohort and according to the dispensing schedule outlined in Section 5.4. The specific capsule strength of BBI608 for a given site and the associated storage conditions will be outlined in the study Laboratory and Procedure Manual.

Briefly, quantity sufficient for 14 days of BBI608 dosing at the assigned dose level is dispensed on Cycle 1, Day 15. Subsequently, quantity sufficient for 28 days of BBI608 dosing at the assigned dose level is dispensed on Cycle 2, Day 1 and on Day 1 of each subsequent cycle.

In addition, on Cycle 1, Day 15, an “extra dose” bottle with 2 days of extra dosing will be dispensed to patients for use in case of loss or visit scheduling issues. Additional “extra dose” bottles can be re-dispensed to patients if the original bottles are used.

7.2.1.1 BBI608 Administration

BBI608 will be administered orally, twice daily, in continuous, repeating, 28-day cycles, at a starting dose-level of 160 mg twice daily. The first dose of BBI608 should be administered shortly after waking in the morning. The second dose should be taken before bedtime, and Approximately 12 hours should separate the two BBI608 doses. BBI608 should not be taken with sorafenib. At least 2 hours should separate a dose of sorafenib from a dose of BBI608.

BBI608 should be taken before the first dose of sorafenib. BBI608 should be administered 1 hour prior to a meal or 2 hours after. BBI608 and sorafenib should be taken around the same time every day.

An example dosing schedule is provided in the Study Manual. Dose escalation of BBI608 in combination with sorafenib will proceed according to the procedures outlined in Section 4.

7.2.2 BBI503

BBI503 capsules or tablets will be supplied to the pharmacy at the clinical sites. BBI503 will be labeled as an investigational agent, limited by federal law. The pharmacist will dispense the appropriate number of BBI503 50 mg to 100 mg capsules or 100mg tablets according to the assigned dose cohort and according to the dispensing schedule outlined in Section 5.4. When the capsule supply is depleted, the site will be resupplied with the tablet formulation. The specific type of BBI503 for a given site and the associated storage conditions will be outlined in the study Laboratory and Procedure Manual.

Briefly, quantity sufficient for 14 days of BBI503 dosing at the assigned dose level is dispensed on Cycle 1, Day 15. Subsequently, quantity sufficient for 28 days of BBI503 dosing at the assigned dose level is dispensed on Cycle 2, Day 1 and on Day 1 of each subsequent cycle.

In addition, on Cycle 1, Day 15, an "extra dose" bottle with 2 days of extra dosing will be dispensed to patients for use in case of loss or visit scheduling issues. Additional "extra dose" bottles can be re-dispensed to patients if the original "extra dose" bottles are used.

7.2.2.1 BBI503 Administration

BBI503 will be administered at a starting dose-level of 100 mg Once Daily given in continuous, repeating, 28-day cycles. BBI503 will be administered before bed and should not be administered at the same time as sorafenib. At least 2 hours should separate a dose of sorafenib from a dose of BBI503. The total daily dose of BBI503 may be divided into sub-doses taken at least 6 hours apart. Dose escalation of BBI503 in combination with sorafenib will proceed according to the procedures outlined in Section 4.

BBI503 is taken 1 hour prior to meals or 2 hours after. A dose of BBI503 and a dose of sorafenib should be separated by at least 2 hours.

7.2.3 Investigational Product Accountability

BBI will provide all study drug (either BBI608 or BBI503) required for completion of this study. The recipient will acknowledge receipt of the drug and will record shipment content and condition. Damaged supplies will be replaced. Until dispensed to the patients, the study drug will be stored as specified in the Pharmacy Manual, in a secure locked area, accessible to authorized personnel only.

Accurate records of all study drug (either BBI608 or BBI503) dispensed from and returned to the study site are to be maintained. The study site must supply a copy of its drug destruction policy to BBI before authorization for destruction will be granted. Product accountability will be monitored throughout the study. Upon completion or termination of the study and after inventory by a BBI monitor or designated representative, all unopened drug will be returned to BBI or designee in the original containers.

7.3 Dose Modifications

The following section outlines the dose-modifications allowed on study for sorafenib and for study drug (either BBI608 or BBI503).

7.3.1 Sorafenib

The starting dose of sorafenib is 400 mg twice daily, in accordance with the standard starting dose. Dose modification is allowed according to the product label and according to standard of care practices. Sorafenib is administered initially as monotherapy for a 2-week run-in period. The tolerability profile of

sorafenib alone should be identified for a given patient during this period, prior to the start of combination therapy.

Dose-modification of sorafenib for non-dermatologic toxicities is allowed. Dose-modification of sorafenib for dermatologic toxicity is as outlined in **Table 8** below:

Table 8: Suggested Sorafenib Dose Modifications for Dermatologic Toxicities in Patients with Hepatocellular Carcinoma

Dermatologic Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with SORAFENIB and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with SORAFENIB and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt SORAFENIB treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease SORAFENIB dose by one dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue SORAFENIB treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt SORAFENIB treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease SORAFENIB dose by one dose level (400 mg daily or 400 mg every other day)
	3rd occurrence	Discontinue SORAFENIB treatment

7.3.2 Study Drug – BBI608 or BBI503

The safety profiles of both BBI608 and BBI503 are well established. The following dose-modification guidelines are based on clinical experience to date.

During the dose-escalation phase of the study, dose-modification of study drug (either BBI608 or BBI503) should adhere to the following guidelines:

- For any intolerable Grade 2 or Grade 3 adverse events, the assigned dose of study drug (either BBI608 or BBI503) should be held.
- If the adverse event resolves to tolerable levels (must be ≤ grade 2 or at the baseline grade), dosing can resume at the assigned dose level with *pharmacologic support measures* administered.
    - Pharmacologic support measures for each study drug (either BBI608 or BBI503) are provided in Section 7.3.2.1 below.
- If the adverse event takes longer than 5 days to resolve to tolerable levels (≤ grade 2) or to the baseline grade, or if the adverse event recurs upon resumed administration despite pharmacologic support, the dose may be reduced by one or more dose levels.

- If the assigned dose is the first dose-level and dose-reduction is required, a lower level can be determined by the Principal Investigator and the medical monitor for the Sponsor.
- A patient who requires dose-reduction is allowed to increase his or her dose back to the assigned dose-level with pharmacologic support.

- Intra-patient dose escalation above the assigned starting dose-level is permitted, provided the increased dose-level has been determined safe according to the criteria for dose-escalation and determination of dose-limiting toxicity (Section 4.6).

During the phase II portion of the study, and once RP2D is determined for a study drug (either BBI608 or BBI503) in combination with sorafenib, dose-modification can occur according to the following guidelines:

- For Grade 2 or Grade 3 gastrointestinal adverse events, or Grade 2 or Grade 3 fatigue, the assigned dose of study drug (either BBI608 or BBI503) may be reduced to a lower dose level with or without holding dose (a dose holiday).
  - When restarting study drug administration or when modifying to a lower dose-level, supportive pharmacology is to be administered as outlined in Section 7.3.2.1.
  - For a given patient who has reduced his or her dose, and for whom the new dose-level is well tolerated, the dose may be increased slowly, as tolerated, with supportive pharmacology measures as outlined in Section 7.3.2.1 to a maximum dose of RP2D.
- For all adverse events other than fatigue, nausea, vomiting, anorexia, diarrhea, or cramping, dose modification is based on tolerability as follows:
  - Dosing should be held for intolerable Grade 2 or Grade 3 adverse events until the event resolves to tolerable levels (≤ Grade 2).
  - If the above criteria are met, dosing can resume at a lower dose level with appropriate pharmacologic support measures, if applicable.
  - If the lower dose level is well tolerated, the dose can be increased slowly, as tolerated, with supportive pharmacology if indicated, to a maximum dose of RP2D.

7.3.2.1 Specific Pharmacologic Recommendations - BBI608 and BBI503

Recommendations for supportive pharmacology for adverse events that can be associated with BBI608 or BBI03 administration are outlined in **Table 9** below, according to symptom.

Table 9: Supportive Pharmacology for Adverse Events Associated with BBI608 or BBI503 Administration

Diarrhea & Abdominal Cramping	Nausea, Vomiting, or Anorexia[1]
Dicyclomine *(e.g., Bentyl)*: Recommended when the predominant issue is cramping or abdominal pain	**1st line:** 5HT3-inhibitorsJD *(Ondansetron, Palonosetron, Granisetron)*
Diphenoxylate/atropine *(Lomotil)* **Loperamide** *(Imodium)* These agents may be useful in combination	**2nd line:** Dexamethasone *(Decadron)*, ideally in combination with a 5HT3-inhibitor. Short term use can be very effective
Hyoscine *(Buscopan, Scopolamine, Levsin)*: Anti-spasmodic agents helpful for abdominal cramping	**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.
Steroid with limited systemic absorption[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

When study drug (either BBI608 or BBI503) administration is resumed following dose-reduction or a dose hold, adverse events that were associated with study drug (either BBI608 or BBI503) administration are typically improved. As such, when a new dose-level of study drug (either BBI608 or BBI503) is tolerated for 4 to 7 days and pharmacologic support is administered, the dose can be re-escalated, as tolerated, in increments allowed by the capsule or tablet in use (e.g., 80 mg for BBI608 and 50 mg for BBI503 capsule or 100mg tablet). The dose can be res-escalated up to either the assigned dose-level (if during dose-escalation) or up to RP2D (if determined).

7.4 Treatment Compliance

A patient is considered compliant with the study protocol when each component of the assigned protocol therapy is taken at a compliance level of greater than 80%. The components of protocol therapy assigned will depend on what study arm the patient is randomized to, and whether the patient is randomized during the phase Ib or phase II portion of the protocol.

Compliance with sorafenib will be calculated using the following equation:

$$\%\ \text{Compliance} = \frac{\text{Number of capsules actually ingested in a given time period}}{\text{Number of capsules that should have been ingested}^{*}} \times 100$$

*During the phase Ib portion of the study, the denominator of the compliance equation (the number of sorafenib capsules that should have been ingested) refers to the dose of sorafenib administered at the start of combination therapy. During phase II, for patients randomized the sorafenib only arm [phase II Arm 3], the denominator of the compliance equation will refer to the dose of sorafenib administered on Cycle 1, Day 15.

Compliance with study drug (either BBI608 or BBI503) will be calculated using the following equation:

$$\%\ \text{Compliance} = \frac{\text{Number of capsules or tablets actually ingested in a given time period}}{\text{Number of capsules or tablets that should have been ingested per dose level}} \times 100$$

7.5 Blinding

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

7.6 Prior Treatment

Reasonable efforts will be made to determine all prior anti-cancer treatments received by the patient, as well as all concurrent medications continuously or occasionally taken at the time of enrollment on study. All relevant information must be recorded on the patient's case report form (CRF). All surgical procedures, prior chemotherapy, and radiation therapy must be recorded on the appropriate CRF. In addition to recording this information on the appropriate CRF, the information must also be reported to the Sponsor on the enrollment form in order to verify eligibility for the study with respect to prior treatments.

7.7 Concomitant Medication

7.7.1 Permitted Treatment

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

Palliative and supportive care for disease-related symptoms will be offered to all patients in this study. Patients may receive palliative radiation therapy.

In addition, the following treatments are allowed:

- Standard therapies for concurrent medical conditions
- Epoetin alfa (Epogen®, Procrit®)
- Hematopoietic growth factors, including filgrastim (Neupogen®) Thrombopoietin (e.g., Romiplostim (Nplate®), or other granulocyte colony stimulating factors (G-CSF), are permitted Prophylactic anti-emetics and/or anti-diarrheal agents may be administered according to standard practice
- Megestrol acetate (Megace®)
- Dexamethasone
- Diphenhydramine
- Cimetidine
- Ranitidine
- Bisphosphonates
- Denosumab

7.7.2 Prohibited Treatment

The following medications may not be administered to any patients while they are on study:

- Alternate chemotherapy, hormonal therapy, immunotherapy (not including corticosteroids), and non-palliative radiotherapy (radiotherapy with curative intent).
- Other investigational agents
- Immunosuppressive therapies, except for corticosteroids that are: 1) used intermittently in an anti-emetic regimen, 2) prescribed at a non-immunosuppressive dose for treatment of fatigue and low-appetite, or 3) prescribed as part of a pre-defined steroid taper for post palliative XRT.

If no alternative treatment option exists for the prohibited treatments, the situation of individual patient should be discussed with medical monitor to decide further course of action.

7.7.3 Drug-Drug Interactions

7.7.3.1 BBI608

No clinically apparent drug-drug interactions have been identified in patients administered BBI608, although a dedicated drug interaction study is currently ongoing in healthy human volunteers.

Napabucasin is primarily metabolized by the CYP P450 isoform 1A2. Therefore, caution should be exercised with drugs that are strong inhibitors or sensitive substrates of CYP1A2.

Examples of strong 1A2 inhibitors and sensitive inducers are presented below:

- Strong CYP 1A2 inhibitors: fluvoxamine, ciprofloxacin, enoxacin, zafirlukast
- Sensitive CYP1A2 substrates: alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine

Possible actions for investigators with patients taking medications as above include: discontinuing the medication entirely, continuing the medication and monitoring for adverse effects, and continuing the medication at a reduced dose and monitoring for adverse effects.

7.7.3.2 BBI503

No clinically apparent drug-drug interactions have been identified in patients administered BBI503, although no dedicated studies have specifically evaluated potential interactions.

BBI503 was shown to have minimal *in vitro* inhibitory activity against the individual CYP P450 isoforms 1A2, 2D6, 2C19, 3A4, and 2C9 with IC_{50}s of ≥10 μM for each isoform. In vivo inhibitory activity against these isoforms is expected to be > 1000 μM, given that the majority of BBI503 (> 99%) is expected to be bound to plasma protein.

In addition, in *in vitro* studies, BBI503 was not metabolized by any of the CYP P450 isoforms tested (1A2, 2D6, 2C19, 3A4, and 2C9).

7.7.3.3 Sorafenib

Effect of Strong CYP3A4 ***Inducers*** on sorafenib

Rifampin, a strong CYP3A4 inducer, administered at a dose of 600 mg once daily for 5 days in combination with a single oral dose of Sorafenib 400 mg in healthy volunteers resulted in a 37% decrease in the mean AUC of sorafenib *[see US approval label, Clinical Pharmacology Section (12.3)]*. Concomitant use of strong CYP3A4 inducers (such as carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, and St. John's wort, see Section 7.7.2 as well) is prohibited in this study during the dose-escalation phase because these drugs can decrease the systemic exposure to sorafenib.

Effect of Strong CYP3A4 ***Inhibitors*** on sorafenib

Ketoconazole, a strong inhibitor of CYP3A4 and P-glycoprotein, administered at a dose of 400 mg once daily for 7 days did not alter the mean AUC of a single oral dose of Sorafenib 50 mg in healthy volunteers. However, for this protocol, use of strong CYP3A4 inhibitors is prohibited during the dose-escalation phase (see Section 7.7.2).

Effect of sorafenib on Levels of Other Drugs

sorafenib 400 mg twice daily for 28 days did not increase the systemic exposure of concomitantly administered midazolam (CYP3A4 substrate), dextromethorphan (CYP2D6 substrate), and omeprazole (CYP2C19 substrate) (see sorafenib product label).

Neomycin

Neomycin administered as an oral dose of 1 g three times daily for 5 days decreased the mean AUC of sorafenib by 54% in healthy volunteers that had also been administered a single oral dose of sorafenib 400 mg. The effects of other antibiotics on the pharmacokinetics of sorafenib have not been studied (see sorafenib product label).

Drugs that Increase Gastric pH

The aqueous solubility of sorafenib is pH-dependent, with higher pH resulting in lower solubility. However, omeprazole, a proton pump inhibitor, administered at a dose of 40 mg once daily for 5 days, did not result in a clinically meaningful change in sorafenib single dose exposure. No dose adjustment for sorafenib is necessary when administered with drugs that increase gastric pH.

8 SAFETY ASSESSMENTS

8.1 Adverse Events

8.1.1 Assessments

The Investigator is responsible for monitoring the safety of patients who have enrolled in the study. All AEs that are considered to be related to study drug (either BBI608 or BBI503) or that occur after any administration of study drug will be followed until the event resolves. AEs will be evaluated using the National Cancer Institute (NCI) CTCAE, Version 4.0, published 28 May 2009.

Investigators are required to document all AEs that occur during the clinical trial, commencing with the first dose of study drug (either BBI608 or BBI503) and including the protocol-defined post-treatment follow-up period (21 Code of Federal Regulations [CFR] §312.64[b]), on designated CRF pages. AEs that occur after signing of the informed consent but prior to the first dose on study will not be reported as AEs*. It is also important to record all AEs, whether serious or non-serious, that result in permanent discontinuation of the investigational product being studied.

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

*Unless they occurred as the result of a screening test that would not have otherwise been performed as a part of standard of care.

8.1.2 Definitions

An AE is defined as any untoward medical occurrence in a patient or clinical investigational patient who is administered a pharmaceutical product; the medical occurrence does not need to have a causal relationship to the pharmaceutical product. An AE can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it is considered related to the medicinal product.

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

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

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

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

Appropriate CTCAE terms for AEs should be used whenever possible. If an appropriate CTCAE term is not available, then the verbatim term should be documented.

8.2 Serious Adverse Events

8.2.1 Definitions

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

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization, except for events that are clearly disease related
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events may be considered an SAE based upon appropriate medical judgment of the investigator and medical monitor for the Sponsor.

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

8.2.2 Reporting Serious Adverse Events

Any SAE, including death, that occurs during this investigation or in the 30 days following the last dose of study drug, regardless of assessed causality, must be reported to the Sponsor immediately (not to exceed 24 hours) by telephone, email, or facsimile. The event must be completely described on the SAE report form provided by the Sponsor. The SAE form should be sent to the Sponsor by email and/or facsimile to the contact listed in **Table 10** below:

Table 10: Primary Medical Monitor & Serious Adverse Event Contact

Matthew Hitron, MD Boston Biomedical, Inc 640 Memorial Drive Cambridge, MA 02139, USA Telephone:1- (617) 674-6800 ext 8563 Fax: (617) 674-8662 Email: mhitron@bostonbiomedical.com
Emergency Number**:** 1-508-410-5512

The SAE should also be entered as an Adverse Event on the Adverse Event CRF, with the fact indicated that it was an SAE (checkbox provided on the CRF).

Follow-up SAE reports are required when there is a significant development in the case. Examples of significant developments include: updates from diagnostic imaging or laboratory testing, new information from specialist consultation, or a change in the clinical status of the patient (either improved or worsened). Follow-up reports for significant developments are required until the case is considered to be concluded (as indicated by resolution of the event such that it is no longer "serious" or as indicated by other means (i.e., patient discharge, patient death)).

9 ASSESSMENT OF ANTI-TUMOR ACTIVITY

Radiologic images obtained on study will be assessed according to both RECIST 1.1 criteria and the criteria outlined in Modified RECIST (mRECIST) Assessment for Hepatocellular Carcinoma. mRECIST for HCC was developed in 2010 by R. Lencioni and JM Llovet to address the poor correlation between conventional methods of response assessment and the clinical benefit observed with the then-available treatment modalities for HCC. The modified approach specifically takes into consideration the level of arterial enhancement within a HCC lesion when determining response.

As BBI608 and BBI503 target cancer stem cells, it is not clear whether clinical benefit will be correlated with the response assessment made using RECIST 1.1 criteria, or with that made using mRECIST for HCC criteria--or correlated with neither set of criteria. As such, it is recommended that the patient be treated clinically and that decisions regarding continuation or discontinuation of protocol therapy be made mainly based on clinical assessment; radiologic imaging should inform, but not be the primary determinant of, the decision to continue or discontinue therapy.

Both sets of guidelines are briefly summarized in this section. For a complete overview, please refer to the original publications. Patient imaging while on study will be categorized according to both RECIST 1.1 criteria and mRECIST for HCC criteria, when possible.

In order to be eligible for enrollment, patients must have measurable disease per RECIST 1.1 definitions (outlined in Section 9.1.1). For that lesion to then qualify as measurable according mRECIST, the lesions must also show intratumoral arterial enhancement on contrast-enhanced CT or MRI.

Patients may enroll if they have at least measurable disease per RECIST 1.1. Please note, however, that since exploratory estimates of time to event endpoints such as TTP and PFS will be summarized using both methods, all patients should continue to be assessed on-study using both criteria (as progression according to mRECIST can be documented even if there is no disease measurable per mRECIST at baseline).

9.1 Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

The definitions and criteria from Response Evaluation Criteria in Solid Tumors [RECIST 1.1, Eisenhauer et al. 2009][1] are briefly summarized below. These criteria should be used to categorize on-study images.

9.1.1 Basic Definitions for RECIST 1.1

Measurable disease - the presence of at least one measurable lesion.

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

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

- All measurements should be taken and recorded in metric notation, using a ruler or calipers.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- External lesions identified on physical exam will be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and when they are ≥ 10 mm when measured using calipers. For the case of skin lesions, documentation by color photography and a measurement with a ruler to estimate the size of the lesion is recommended.

9.1.2 RECIST 1.1 Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous slices of 10 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
- All imaging methods should be performed according to institutional standards, and each patient should have a consistent method from baseline through the course of the study.

9.1.3 RECIST 1.1 Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of five lesions total with a maximum of 2 lesions per organ, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinical assessments).
- A sum of the longest diameter (LD) for all target lesions (for lymph nodes, use short-axis) will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference from which to characterize the objective tumor response.
- All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.
- Importantly, pre-study images should be assessed by either a member of the clinical investigative team at the study site or by a radiologist who is familiar with RECIST guidelines. The image report is not sufficient for identification of lesions per RECIST. The images themselves should be assessed at baseline for measurable disease that can qualify as target lesions.

9.1.4 Response Criteria and Classification for RECIST 1.1

The criteria for response categorization of radiologic imaging assessments per RECIST are highlighted in **Table 11** and **Table 12** below.

Table 11: RECIST 1.1 Categorization & Evaluation of Target Lesions

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

Table 12: RECIST 1.1 Categorization & Evaluation of Non-Target Lesions

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

9.1.5 Evaluation of Overall Response for RECIST 1.1

The overall response at any time-point is determined from the assessment and categorization of target lesions, non-target-lesions, and new lesions as indicated in the **Table 13** below:

Table 13: RECIST 1.1 Overall Response

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

The best overall response per RECIST 1.1 is determined from review of each overall response recorded from the start of the treatment until disease progression.

9.2 Modified RECIST Assessment for Hepatocellular Carcinoma (mRECIST)

The definitions and criteria from mRECIST (R Lencioni, JM Llovet, 2010) are summarized below. On-study images should be categorized according to the definitions and descriptions outlined.

9.2.1 Basic Definitions for mRECIST

Only intrahepatic target lesions that are well-delineated and demonstrate arterial enhancement can be selected for mRECIST for HCC. Poorly demarcated lesions or those that show atypical enhancement, possibly as a result of previous interventions, cannot be selected as target lesions according to mRECIST.

In order to qualify as measurable according to mRECIST for HCC, a target lesion must meet the following criteria:

- The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

When measuring the diameter of viable tumor for a potential target lesion according to mRECIST, the measurement should not include major intervening areas of necrosis.

If there are more than two lesions that meet mRECIST criteria for target lesions, then the two largest or best demarcated ones should be followed as target lesions, while the others can be considered non-target lesions.

9.2.2 Image Acquisition for mRECIST

In order to maximize contrast between viable vascularized tumor tissue and non-enhancing necrotic tissue, mRECIST requires bi-phasic or tri-phasic imaging techniques. This protocol specifies bi-phasic or tri-phasic liver scan.

In both bi-phasic and tri-phasic scans, the intra-venous contrast material administration should be timed so that high-quality arterial-phase imaging is obtained throughout the liver on the first run. Subsequently, on the second run, high-quality portal venous-phase imaging should be obtained. In tri-phasic scans, delayed imaging obtained in the equilibrium phase.

9.2.3 Response Criteria and Classification for mRECIST

The response categorization of target and non-target lesion observations according to mRECIST is summarized in **Table 14** and **Table 15** below.

Table 14: mRECIST Categorization & Evaluation of Target Lesions

RECIST Response Category	Description
Complete Response (CR):	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial Response (PR):	At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Progressive Disease (PD):	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
Stable Disease (SD):	Any cases that do not qualify for either partial response or progressive disease

Table 15: mRECIST Categorization & Evaluation of Non-Target Lesions

RECIST Response Category	Description
Complete Response (CR):	Disappearance of intratumoral arterial enhancement
Stable Disease (SD):	Persistence of intratumoral arterial enhancement in one or more non-target lesions
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

For further guidance and details on specific clinical scenarios, please consult Lencioni and Llovet, 2010.

9.2.4 Evaluation of Overall Response in mRECIST

The determination of overall response at a given time-point for mRECIST is identical to the determination of the overall response at a given time-point in RECIST 1.1, and is highlighted again in **Table 16** below.

Table 16: mRECIST Overall Response

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

The best overall response is determined from all overall responses recorded from the start of the treatment until disease progression.

9.3 Assessment of New Lesions

As outlined in **Table 13** and in **Table 16**, the appearance of a new lesion by either RECIST or mRECIST declares progression as the overall response at that imaging time-point regardless of the response assessed in target or non-target lesions. Given the significant impact this has on determination of time-to-progression endpoints, care must be taken to ensure new lesions are recorded accurately.

Determination of new lesions in HCC can often be complicated because of the underlying diagnosis of cirrhosis in most patients. As such, a newly appearing lesion must meet certain conditions in order to qualify as a "New Lesion" for the purpose of response assessment. These conditions for both RECIST 1.1 and for mRECIST are outlined below in Section 9.3.1 and Section 9.3.2.

9.3.1 New Lesions in RECIST 1.1

New lesions should be unequivocal and not attributable to differences in imaging modality or techniques. Findings from processes not directly related to tumor progression should also be excluded.

If a new lesion is equivocal, or uncertain as to etiology, protocol treatment should continue until a subsequent radiologic image is obtained at least 4 weeks later. If repeat imaging confirms the original diagnosis of new lesion, then the original scan date should be used for the radiologic diagnosis of progressive disease.

9.3.2 New Lesions in mRECIST for HCC

The approach to a potential new lesion when assessing response according to mRECIST for HCC is outlined below:

- A newly detected hepatic nodule will be classified as HCC if its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC if repeat radiologic imaging shows at least 1-cm-interval growth.
- If repeat imaging confirms the original diagnosis of new lesion, then the original scan date should be used for the radiologic diagnosis of progressive disease.

10 PLANNED STATISTICAL METHODS

10.1 Analysis Populations

The study populations for subsequent analyses below will be defined for phase Ib, phase II, and overall.

Enrolled Patients:	A patient is considered enrolled upon receiving the first dose of sorafenib on Cycle 1, Day 1.
Study Drug Safety Population:	Defined by all patients receiving at least one dose of study drug (either BBI608 or BBI503).
Pharmacokinetic Population:	Defined as those patients who have completed all pharmacokinetic assessments.
Dose-Escalation Population:	Patients are considered evaluable for the determination of dose-escalation if they: a) Experience dose-limiting toxicity (DLT) b) Complete 28-days of combination dosing at the assigned dose-level
Population Evaluable for Response:	The evaluable population is those patients who have received at least one cycle of study drug (either BBI608 or BBI503) and who have had at least one objective disease assessment following the initiation of therapy.
Intent to Treat Population:	All randomized patients, regardless of receiving a dose of sorafenib or study drug.

10.2 Phase Ib Randomization

Randomization is appropriate for this portion of the study as, once all inclusion and exclusion criteria for the study have been met, there are no absolute or relative medical contraindications specific to either BBI608 or BBI503. The adverse event profiles for the agents are similar and there is no difference between the agents at this time with respect to the balance of relative clinical risk and potential clinical benefit of combination therapy with sorafenib. Patients who meet all inclusion and exclusion criteria will be eligible for randomization.

A central randomization will be performed whereby patients will be assigned to Arm 1 (BBI608 plus sorafenib) or Arm 2 (BBI503 plus sorafenib) using block randomization. Each block will be considered a cohort with 3 subjects on Arm 1 and 3 subjects on Arm 2. After the first cohort for an Arm is complete, the dose level for the next cohort will be determined by the dose escalation rules. It is therefore possible that Arm 1 and Arm 2 will have different dose levels for a given cohort.

Eligible patients will be assigned to a study arm according to the first available patient slot on the randomization list (determined a-priori). Slots on the randomization list will be available or unavailable based on the status of dose-escalation for a given study arm.

10.3 Phase II Randomization

Approximately 90 patients (30/arm) were planned to be randomized in a 1:1:1 ratio into three treatment arms: Arm 1 (sorafenib plus BBI608), Arm 2 (sorafenib plus BBI503), and Arm 3 (sorafenib alone) before Amendment 3 was in effect. After amendment 3 was in effect, Arm 2 in the Phase II portion was closed for enrollment and randomization is now conducted in a 1:1 ratio in the two remaining treatment arms: Arm 1 and Arm 3. The targeted sample size remains 30 for Arm 1 and 30 for Arm 3. There were approximately 10 subjects already enrolled in Arm 2 by the time amendment 3 was in effect. Therefore, the total actual sample size in Phase II in the end is projected to be approximately 70 patients after amendment 3.

10.4 Primary and Secondary Study Objectives

10.4.1 Primary Objectives

Phase Ib:

The primary objective of the phase Ib portion of this study is to determine the safety and tolerability of each study drug in combination with sorafenib in order to define a recommended phase II dose for BBI608 plus sorafenib as well as for BBI503 plus sorafenib. Safety analysis is defined further in Section 10.5.

Phase II:

The primary objective of the phase II portion of this study is to evaluate the tolerability, safety. and preliminary anti-tumor activity in patients with advanced hepatocellular carcinoma randomized to receive treatment with sorafenib in combination with BBI608, sorafenib in combination with BBI503*, or sorafenib alone, with BBI608 and BBI503 administered at their respective RP2D dose levels for combination administration with sorafenib which were determined during phase Ib.

*Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

10.4.2 Secondary Objectives

Other key study objectives include the evaluation of pharmacokinetics and pharmacodynamics (when biopsy is possible), and the evaluation of preliminary anti-tumor activity of each agent in combination with sorafenib. The activity of sorafenib alone will also be evaluated in this study.

Preliminary anti-tumor activity will be explored using different efficacy parameters. Efficacy parameters which involve disease progression as an endpoint will be generated twice: once using disease progression as defined by RECIST 1.1, and again using disease progression defined by mRECIST for HCC. This is because the two response evaluation criteria are different, and will produce different results for a given efficacy parameter. The data accumulated on this trial will help to determine whether the use of one approach over the other may be preferred in future trials of either BBI608 or BBI503 in hepatocellular carcinoma.

Proportional efficacy parameters will be defined for both phase Ib, phase II, and combined according to study arm. The following parameters will be calculated for all randomized patients and for patients evaluable for response: Disease control rate (DCR), defined as the proportion of patients with best response of complete response (CR), Partial Response (PR), or stable disease (SD); and Objective response rate (ORR), defined as the proportion of patients with a documented complete response (CR) or partial response (PR). As above, DCR and ORR will be defined according to RECIST 1.1 and, in a separate analysis, according to mRECIST for HCC.

The following time-to-event parameters will also be evaluated: time-to-progression (TTP), defined as the time from initiation of therapy until disease progression; and progression free survival (PFS) defined as time from the initiation of therapy until disease progression or death from any cause. Also, as above, disease progression in both PFS and TTP will be defined according to both RECIST 1.1 and, in a separate analysis,

according to mRECIST for HCC criteria. Estimates for PFS and TTP will be generated using Kaplan-Meier curves.

Since BBI608 and BBI503 both affect cancer stem cells, Disease-Specific Survival (DSS) and overall survival (OS) will also be evaluated. DSS is defined as the time from initiation of therapy until death from hepatocellular carcinoma. Overall survival is defined as time from initiation of therapy until death from any cause. Estimates of DSS and OS for each cohort will be displayed using Kaplan-Meier curves.

Other evidence for anti-tumor activity will be evaluated on an exploratory basis and will be summarized using descriptive statistics or graphics. These may include but are not limited to: a summary of tumor marker values over time, a description of the duration of response or duration of disease control, and summaries of the proportion with PFS, TTP, DSS, and OS, at 3, 4, 6, and/or 12 months.

The potential effects of baseline demographic, clinical, and biologic factors on study outcomes will also be explored. Examples include evaluating the effect of baseline performance status, comorbidities, estimated portal pressure, or plasma IGF-1 levels on measures of clinical activity such as time to progression or progression free survival.

10.5 Determination of Sample Size

Phase Ib:

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

Phase II:

There are no statistical hypothesis testing and the sample size is considered to be clinically adequate to assess tolerability, safety, and preliminary anti-cancer activity of study drug of interest. Estimation and 95% confidence intervals will be provided for the proportion of patients with grade 3 adverse events by treatment, as well as for the proportion of patients that are alive and progression free 4 months (PFS-4) after randomization for each arm. Other anti-cancer activity parameters will also be estimated

10.6 Safety Analysis

Safety and adverse events will be summarized for all enrolled patients in the phase Ib portion, phase II portion, and for the study overall. In addition, all patients receiving at least one dose of study drug (either BBI608 or BBI503) will be considered in the study drug safety population. Safety and adverse events will be summarized for the study drug safety population of phase Ib, phase II, and overall.

During the phase Ib portion of the study, adverse events will be summarized by dose-level and overall by arm. The numbers of patients enrolled, number with DLT, and number evaluable for determination of dose-escalation at each dose-level by arm will be reported. In addition to the evaluation and categorization of adverse events, listings of laboratory test results collected at baseline and during the study will be generated. Descriptive statistics summarizing the changes in those laboratory tests over time will be presented.

Adverse events will be graded according to the NCI CTCAE, version 4.0. The incidence of adverse events will be evaluated for each cohort. Patients will be followed for adverse events for at least 30 days after the last dose of study drug (either BBI608 or BBI503), or until they have recovered from all related study drug (either BBI608 or BBI503) adverse events.

Safety and adverse events will be reported by study arm for the intent to treat population and for all enrolled patients during the phase II portion of the study.

10.7 Pharmacokinetics, Pharmacodynamics and Exposure-Response Variables

Exposure-Response evaluations on this study will be exploratory in nature. Descriptive summaries may be generated about plasma levels of study drug (either BBI608 or BBI503) basic demographic variables, clinical and biologic factors, pharmacodynamic parameters from biopsy and/or PBMC analysis, and safety and efficacy outcome data.

11 QUALITY CONTROL AND ASSURANCE

The study will be initiated and conducted under the Sponsorship of BBI. The clinical supplies of study drug (either BBI608 or BBI503) and CRFs will be supplied by BBI or its representative. Representatives of BBI will monitor the study to verify study data, medical records, and CRFs in accordance with current ICH GCPs and other applicable regulations and guidelines.

11.1 Compliance with the Protocol

The Investigator will notify the Sponsor of any deviations from the protocol. Such contact with the Sponsor will be made as soon as possible to permit a decision as to whether the subject (for whom the deviation from the protocol was affected) is to continue in the study. The case records will describe both the details of and rationale for the protocol deviation.

11.2 Registration and Enrollment

This is an open-label study. BBI will allocate enrollment slots to clinical sites according to random assignment of currently available openings in dosing cohorts for both agents. BBI should be notified as soon as a subject qualifies for entry into the protocol. Subjects will be registered by faxing or emailing a completed enrollment form to BBI or its designee within 7 days prior to the first drug administration. The subject will be enrolled into the study when the subject receives the first dose of protocol therapy. Registration and enrollment forms as well as faxing/emailing instructions will be provided. The site is required to maintain a log of all subjects who sign consent, and the log must indicate whether the subject was enrolled (received a dose of protocol therapy). The reason for disqualification should be noted in the log.

11.3 Removal, Replacement, or Early Withdrawals of Subjects

If a subject exits the study prior to receiving four weeks of study drug (either BBI608 or BBI503) for reasons other than a DLT, and is not evaluable for dose-escalation then another subject may be enrolled to replace the patient in order to fully evaluate safety and tolerability of a given dose-level.

If a subject exists the study after receiving four weeks of study drug (either BBI608 or BBI503), but before receiving an on-study objective disease assessment (and is therefore not evaluable for response), then that subject may be replaced.

12 GCP COMPLIANCE AND ETHICAL CONSIDERATIONS

12.1 Institutional Review Board

The protocol, any protocol modifications, the informed consent form that will be used, and, if applicable, the permission to use private health information, must be approved by the Investigator's IRB or Independent Ethics committee (IEC) (compliant with federal regulations 21 CFR 56) before the study is initiated. Documentation of this approval (i.e., a copy of the document showing IRB/IEC approval including the chairperson's signature and the date of approval) must be provided to BBI or its designee and made available during an inspection by loco-regional regulatory agency inspectors. The Investigator will submit to BBI:

- A list of the names, occupations, and affiliations of the members of the IRB
- Documentation that the IRB is duly constituted or a General Assurance Number

No patients may be enrolled until the IRB has given written approval of the protocol and informed consent and BBI has received copies of the approvals.

It is the responsibility of the Investigator to:

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

12.2 Compliance with Good Clinical Practice and Ethical Considerations

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

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

Before initiating a trial, the Investigator/institution should have a written and dated approval/favorable opinion from the IRB/IEC for the trial protocol/amendment(s), a written informed consent form, patient recruitment procedures (e.g., advertisements) and written information to be provided to patients.

Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients.

12.3 Informed Consent and Permission to Use Private Health Information

The Investigator, or designee, is responsible for the content of the informed consent form, but the content must be submitted and approved by BBI prior to submission to the IRB. Before the start of required study procedures, the Principal Investigator or associate must obtain informed consent from each study participant

(or the subject's parent/guardian) in accordance with the US federal regulations (21 CFR Part 50) and ICH document "Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. The informed consent form should also include any additional information required by local laws relating to institutional review.

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

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

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

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

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

13 STUDY MANAGEMENT

13.1 Amendments to the Protocol

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

13.2 Investigator Brochure and Information Materials

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

13.3 Pre-investigational Documents

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

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

For clinical sites in the US, Form FDA 1572 must be completed. The form must list the Principal Investigator and sub-investigators, all laboratories where study labs will be performed, and the local ethics authority responsible for reviewing the clinical protocol and informed consent form.

*The Delegation of Authority document lists the site personnel and the specific study tasks that they will be responsible for. The Delegation of Authority document may be updated during the course of the clinical trial. The update must be signed by the Principal Investigator for the trial and the document submitted to the Sponsor. A template document and legend will be supplied by the Sponsor.

13.4 Drug Inventory Record

The Investigator, or a responsible party (research pharmacist or other) designated by the Investigator, must maintain an inventory record of drug received and dispensed. BBI will provide forms to facilitate the inventory control. These forms must be used unless the Investigator has previously established a system that complies with loco-regional regulations and is approved by BBI. The study drug must be dispensed only to the institutions(s) specified on the appropriate loco-regional regulatory documentation.

13.5 Disposition of Used and Unused Study Drug

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

13.6 Study Records

BBI will provide the Investigator with drug shipment records, CRFs designed to collect the data specified for each individual, and other forms as necessary. CRFs provided in electronic format will be United States CFR 21 part 11 compliant.

The Investigator and/or institution is required to prepare and maintain these forms in accordance with local, regional, and national regulations, and to sign, date, and return them to the Sponsor.

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

13.7 Record Retention

Records must be maintained for 25 years:

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

BBI will notify the Investigator when records are no longer required.

13.8 Subject Confidentiality

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

In connection with this study, representatives of regional regulatory authorities or of the local IRB may, in certain circumstances, review study source documentation including subject medical records.

13.9 Monitoring

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

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

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

13.10 Case Report Form (CRF) Completion

A set of CRFs or eCRF access will be provided for each study subject. All forms must be filled out in non-erasable ink or typed (or entered electronically). Training will be provided in the case of electronic CRFs. The Investigator will sign and date each CRF as indicated.

Correction of data on a CRF will depend on whether paper or electronic CRFs are utilized. Paper CRF corrections will be made by crossing out the incorrect data in a manner that leaves the previous entry legible and writing the correct information next to the crossed out entry. "White-out" and erasures are not

permitted. Each correction must be initialed and dated by the individual making the correction. After the CRFs have been collected by Boston Biomedical, all corrections will be made via a query resolution form, and no further corrections should be made on the site's copy of the CRF.

Corrections to electronic CRFs will be audit-tracked in compliance with United Sates CFR 21 part 11.

13.11 Final Site Report

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

13.12 Final Study Report

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

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

13.13 Use of Information

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

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

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

13.14 Publication

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

publication or presentation any Confidential Information (other than the Clinical Data) of BBI and to require that any publication or presentation concerning the Study to acknowledge the Sponsor's support.

13.15 Research Outside the Terms of this Protocol

BBI 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 BBI. The nature and results of any such procedures must be recorded and reported by a method agreed between BBI 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.

14 APPENDIX A: SCHEDULE OF ASSESSMENTS - PHASE IB

Tests & Procedures	Pre-Study Evaluation	Study Evaluations									End of Study Visit
		Cycle 1					Cycle 2		Cycle 3+		
Week	0	1	2	3	3	4	1	3	1	3	14- 30 days from last dose of study drug
Day	0	1	8	15	16	22	1	15	1	15	
Window	-5 (+ 2) days	± 2 days					± 2 day		± 2 day		
Medical history	X										
Physical examination	X			X			X		X		X
Serum pregnancy test[1]	X										
ECOG performance status	X			X			X		X		X
Vital signs, Weight, Height[2]	X	X	X	X		X	X	X	X	X	X
Hematology	X			X			X		X		X
Blood chemistry	X			X			X		X		X
Urinalysis	X			X			X		X		X
Child Pugh Class assessment	X										X
12-Lead electrocardiogram	X			X[3]				X[10]			
Serum AFP	X			X			X		X		X
Optional Tumor biopsy	X[4]							X[5]			
Pharmacokinetics				X	X[6]			X			
Concomitant medications	X	X	X	X		X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X[7]
Dispense BBI608 or BBI503				X[9]			X		X		
Schedule 8-week Scan		X									
Tumor Measurements & staging	At baseline and then at every 8 weeks (56 days, ±7) beginning with Cycle 1, Day 1										X[8]

[1]For women of child-bearing potential (WOCBP)

[2]Height will be assessed at pre-treatment (baseline) only

[3]ECG will be done **twice** on this day—once before the first dose of study drug is administered, and once ~ 3.5 hours (± 15 min) after study drug is administered.

[4]The pre-treatment (Baseline) optional tumor biopsy may be performed at any time prior to the first sorafenib dose on Cycle 1 Day 1

[5]If the on-study biopsy is performed on a day other than a PK day, then a single blood draw is needed within 30 minutes of the biopsy

[6]For patients in Arm 2 (BBI503 + sorafenib) only

[7] Patients who are identified at the EOS visit as having persistent adverse events related to study drug (either BBI608 or BBI503) should continue to be followed on a monthly basis (or more frequently if clinically indicated) until resolution of study drug-related adverse events or until the AEs are deemed irreversible.

[8] If a patient discontinues protocol therapy due to radiologic progression of disease, an End of Study imaging assessment is not required

[9] For ARM 2 only-BBI503 will be administered in the morning ONLY on C1D15 and in the evenings thereafter

[10] ECG will be done 3.5 hrs after study drug is administered

15 APPENDIX B: SCHEDULE OF ASSESSMENTS - PHASE II

Tests & Procedures	Pre-Study Evaluation	Study Evaluations								End of Study Visit
		Cycle 1				Cycle 2		Cycle 3+		
Week	0	1	2	3	4	1	3	1	3	14- 30 days from last dose of study drug
Day	0	1	8	15	22	1	15	1	15[6]	
Window	-5 (+ 2) days	± 2 days				± 2 day		± 2 day		
Medical history	X									
Physical examination	X			X		X		X		X
Serum pregnancy test[1]	X									
ECOG performance status	X			X		X		X		X
Vital signs, Weight, Height[2]	X	X	X	X	X	X	X	X	X[6]	X
Hematology	X			X[3]		X		X		X
Blood chemistry	X			X[3]		X		X		X
Urinalysis	X			X[3]		X		X		X
Child Pugh Class assessment	X									X
12-Lead electrocardiogram	X			X[11]			X[11]			
Serum AFP	X			X[3]		X		X		X
Optional Tumor biopsy	X[7]						X			
Pharmacokinetics							X[5]			
Concomitant medications	X	X	X	X	X	X	X	X	X[6]	X
Adverse events		X	X	X	X	X	X	X	X[6]	X[9]
Dispense BBI608 or BBI503[4]				X[10]		X		X		
Schedule 8-week Scan		X								
Tumor Measurements & staging	At baseline and then at every 8 weeks (56 days, ±7) beginning with Cycle 1, Day 1									X[8]

[1] For Women of Child Bearing Potential

[2] Height will be assessed at pre-treatment (baseline) only

[3] For patients in Phase II who were randomized to receive sorafenib alone (Arm 3), labs may be obtained at any time on C1D15 (either before or after dosing with sorafenib on that day)

[4] Applies only to patients randomized to either Arm I (BBI608 plus sorafenib) or Arm 2 (BBI503 plus sorafenib). Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

[5] Single blood draw should be obtained in the morning for Arm 1 and Arm 2 only prior to the first dose of BBI608 or BBI503. Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

[6] For patients in Phase II, C3D15 visits (and Day 15 visits of each subsequent cycle) need not be in person. In this case, the patient should be contacted by phone. Vital signs and weight need not be taken.

[7] Optional tumor biopsy may be performed at any time between the screening visit and administration of the first sorafenib dose on Cycle 1 Day 1.

[8] If a patient discontinues protocol therapy due to radiologic progression of disease, an End of Study imaging assessment is not required

[9] Patients who are identified at the EOS visit as having persistent adverse events related to study drug (either BBI608 or BBI503) should continue to be followed on a monthly basis (or more frequently if clinically indicated) until resolution of study drug-related adverse events or until the AEs are deemed irreversible.

[10] For ARM 2 only-BBI503 will be administered in the morning ONLY on C1D15 and in the evenings thereafter. Once the amendment 3 is in effect, Arm 2 in the Phase II portion will be closed for enrollment.

[11] for phase II 12 Lead ECG should be performed pre dose BBI608 on C1D15 and after dose of BBI608 on C2D15.

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16 APPENDIX C: PERFORMANCE STATUS

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

17 SPONSOR SIGNATURE

Study Title: **A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma**

Study Number: BBI608-503-103HCC

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

Signed: [redacted] Date: [redacted]

Dirk Huebner, MD
VP and Head of Development
Boston Biomedical, Inc.

18 INVESTIGATOR'S SIGNATURE

Study Title: **A Phase Ib/II Clinical Study of BBI608 in Combination with Sorafenib or BBI503 in Combination with Sorafenib in Adult Patients with Hepatocellular Carcinoma**

Study Number: BBI608-503-103HCC

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

Printed Name:_____

Signature: _____Date: _____

19 REFERENCES

[Please find a list of reviews on cancer stem cells in all major cancer types in the **June 10 special issue of Journal of Clinical Oncology on cancer stem cells** (J Clin Oncol. 2008 Jun 10;26(17)).]

Boman BM, and Wicha MS. (2008) "Cancer stem cells: a step toward the cure." J Clin Oncol. 26(17): 2795-2799.

Bruix J, Llovet JM, et al. (2012) "Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial" J Hepatol. 57(4):821-9.

Bruix J and Sherman M (2011) "Management of hepatocellular carcinoma: an update." Hepatology 53(3): 1020-1022.

Clevers H (2011) "The cancer stem cell: premises, promises and challenges." Nature Med.17(3): 313-319.

Hwang JP, Somerfield MR1, et al (2015) "Hepatitis B Virus Screening for Patients With Cancer Before Therapy: American Society of Clinical Oncology Provisional Clinical Opinion Update." J Clin Oncol. 33(19):2212-20.

Kelley RK and Venook AP (2013) "Novel therapeutics in hepatocellular carcinoma: how can we make progress?" Am Soc Clin Oncol Educ Book. doi: 10.1200/EdBook_AM.2013.33.e137.

Lencioni R, and Llovet, JM (2010) "Modified RECIST (mRECIST) assessment for hepatocellular carcinoma." Sem. Liv. Dis. 30(1): 52-60.

Llovet JM, Bruix J, et al (2008) "SHARP Investigators Study Group; Sorafenib in advanced hepatocellular carcinoma." N Engl J Med. 359(4):378-90

Lobo NA, Shimono Y, et al. (2007) "The biology of cancer stem cells." Annu Rev Cell Dev Biol 23: 675-699.

Eisenhauer EA, Therasse P, et al. (2009) "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)." Eur J Cancer 45(2):228-47.

Singh, A and Settleman J (2010) "EMT, cancer stem cells and drug resistance: an emerging axis of evil in the war on cancer." Oncogene 29(34): 4741–4751.