HUMAN GENOME SCIENCES

CLINICAL PROTOCOL HGS1012-C1103
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Date: 15 July 2015

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TITLE OF STUDY:

A RANDOMIZED, MULTI-CENTER, BLINDED, PLACEBO-CONTROLLED STUDY OF MAPATUMUMAB ([HGS1012], A FULLY-HUMAN MONOCLONAL ANTIBODY TO TRAIL-R1) IN COMBINATION WITH SORAFENIB AS A FIRST-LINE THERAPY IN SUBJECTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

STUDY SPONSOR: Human Genome Sciences, Inc.
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Rockville, Maryland 20850

EudraCT Number: 2010-020798-17

Confidentiality

REVISION CHRONOLOGY FOR HGS1012-C1103 (200149)

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*A Summary of Modifications which provides a detailed list of changes for the amendment is included in Appendix 9.

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator:

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Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

Study Synopsis

Study Number: HGS1012-C1103

Title of the Study: A Randomized, Multi-Center, Blinded, Placebo-Controlled Study of Mapatumumab ([HGS1012], a Fully-Human Monoclonal Antibody to TRAIL-R1) in Combination with Sorafenib as a First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma

Clinical Development Phase: 2

Objectives:

Primary:

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

Secondary:

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

Diagnosis & Inclusion Criteria:

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
   - Located in the liver.
   - Can be accurately measured in at least 1 dimension.
   - Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
   - Suitable for repeat measurement.
   - Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be confirmed by the blinded, independent, central read (BICR) prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x 10^9 /L or ≥ 1500 /mm^3.
   - Platelet count ≥ 50 x 10^9 /L or ≥ 50,000 /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal.
   - Serum albumin ≥ 2.8 g/dL or ≥ 28 g/L. AM01 21Dec10
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

Exclusion Criteria:

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. History of organ allograft. AM02 23Feb11
4. Previously received mapatumumab and/or sorafenib.
5. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.
6. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
7. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
8. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
9. Hepatic encephalopathy, per the investigator's evaluation.

10. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
11. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
12. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
13. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
14. Known human immunodeficiency virus infection.
15. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
16. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
17. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
18. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
19. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
20. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
21. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
22. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
23. Hepatitis B virus DNA levels > 2,000 IU/mL.

Study Design and Schedule:

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma. In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive 30 mg/kg mapatumumab or placebo.

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Approximately 100 advanced HCC subjects will be randomized/enrolled.

Study Treatment:

Mapatumumab will be supplied in open label vials and third party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent but independent of all other study activities. All other study personnel, the subject, the Sponsor will remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle.

Arm B: Sorafenib 400 mg orally twice daily continuously + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle.

Subjects will continue to receive study treatment(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiographic progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiographic progression. Subjects who completed more than 24 months of study treatment with sorafenib with or without mapatumumab and who in the opinion of the investigator obtain clinical benefit from treatment, will be allowed to continue treatment with sorafenib with or without unblinded mapatumumab in the clinical trial. This extension of treatment will continue until the subject's disease progresses or they withdraw from study. In addition extension of treatment with mapatumumab will not extend beyond the expiry date of the drug batch (March 2016). AM03 15Jul15

All subjects will have an end of treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo whichever is later, for scheduled safety follow-up assessments.

During the Extended Access phase, subjects will have regular visits for assessment of disease response at least every 3 months or as per standard of care, whichever is sooner. In addition, BP will be monitored every 6 weeks and recorded in the eCRF. Serious AEs will continue to be collected during this Extended Access phase according to Section 8. Study drug administration and inventory/accountability will continue to be recorded during this period according to Section 5. AM03 15Jul15

Disease Assessments:

Radiologic disease assessments along with assessment of alpha fetoprotein will be performed at the end of every two 21-day cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The

disease assessment will be performed and documented no earlier than 5 days before the start of the next cycle. Clinical responses will be evaluated according to mRECIST for HCC (see Section 6.8 and Appendix 5). The same assessment method will be used throughout the study for each subject. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent, central reader (BICR) for confirmation of disease progression. Partial response (PR) and complete response (CR) will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR). All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

During the Extended Access phase, subjects will have regular visits for assessment of disease response at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. Independent radiological review for confirmation of disease progression is not required. AM03 15Jul15

Safety Assessments:

The safety of sorafenib and mapatumumab will be assessed by evaluation of the type, frequency, and severity of adverse events (ie, according to the NCI-CTCAE Version 4.0 grading) and changes in clinical laboratory tests (hematology and clinical chemistry) and immunogenicity over time. In the event that an adverse event does not have an NCI-CTCAE Version 4.0 grading, the severity grades in Section 8.6 will be used. Adverse events (including serious adverse events) will be captured from the start of study agent administration (sorafenib and/or mapatumumab/placebo) through at least 30 days following the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. Laboratory assessments will be performed at screening, and during each study visit outlined in the study calendar found in Section 6.3. During the Extended Access phase, laboratory assessments will be performed as per standard of care; SAEs will continue to be collected according to Section 8. AM03 15Jul15

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

Immunogenicity:

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

Dose Modification/Delay:

Dose modifications will not be allowed for mapatumumab/placebo. Dose modifications of sorafenib for toxicity will be made according to the guidelines provided in the treatment section (Section 5.2.3) of the protocol.

Details regarding pre-treatment and management of hypersensitivity reactions related to mapatumumab are provided in Section 5.1.5 and Appendix 8.

Pharmacokinetics:

Multiple blood specimens will be obtained from subjects for serum mapatumumab concentration determinations as outlined in Table 6-1.

Pharmacodynamics:

Subjects will be given the option to participate in a biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and several blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The biomarker sub-study is detailed in Appendix 6.

Exploratory Assessments:

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

Study Endpoints:

The following will be evaluated (these endpoints and the respective analyses are defined in Section 9):

Primary:

- Time to progression (TTP).

Secondary:

- Overall survival.
- Progression-free survival.
- Objective response (complete response [CR] + partial response [PR]).
- Disease control (CR + PR + stable disease [SD]).
- Response duration and time to response in responders.
- Frequency and severity of treatment-emergent adverse events.
- Laboratory parameters.

- Serum mapatumumab concentrations for use in a population pharmacokinetic analysis.

Statistical Methods:

Sample Size:

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

Statistical Analysis:

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with testing the hazard ratio for time to progression at a 1-sided significance level of 0.10 with a Cox proportional hazards model controlling for the factors stratifying the randomization as covariates. Secondary analyses include estimates, using Kaplan Meier methods, of median progression-free survival (PFS) and median overall survival (OS) along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test). For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented. AM01 21Dec10

Study Calendar:

The study calendar is located in Section 6.3 of the protocol.

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List of Tables

List of Abbreviations

AE	adverse event
AFP	α - fetoprotein
ALT	alanine transaminase
AST	aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central read
CR	complete response
CT	computerized tomography
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
Fc	heavy chain constant region or fragment of antibody
GGT	gamma-glutamyl transpeptidase
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGS	Human Genome Sciences
HGSRC	Human Genome Sciences Review Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IR	incomplete response
IRB	Institutional Review Board
kg	kilogram
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mRECIST	modified RECIST assessment for HCC
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ng	nanogram
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease
PK	pharmacokinetics
PPT	partial thromboplastin time
PR	partial response
PS	performance status
PT	prothrombin time

RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TRAIL-R1	TRAIL receptor 1
TRAIL-R2	TRAIL receptor 2
TTP	time to progression

1 Background

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma is the 5th most common cancer worldwide accounting for 2% of all malignancies. It is the 3rd leading cause of cancer-related death globally with 1 million new cases a year (WHO, 2002; IACR, 2002; Ferlay et al, 2004; Lopez et al, 2006).

Hepatocellular carcinoma is more prevalent in males with a male:female ratio as high as 8:1. Depending on the endemic risk factors, hepatocellular carcinoma is diagnosed during the 4th through 6th decades of life. The reported incidence of hepatocellular carcinoma is increasing because of a better ability to diagnose the disease and because of the long-term consequences of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection (Ries et al, 2006). Worldwide the most common cause of hepatocellular carcinoma is chronic HBV infection (El-Serag et al, 2003). Endemic areas thus include China, South Asia and South Africa where the incidence of hepatocellular carcinoma can be as high as 120 cases per 100,000. In the United States, where HCV and alcohol are the main risk factors, the age-adjusted incidence rates have increased from 1.4 cases per 100,000 in 1980 to a current incidence of 4 cases per 100,000. This equates to about 8500-11,000 new cases diagnosed each year (IACR, 2002; Ferlay et al, 2004; Pawlik et al, 2004; Edwards, et al, 2005; Jemal et al, 2007; Bosch et al, 2004).

1.2 Treatment Options for Patients with Hepatocellular Carcinoma

Surgery, including transplantation, is the only curative modality for hepatocellular carcinoma (Venook, 1994; Cha et al, 2003). The 5-year survival rate for patients with unresectable hepatocellular carcinoma is 11% in the US (ACS, 2007), < 8% in Europe (Capocaccia et al, 2007), and < 10% in Asia (Teo and Fock, 2001). Symptomatic hepatocellular carcinoma has a very poor prognosis with a median survival of 1–8 months (Forner et al, 2006; Llovet et al, 1999a, Llovet et al, 1999b).

Sorafenib, a multikinase inhibitor, is the 1st systemic therapy to significantly impact survival in patients with advanced hepatocellular carcinoma, as demonstrated in an international, multicenter Phase 3, placebo-controlled trial (Llovet et al, 2008). Sorafenib was approved in the United States and European Union for the 1st-line treatment of advanced hepatocellular carcinoma in late 2007 and the 2008 National Comprehensive Cancer Network guidelines have been updated with the addition of sorafenib as a treatment option for hepatocellular carcinoma patients. The updated Barcelona Clinic Liver Cancer (BCLC) guidelines recommend sorafenib for hepatocellular carcinoma patients with BCLC Advanced Stage (C) (Forner et al, 2010).

1.3 The Role of the TRAIL Pathway in HCC

1.3.1 TRAIL and TRAIL Receptors

TRAIL is a member of the tumor necrosis factor (TNF) ligand superfamily, with homology to Fas/Apo1 ligand (Pitti et al, 1996; Wiley et al, 1995). TRAIL induces programmed cell death primarily in tumor cells through activation of TRAIL death receptors, TRAIL-R1

(death receptor 4) or TRAIL-R2 (death receptor 5) (Ashkenazi et al, 1999; Evdokiou et al, 2002; Kothny-Wilkes et al, 1998; Lawrence et al, 2001; Pitti et al, 1996; Walczak et al, 1999; Wiley et al, 1995).

TRAIL-R1, the target of mapatumumab, is detectable on tumor cells derived from colon, lung, liver, gastric, pancreas, uterus and esophagus and in tissue sections from various tumors of the colon, lung, pancreas, liver and stomach without significant expression in parallel normal tissues (Halpern et al, 2004; Roach et al, 2004).

1.3.2 TRAIL and HBV/HCV Infection

Acutely infected tissues, including the liver, utilize the TRAIL pathway to eliminate virally and bacterially infected cells (Herr et al, 2007). In viral hepatitis, TRAIL and 1 of its receptors, TRAIL-R2, are upregulated and contribute to the elimination of infected hepatocytes associated with viral hepatitis (Bantel and Schulze-Osthoff, 2003; Lin et al, 2002; Matsuda et al, 2005). In addition to HBV and HCV infection, steatosis, exposure to bile acids and chronic alcohol exposure induce increased expression of TRAIL and TRAIL-R2, but not TRAIL-R1, in human hepatocytes (Dunn et al, 2007; Mundt et al, 2005). Cell surface expression of TRAIL-R2, but not TRAIL-R1, was altered and responsible for sensitization to TRAIL in hepatocytes exposed to bile acids (Higuchi et al, 2001; Malhi et al, 2007). These findings have been reproduced in preclinical models. Non-virally infected hepatocytes are refractory to TRAIL and TRAIL-R agonists but exposure of HCV-infected hepatocytes to TRAIL leads to a significant level of apoptosis (Volkmann et al, 2007). Inhibition of the TRAIL pathway may protect infected cells from apoptosis and allow for chronic infection (Mundt et al, 2003). Recent non-clinical observations demonstrated that natural killer cells expressing the ligand TRAIL, are enriched in the livers of patients with chronic HBV infection, and TRAIL is overexpressed in the livers of patients with HCV-associated steatosis (Mundt et al, 2005).

In summary, preclinical data suggest that mapatumumab may promote apoptosis of cancer cells, including hepatocellular carcinoma cells. Whether viral infection, including HBV or HCV infection, will attenuate or modulate the effects of mapatumumab on hepatocytes is not yet known, but experience to date in a Phase 1b trial of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody indicates that the safety experience is consistent with underlying disease and known sorafenib toxicities (see Section 1.2).

1.4 Mapatumumab

1.4.1 Mapatumumab Pharmacology

Mapatumumab is a fully human, agonist monoclonal antibody that activates the cell death pathway in tumor cells by specifically binding to TRAIL-R1 with high affinity. Mapatumumab efficiently induces apoptosis in human cancer cell lines expressing the TRAIL-R1 protein on the cell surface. Nonclinical studies have demonstrated that mapatumumab can induce cytotoxicity in multiple tumor cell lines representing both solid and hematological malignancies, including cancers of the biliary tract, colon, lung, breast,

pancreas, esophagus, ovary, kidney, uterus, as well as lymphoma and various leukemias. Mapatumumab has also demonstrated anti-tumor activity as a single agent, preventing tumor growth and in some cases causing regression of tumors in xenograft tumor models of multiple human malignancies, including lung, colon, kidney, and uterus (Camidge, 2007; Georgakis et al, 2005; Jin et al, 2007; Humphreys, 2004; Marini et al, 2006; Menoret et al, 2006; Pukac et al, 2005).

The relationship between receptor expression and response to therapy with mapatumumab remains unclear. In vitro studies of cell lines have shown that TRAIL-R1 expression level is not a consistent predictor of response to mapatumumab. Although both TRAIL-R1 expression and apoptosis in response to mapatumumab are increased in many tumor cell lines as compared with normal diploid cells, there are examples of mapatumumab cytotoxicity on cell lines with very low levels of detectable receptor, and conversely, mapatumumab resistant cell lines that have relatively high levels of TRAIL-R1 cell surface expression.

Tumor cell cytotoxic activity can be enhanced when mapatumumab is administered in combination with chemotherapeutics or other anti-neoplastic agents. Enhanced apoptotic signaling, in vitro cell killing and in vivo anti-tumor activity have been observed when mapatumumab has been combined with various types of therapeutic agents and treatments including microtubule poisons, anti metabolites, topoisomerase inhibitors, proteosome inhibitors, platinum agents and radiation. Both the level and spectrum of activity of mapatumumab is enhanced in in vitro cytotoxicity and in vivo xenograft studies in combination with various chemotherapeutic and anti-neoplastic agents, including a xenograft model of hepatocellular carcinoma in combination with cisplatin and gemcitabine (Camidge, 2007; Pukac et al, 2005; Georgakis et al, 2005; Humphreys, 2004; Jin et al, 2007; Human Genome Sciences data on file).

Please refer to the mapatumumab Investigator's Brochure for detailed information regarding the nonclinical pharmacology, toxicology, and PK of mapatumumab.

1.4.2 Non-Clinical Mapatumumab Safety Studies

To assess the nonclinical safety of mapatumumab, a 6-month toxicity study, with a 4-month recovery period, was conducted in chimpanzees. Mapatumumab was administered intravenously at up to 40 mg/kg every 10 days. No mapatumumab-specific toxicity was identified and no anti-mapatumumab antibodies were detected.

To assess its off-target effects, mapatumumab was administered intravenously weekly to cynomolgus monkeys, whose TRAIL R1 homolog does not bind mapatumumab. Mapatumumab was well tolerated at doses of up to 50 mg/kg and was not highly immunogenic: of the 40 monkeys treated, 1 developed anti-mapatumumab antibodies. The positive response was observed in an animal in the high dose (50 mg/kg) group.

In vitro, mapatumumab was found to decrease viability of normal human hepatocytes, although the observed effect was less than that observed with TRAIL. This effect was variable across donors and did not amplify with increasing concentrations of mapatumumab. It should

be noted that in clinical studies, plasma mapatumumab concentrations have been achieved that are > 1100–fold greater than the minimum exposure resulting in reduced in vitro hepatocyte viability. Despite this, the clinical results do not reveal evidence of hepatotoxicity in those studies. Hence it appears that the in vitro hepatocyte viability assay is not predictive of mapatumumab effects in vivo.

1.4.3 Clinical Experience with Mapatumumab

Over 400 subjects have received mapatumumab in clinical trials to date. Preliminary clinical data are available from 218 subjects who received mapatumumab as a single agent at doses ranging from 0.01 to 20 mg/kg across 6 clinical trials.

Based on available data, mapatumumab appears to be well tolerated and no significant safety issues have been observed. Adverse events have generally been mild to moderate in severity, manageable, and do not appear related to dose. The most frequently reported treatment-related adverse events occurring in > 10% of subjects were fatigue, hypotension, nausea and pyrexia. Severe events have been uncommon and generally judged not related to mapatumumab. Severe events judged at least possibly related to mapatumumab have been observed and a complete list can be found in the mapatumumab Investigator's Brochure. Grade 3 or Grade 4 hematologic, renal, or hepatic laboratory abnormalities also have been relatively uncommon with no significant trend or dose-response evident. Lymphopenia was the most commonly observed laboratory abnormality, but tended to be intermittent and reversible and was not associated with infectious events.

In subjects with solid tumors, stable disease has been the best response observed with mapatumumab as a single-agent. However, 2 complete responses (CRs) and 1 partial response (PR) were observed in subjects with follicular lymphoma.

In addition, preliminary clinical data are available from 234 subjects who received mapatumumab at doses ranging from 1 to 30 mg/kg every 21 days in combination with chemotherapy in 5 clinical trials (carboplatin/paclitaxel [N = 100], gemcitabine/cisplatin [N = 49], bortezomib [n = 69], or sorafenib [n = 16]. Mapatumumab has been generally well tolerated; adverse events and laboratory abnormalities have been consistent with those expected with underlying disease or chemotherapy. A listing of severe events considered at least possibly related to mapatumumab can be found in the mapatumumab Investigator's Brochure. The most commonly occurring laboratory abnormalities have been hematologic (ie, anemia, neutropenia, thrombocytopenia, and leukopenia), as expected with chemotherapy. Grade 3/4 laboratory abnormalities have been relatively uncommon. Higher frequencies of Grade 3/4 neutropenia, leukopenia, lymphopenia, and thrombocytopenia have been observed. Data from randomized Phase 2 studies in combination with chemotherapy suggest that mapatumumab may increase rates of lymphopenia.

One subject receiving mapatumumab in combination with carboplatin/paclitaxel has achieved a CR. Twenty-two subjects receiving mapatumumab in combination with paclitaxel/carboplatin and 12 subjects receiving mapatumumab in combination with gemcitabine/cisplatin have achieved PRs. Three subjects receiving mapatumumab in

combination with bortezomib achieved CRs; 25 subjects receiving mapatumumab in combination with bortezomib achieved a PR.

1.5 Rationale for the Evaluation of Mapatumumab in Combination with Sorafenib in Hepatocellular Carcinoma

Sorafenib is the standard of care for treatment of patients with advanced hepatocellular carcinoma. Sorafenib is a multikinase inhibitor that targets the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway, blocks tumor angiogenesis and induces apoptosis (Panka et al, 2006; Rahmani et al, 2005; Yu et al, 2005; Wilhelm et al, 2004). Sorafenib was approved by the European Medicines Agency and the Food and Drug Administration in 2007 for treatment of patients with hepatocellular carcinoma based on the demonstration of improved overall survival in the 602 patient randomized, placebo-controlled, Phase 3 "Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol" (SHARP) trial. Approximately half the 602 patients had either hepatitis C virus or hepatitis B virus as underlying etiology and 26% had alcohol-related cirrhosis. The median overall survival was 10.7 months for patients in the sorafenib arm compared with 7.0 months for patients in the placebo arm (hazard ratio in the sorafenib group, 0.69 95% confidence interval, 0.55 to 0.87; $p < 0.001$). The median time to radiologic progression was 5.5 months in the sorafenib arm, compared with 2.8 months in the placebo arm ($p < 0.0001$) (Llovet et al, 2008). Seven patients in the sorafenib group (2%) and 2 patients in the placebo group (1%) had a PR; no patients had a CR.

A 2nd randomized, placebo-controlled Phase 3 trial was conducted in the Asia-Pacific region (Cheng et al, 2009). The 226 patients randomly assigned to sorafenib or placebo in this trial appeared to have more advanced disease than those in the SHARP trial, with a higher frequency of extrahepatic spread, poorer ECOG PS, and higher levels of AFP, but still showed a benefit from treatment with sorafenib. The majority (73%) had hepatitis B virus as an underlying etiology. The median overall survival was 6.5 months for patients in the sorafenib arm, compared with 4.2 months in the placebo group (hazard ratio, 0.68, 95% confidence interval, 0.50-0.93; $p = 0.014$). The median time to progression was 2.8 months in the sorafenib group, compared with 1.4 months in the placebo group (hazard ratio, 0.57, 95% confidence interval 0.42-0.79; $p = 0.0005$).

The mechanisms of sorafenib and mapatumumab action suggest that these agents could interact synergistically. Sorafenib sensitizes human cancer cell lines, including cell lines derived from hepatocellular carcinoma, to apoptotic stimuli by reducing expression of apoptotic regulatory proteins; Mcl-1, Bcl-xL, and FLIP (Kim et al ,2008; Koehler et al, 2009; Rosato et al, 2007; Liu et al, 2006; Rahmani et al, 2005; Yu et al, 2005). Mcl-1, Bcl-xL and FLIP have also been shown to mediate sensitivity of a wide range of tumor cell lines to TRAIL receptor agonists (Meng et al, 2007; Rosato et al, 2007; Llobet et al 2010; Blechacz et al, 2009; Katz et al, 2009; Huang and Sincrope, 2010; and Menoret et al, 2006). Recent studies demonstrated the combination of sorafenib with TRAIL or TRAIL receptor antibodies has significant activity in hepatocellular carcinoma cell lines (Koehler et al, 2009) and colon tumor xenografts (Ricci et al, 2007) that were resistant to TRAIL and an antibody against TRAIL-R2.

Mapatumumab activity has been evaluated preclinically in hepatocellular carcinoma cell lines by in vitro cytotoxicity assays both as a single agent and in combination with doxorubicin, cisplatin, gemcitabine or sorafenib. Single agent mapatumumab activity was observed in 4 of 10 hepatocellular carcinoma cell lines. Increased in vitro cytotoxicity, including examples of synergy, were observed in 8 of 10 cell lines when mapatumumab was combined with doxorubicin or cisplatin or the combination of cisplatin and gemcitabine (Humphreys et al, 2008). Two of these hepatocellular carcinoma cell lines were evaluated for in vitro cytotoxicity of mapatumumab in combination with sorafenib. One displayed an increase in cytotoxicity from 30% to 60% when treated with a combination of sorafenib and mapatumumab. Importantly, treatment of a primary human hepatocyte cell line did not induce any apoptosis at doses of mapatumumab that were cytotoxic to hepatocellular carcinoma cell lines (Abdulghani et al, 2008). Therefore, collectively, the expression of TRAIL-R1 in hepatocellular carcinoma and preclinical activity observed with combinations of mapatumumab with chemotherapy or sorafenib supports the rationale that this combination may be able to effectively target hepatocellular carcinoma.

1.6 Rationale for Dose Selection

As of June 2010, mapatumumab has been administered with chemotherapy (ie, carboplatin/paclitaxel, gemcitabine/cisplatin, bortezomib, or sorafenib) to 234 subjects, including 61 subjects who received 20 mg/kg and 50 subjects who received 30 mg/kg mapatumumab. Based on available data, mapatumumab in combination with chemotherapy is generally well tolerated at dose levels up to and including 30 mg/kg, and no significant safety issues have been observed in the course of the clinical trials even at the higher doses.

Preliminary PK data are available for subjects who received 1, 10, 20 or 30 mg/kg mapatumumab in combination with gemcitabine and cisplatin (n = 49), 10 or 30 mg/kg mapatumumab in combination with paclitaxel and carboplatin (n = 73), and 3, 10, or 30 mg/kg mapatumumab in combination with sorafenib (n = 17). Serum or plasma mapatumumab concentrations are consistently within the range of expected concentrations predicted from Phase 1 study results in solid tumor patients administered mapatumumab as monotherapy. Mapatumumab PK is linear and not affected by the addition of therapeutic agents. As expected, the observed peak and trough levels of mapatumumab at 30 mg/kg are 2 to 3 times higher than those observed at 10 mg/kg. Exposure appears to increase in proportion to dose and exposures for a given dose are similar across studies.

A Phase 1b dose escalation study of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody is being conducted. Safety observations have been consistent with the underlying disease and known sorafenib toxicities. As of June 2010, 6 subjects have received 3 mg/kg, 9 subjects have received 10 mg/kg, and 1 subject has received 30 mg/kg mapatumumab. The number of cycles completed ranges from 1 to 20; 4/16 (25.0%) of subjects have completed 11 or more cycles. Adverse events have generally been consistent with published reports of the toxicities associated with sorafenib and previous experience with mapatumumab, as well as underlying disease. The most frequently occurring treatment-emergent adverse events, regardless of severity or attribution of causality,

include diarrhea (10/16, 62.5%), fatigue (9/16, 56.3%), nausea (9/16, 56.3%), and vomiting (7/16, 43.8%). Serious adverse events, regardless of attribution of causality, include hypertension, upper respiratory tract infection, atrial fibrillation, hyperbilirubinemia, hypoglycemia, and hepatic pain. Severe adverse events considered at least possibly related to mapatumumab or its interaction with sorafenib include elevated lipase (3/16, 18.8%), hepatic pain (1/16, 6.3%), and thrombocytopenia (1/16, 6.3%). Laboratory abnormalities have generally been mild or moderate in severity, manageable, and/or consistent with those expected with chemotherapy or the underlying disease. The most frequent Grade 3 or Grade 4 laboratory abnormalities include elevated total bilirubin (Grade 3, 4/16, 25.0%; Grade 4, 1/16, 6.3%) and lymphopenia (Grade 3, 3/16, 18.8%; Grade 4, 2/16, 12.5%). Additional information on the safety experience can be found in the mapatumumab Investigators' Brochure.

Based on the information currently available, the safety profile continues to be favorable, supporting continued evaluation of mapatumumab in combination with chemotherapy, including sorafenib. The maximum tolerated dose has not been reached in any of the Phase 1 or Phase 2 trials conducted to date. Thus, further evaluation of the 30 mg/kg dose is warranted.

The dose of sorafenib for this study, 400 mg twice daily, is the approved dose for the treatment of unresectable hepatocellular carcinoma.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

2.2 Secondary Objective

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

3 Study Design

3.1 Basic Design Characteristics

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio: 30 mg/kg mapatumumab or placebo.

Mapatumumab will be supplied in open label vials and 3rd party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent, but independent of all other study activities. All other study site personnel, the subject, and the Sponsor will remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Number of Subjects:

Approximately 100 subjects with advanced HCC will be randomized/enrolled.

Treatment Groups:

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle

Arm B: Sorafenib 400 mg orally twice daily continuously in each cycle + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle

Randomization

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Estimated Study Duration:

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib with or without mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Estimated median length of subject treatment is 6-8 months. Subjects who completed more than 24 months of study treatment with mapatumumab and/or sorafenib and who in the opinion of the investigator obtain clinical benefit from treatment, will be allowed to continue treatment with unblinded mapatumumab and/or sorafenib in the clinical trial. This extension of treatment will continue until the subject's disease progresses or they withdraw from study. In addition extension of treatment with mapatumumab will not extend beyond the expiry date of the drug batch (March 2016). AM03 15Jul15

All subjects will have an End of Treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, whichever is later, for scheduled safety follow-up assessments.

During the Extended Access phase, subjects will have regular visits for disease assessments according to local standard of care. The response assessment will be performed and documented at 12 week intervals (± 6 days). In addition BP will be monitored every 6 weeks and recorded in the eCRF. Serious AEs will continue to be collected during this Extended AM03 15Jul15

Access phase according to Section 8. Study drug administration and inventory/accountability will continue to be recorded during this period according to Section 5.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
   - Located in the liver.
   - Can be accurately measured in at least 1 dimension.
   - Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
   - Suitable for repeat measurement.
   - Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).
4. Radiologic eligibility (measurable disease) must be must be confirmed by the BICR prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count $\geq 1.5 \times 10^9$ /L or ≥ 1500 /mm^3.
   - Platelet count $\geq 50 \times 10^9$ /L or $\geq 50{,}000$ /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal. AM01 21Dec10
   - Serum albumin ≥ 2.8 g/dL or ≥ 28 g/L.
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.

8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

4.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. History of organ allograft. AM02 23Feb11
4. Previously received mapatumumab or sorafenib.
5. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.
6. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
7. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
8. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
9. Hepatic encephalopathy, per the investigator's evaluation.
10. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
11. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
12. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
13. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
14. Known human immunodeficiency virus infection.
15. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
16. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
17. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).

18. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
19. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
20. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
21. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
22. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
23. Hepatitis B virus DNA levels > 2,000 IU/mL.

5 Study Treatment Regimen

Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, the sorafenib should be taken at the same time as any other calendar day.

5.1 Mapatumumab and Placebo

5.1.1 Formulation

Mapatumumab will be supplied as a lyophilized formulation in sterile, single-use 10 mL vials containing 100 mg mapatumumab. Upon reconstitution with 5.0 mL of sterile water for injection, each vial will contain 20 mg/mL mapatumumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 19 mg/mL glycine, 5 mg/mL sucrose, 0.2 mg/mL polysorbate 80, pH 6.5.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

5.1.2 Packaging, Labeling, Preparation, and Storage

The Pharmacy Manual will provide instructions for preparation and storage of study agent. The product will be securely stored at 2-8ºC.

The study agent label will contain, at a minimum, the following information:

- Product name
- Concentration

- Lot number
- Storage instructions
- Investigational drug statement
- Manufacturer's name and address

Study agent inventory/accountability forms will be examined and reconciled by the unblinded study monitor or designee. At the end of the study, all used and unused investigational study agent will be accounted for on a study agent accountability form provided to the investigator by the Sponsor or designee. Please refer to the HGS1012-C1103 Pharmacy Manual for more details regarding storage, handling and drug accountability.

5.1.3 Mapatumumab/Placebo Dose, Route of Administration and Schedule

The dose of mapatumumab is 30 mg/kg. Mapatumumab dose calculations will be based upon the subject's weight measured on Day 1 or within 3 days before Day 1 of each cycle. The planned duration of each treatment cycle will be 21 days. Mapatumumab/placebo will be administered on Day 1 of each cycle.

After reconstitution with sterile water for injection, the calculated mapatumumab dose to be administered to the subject will be further diluted in normal saline to a total volume of 250 mL for intravenous infusion. After adding the reconstituted product, the bag will be gently inverted to mix the solution. Following reconstitution and/or dilution in normal saline, mapatumumab will be stored at 2-8ºC. The product will be administered to the subject within 8 hours of reconstitution. Refer to the HGS1012-C1103 Pharmacy Manual for instructions on admixing and administering study agent.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

Mapatumumab/placebo will be infused at a constant rate over 1 hour.

Infusion and hypersensitivity reactions may occur. A suggested pre-medication regimen for mapatumumab/placebo consists of diphenhydramine and acetaminophen administered within 1 hour prior to the start of the mapatumumab/placebo dose. Use of a pre-medication regimen and alternatives to this regimen are at the investigator's discretion.

Subjects will be monitored closely during and after infusion for any sign of acute adverse reaction. If an allergic reaction occurs, see Section 5.1.5 and Appendix 8 for suggested medical management.

5.1.4 Mapatumumab/Placebo Dose Toxicity/Delay

Mapatumumab/placebo will be discontinued for Grade 4 transaminase elevations of any duration if they are considered related to mapatumumab. AM01 21Dec10

Mapatumumab/placebo may be delayed up to 2 weeks for toxicities considered related to mapatumumab as described below or if the investigator believes that a delay in dosing is warranted in the interest of subject safety.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0) will be used to grade AEs.

- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transient transaminase, amylase and lipase abnormalities for which the following criteria will apply:
  - Grade 3 or Grade 4 elevations in transaminases that do not resolve to baseline or Grade 1 before the next cycle.
  - Grade 3 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, or resulting in chronic damage to the pancreas.
  - Any Grade 4 elevations in lipase or amylase for > 4 consecutive days.

If mapatumumab/placebo is delayed for toxicity and the toxicity does not resolve (≤ Grade 1) or return to baseline within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from further treatment with mapatumumab/placebo. If mapatumumab/placebo is delayed because the investigator believes a delay is warranted in the interest of subject safety and dosing of mapatumumab/placebo is not resumed within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from future treatment with mapatumumab/placebo. Sorafenib dosing will continue while mapatumumab/placebo dosing is held. The subject will continue receiving sorafenib until radiologic progressive disease or an unacceptable toxicity occurs, at the discretion of the Investigator.

Doses of mapatumumab may not be altered.

5.1.5 Management of Allergic/Hypersensitivity Reactions to Mapatumumab/Placebo

The administration of any recombinant protein has the potential to induce local or system immunologic reactions; subjects could experience, for example, acute allergic reactions. To date, 2 such SAEs have been reported which were considered related to mapatumumab (hypersensitivity and angioedema/facial edema). In the event of allergic/hypersensitivity reactions, investigators will institute treatment measures according to best medical and nursing practice. Guidelines for treatment are provided in Appendix 8.

For a NCI-CTCAE Version 4.0 Grade 3 or Grade 4 hypersensitivity reaction, treatment with mapatumumab/placebo will be discontinued.

If mapatumumab/placebo is discontinued for Grade 3 or Grade 4 hypersensitivity reactions, the subject will continue to receive sorafenib, until radiologic progression or unacceptable toxicity.

5.2 Sorafenib

5.2.1 Packaging, Labeling, Preparation, and Storage

Sorafenib is supplied as tablets, each containing 274 mg sorafenib tosylate, equivalent to 200 mg of sorafenib.

The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken orally twice daily without food (at least 1 hour before or 2 hours after a meal).

Sorafenib will be stored at room temperature (15-30°C, 59-86°F) in a dry place.

For country-specific formulation and packaging information, please refer to the instructions provided in the sorafenib product labeling.

Supplier: Commercially available.

5.2.2 Anticipated Toxicities with Sorafenib

Toxicities anticipated with the use of sorafenib include the following:

- Cardiac: Cardiac ischemia and/or infarction, hypertension.
- Dermatologic: Hand-foot skin reaction, rash/desquamation.
- Hemorrhagic: Increased risk of bleeding.
- Gastrointestinal: Gastrointestinal perforation.
- Other: Wound-healing complications, fatigue, weight-loss, alopecia, pruritis, dry skin, diarrhea, anorexia, nausea, vomiting, constipation, liver dysfunction and abdominal pain.

Laboratory abnormalities observed in hepatocellular carcinoma patients treated with sorafenib include hypophosphatemia, lipase elevations, amylase elevations, hypoalbuminemia, international normalized ratio elevations, lymphopenia and thrombocytopenia.

Refer to the product labeling accompanying the product for information approved in your country.

5.2.3 Alteration of Sorafenib Dose/Schedule Due to Toxicity

Sorafenib may be reduced or delayed for toxicities considered related to sorafenib as described below, or if the investigator believes that a reduction in dose is warranted in the interest of subject safety. When a dose reduction is necessary, sorafenib dose may be reduced to 400 mg once daily. If an additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day (see Table 5-1). A maximum of 2 dose reductions of sorafenib will be allowed per subject. Additional dose reductions not mentioned in Table 5-1 will need to be discussed with the medical monitor.

Table 5-1 Sorafenib dose levels

Dose Levels	Sorafenib
0	400 mg twice daily
-1	400 mg once daily
-2	400 mg once every other day

Skin toxicity and hypertension are associated with sorafenib. Guidelines for the management of these events are provided in Table 5-2 and Table 5-3, respectively.

Skin Toxicity

Hand-foot skin reaction and rash are common in subjects treated with sorafenib. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, or in severe or persistent cases, permanent discontinuation. Skin toxicities will be managed according to Table 5-2.

Table 5-2 Dose modifications of sorafenib for skin toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, parethesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subject'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 subject'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 1 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 subject 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 1 dose level (400 mg daily or 400 mg every other day).
	3rd occurrence	Discontinue sorafenib treatment.

Hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Subjects will have their blood pressure monitored and recorded. If the subject's blood pressure is elevated at any time (> 150/100 mmHg), even outside clinic visits, they will contact their study investigator. Guidelines for the management of hypertension are provided in Table 5-3.

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (suggest dihydropyridine calcium channel blocker)	Increase frequency and monitor by a health professional every 2 days until stabilized.	No change
Grade 2 (symptomatic/ persistent) **OR** diastolic BP > 110 mm Hg **OR** Grade 3	Add agent(s): calcium channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor by health professional every 2 days until stabilized; continue monitoring every 2 days to stabilization after dosing restarted.	Hold* sorafenib until symptoms resolve and diastolic BP < 100 mm/Hg Resume treatment at 1 dose level lower**
Grade 4	Discontinue sorafenib	Discontinue sorafenib	Discontinue sorafenib

*Subjects requiring a delay of > 21 days will discontinue sorafenib, unless in the study investigator's opinion, the subject may benefit from continued treatment.

**Subjects requiring > 2 dose reductions will discontinue sorafenib.

BP = Blood pressure.

Refer to NCI-CTCAE v4.0 for grade definitions.

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(concluded)

Guidelines for the management of other non-hematologic and hematologic sorafenib-associated toxicities are provided in Table 5-4. Those toxicities that are at least possibly related to an interaction with mapatumumab/placebo will have the mapatumumab toxicity guidelines in Section 5.1.4 applied.

Table 5-4 Dose modifications of sorafenib for sorafenib-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 1, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.
Hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 2, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.

See Table 5-2 and Table 5-3 for dose modifications due to skin toxicity and hypertension respectively.

*Subjects who develop Grade 3 fever/chills, Grade 3 elevation of hepatic transaminases with ALT and AST < 10X upper limit of normal, Grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, Grade 3 leukopenia, or Grade 3/Grade 4 lymphopenia may continue sorafenib treatment without interruption at the discretion of the investigator.

Sorafenib Discontinuation

Temporary or permanent discontinuation of sorafenib will be considered in subjects who develop cardiac ischemia and/or infarction or severe or persistent hypertension despite institution of antihypertensive therapy. If a subject experiences a bleeding event that necessitates medical intervention or a gastrointestinal perforation, sorafenib will be permanently discontinued. Subjects, who undergo a surgical procedure or intervention to decrease portal hypertension, including transjugular intrahepatic portosystemic shunt, will discontinue sorafenib.

If the subject is withdrawn from further treatment with sorafenib, the subject may continue to receive mapatumumab/placebo alone every 21 days until radiologic progression or unacceptable toxicity.

5.3 Concurrent Medications and Therapies

5.3.1 Allowable Regimens

Subjects may continue their baseline medication(s). The daily dose of each medication will be maintained throughout the study if possible. If for any reason deemed necessary by the investigator, a subject requires additional medication(s), the medication(s) route of administration and the indication for which it was given must be recorded in the source documents. All concomitant medications will be recorded on the appropriate case report form. AM01 21Dec10

Systemic, inhaled and topical steroids used as part of an antiemetic regimen or maintenance-dose for non-cancerous disease are permitted.

5.3.2 Prohibited Medications

Subjects who require the use of strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) are not eligible for this study and use of these agents is prohibited as long as the subject is receiving sorafenib in this study.

Subjects will not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies), immunotherapy or any locoregional therapy (such as embolization, RFA or percutaneous ethanol injection) to treat hepatocellular carcinoma during the treatment period. Alternative anticancer therapies may be administered after radiologic disease progression has been documented, but will be avoided if possible during the 30 day safety follow up period after the last dose of study agent (mapatumumab/placebo and/or sorafenib) whichever is last. These medications are allowed in the long-term follow-up period after the 30 day safety follow-up period and documentation of radiologic disease progression. AM02 23Feb11

5.3.3 Prohibited Therapies

Subjects will not undergo major or elective surgery during the treatment period of the study; if surgery is required, the subject will be withdrawn from study treatment.

6 Study Procedures

6.1 Screening Procedures

The nature of this study and the potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained before any screening procedures are performed that are not considered standard of care.

All of the following assessments must be performed within 28 days prior to enrollment:

- Obtain written informed consent for participation in the study.
- Obtain informed consent for participation in the optional biomarker sub-study.
  - If consented, obtain tissue block/slides or cell pellet from diagnostic histologic/ cytologic sample.
- Record demographics.
- Obtain medical history, to include history of all treatments used to treat the current cancer and all prior cancer treatments.
- Perform baseline complete physical examination including body weight and height.
- Assess vital signs (blood pressure, heart rate, respiratory rate and temperature).
- Evaluate performance status (ECOG scale; see Appendix 3).

- Draw blood for laboratory tests (see Appendix 7): complete blood count with differential, chemistry**,** hepatitis B surface antigen, Hepatitis B virus DNA, hepatitis C antibody and testing for serum pregnancy (all females with an intact uterus [unless amenorrheic for the previous 24 months] regardless of age).
- Obtain radiologic disease and AFP assessments. The method of disease assessment, as per mRECIST for HCC (see Appendix 5), will be consistent throughout the study.
- Obtain electrocardiogram.
- Record medications used within 28 days before enrollment.
- Confirm that subject meets all inclusion/exclusion criteria.

6.2 Study Enrollment/Randomization Procedures

Subjects that meet the eligibility criteria will be randomly assigned treatment by a central interactive voice response system in a 1:1 ratio to 1 of 2 treatment arms. The randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2). The 1st planned dose of sorafenib and mapatumumab/placebo will be administered no more than 3 days following randomization and not prior to randomization. All study site personnel (with the exception of the unblinded site pharmacist or unblinded designee), the subject, and the Sponsor will remain blinded to the study agent received.

6.3 On-treatment Study Procedures

Table 6-1 Study calendar

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			Cycle 1					Cycle 2				Additional Cycles[13]			Extended Access Phase	Safety Follow-up Phase
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15		≥ 30 days following last dose
Informed consent		X													X	
Laboratory																
CBC with differential; Coagulation parameters	1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy	2	X	X													
Hepatitis	1	X														
B and T lymphocyte subsets	3		X				X	X			X					
Immunogenicity	4		X					X				X				
Pharmacokinetics	5		X			X		X				X				
Biomarkers	6		X	X	X	X	X	X	X	X	X					
Study Agent Admin																
Sorafenib	7		Twice daily												X	
Mapatumumab/ Placebo	7		X					X				X			X	
Physical/Clinical																
Med Hx / Phys.Exam	-	X														
Vital signs	8	X	X			X	X	X		X	X	X			X	
Body weight	9	X	X					X				X				
Performance Status	10	X	X					X				X				
Record AEs/	11	X	<----------Throughout the study---------->													

Table 6-1 Study calendar

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			Cycle 1					Cycle 2				Additional Cycles[13]			Extended Access Phase	Safety Follow-up Phase
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15		≥ 30 days following last dose
Conmeds																
Disease Assessments	12	X	Performed at the end of every 2 cycles (ie, Cycles 2, 4, 6) and every 2 cycles thereafter until radiologic PD is documented.												X	
α – Fetoprotein (AFP)	12	X	Performed at the end of every 2 cycles (ie Cycles 2, 4, 6) and every 2 cycles thereafter until radiographic PD is documented.													
ECG	-	X	Repeat as clinically indicated													

AE = adverse event; CBC = complete blood count; CT = computerized tomography; ECG -= electrocardiogram; PD = progressive disease.

1 Safety Labs: Day 1 (complete blood count with differential, coagulation parameters [INR, PT, PTT] and chemistry) must be performed within 3 days prior to dosing on Day 1 of each cycle. See Appendix 7 for a detailed list of required laboratory assessments.

2 Pregnancy: Serum test at screening, urine test pre-dose Cycle 1 Day 1; must be negative to receive treatment.

3 B and T lymphocyte subsets: Blood samples for quantification of B and T lymphocytes will be obtained in Cycles 1 and 2 only. Samples will be obtained on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

4 Immunogenicity: Obtain prior to dosing on Day 1 of Cycles 1, 2, 4, 6, every 2 cycles thereafter and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

5 Pharmacokinetics: Blood specimens will be collected for determination of serum mapatumumab concentrations from subjects as follows: Cycle 1 (on Day 1 prior to the administration mapatumumab/placebo and at the completion of the mapatumumab/placebo infusion, and on Day 8), Cycles 2, 4 and 6 and thereafter on each even cycle (prior to dosing on Day 1), on the day of each disease assessment, and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

6 Biomarkers: For subjects participating in the optional biomarker sub-study, historical biopsy samples will be collected, if available, and samples will be collected if obtained during the treatment period in Cycle 1 Days 1 (pre-dose mapatumumab), 2, 3, 8 and 15 and Cycle 2 Days 1 (pre-dose mapatumumab), 3, 8 and 15. In addition, blood samples will be obtained as follows: blood for isolation of DNA will be collected once, preferably in Cycle 1. Blood for isolation of serum will be collected in Cycles 1 and 2 (pre-dose on the day of mapatumumab/placebo dosing). Further details on the biomarker sub-study are outlined in Appendix 6.

7 Study Agent Administration: Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, sorafenib should be taken at the same time as any other calendar day.

8 Vital Signs: Blood pressure will be monitored weekly for the first 6 weeks. Vital signs will be obtained within 30 minutes prior to administration of mapatumumab/placebo and at the end of infusion on Day 1 of each cycle. For subjects in the Extended Access Phase, only BP is required to be monitored and this should be performed every 6 weeks (± 3 days).

9 Body Weight: To be obtained on the day of or within 3 days before dosing on Day 1 of each cycle.

10 Performance Status: Obtained prior to dosing on Day 1 of each cycle.

[11] Adverse Events: (S)AE collection begins with the start of 1st study agent administration. Concurrent medications will be recorded within 28 days prior to Cycle 1 Day 1. For subjects in the Extended Access Phase, only SAEs will be recorded.

[12] Disease and α – Fetoprotein (AFP) Assessments: Radiologic and AFP assessments will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6, etc). For subjects discontinuing treatment prior to documentation of radiologic disease progression, disease assessments will be performed every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on study, until radiologic disease progression is documented. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent reader for confirmation of disease progression. All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee. For subjects in the Extended Access Phase, disease assessments will be performed as at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. Independent radiological review of response or for confirmation of disease progression is not required.

[13] Subjects who discontinue mapatumumab/placebo will complete the current cycle assessments per the study calendar. Subsequently, for subjects in the Extended Access Phase, subjects receiving sorafenib alone will be assessed as per local standard of care and will return at least every 6 weeks for BP monitoring. Serious adverse events will be recorded throughout the study

(concluded)

6.4 Extended Access to Study Drug

Subjects who completed more than 24 months of study treatment sorafenib with or without mapatumumab and who in the opinion of the investigator obtain clinical benefit from treatment, will be allowed to continue treatment with sorafenib with or without unblinded mapatumumab in the clinical trial. Prior to continuing into the Extended Access phase, subjects will be re-consented to agree to the study assessments and a local re-review of their pathology/cytology. This extension of treatment will continue until the subject's disease progresses (Section 6.8) or they withdraw from study (Section 6.7). In addition extension of treatment with mapatumumab will not extend beyond the expiry date of the drug batch (March 2016). AM03 15Jul15

During the Extended Access phase, subjects will have regular visits for disease assessments at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. In addition BP will be monitored every 6 weeks and recorded in the eCRF. Serious AEs will continue to be collected during this Extended Access phase according to Section 8. Study drug administration and inventory/accountability will continue to be recorded during this period according to Section 5. Laboratory assessments will be performed as per the standard of care.

6.5 Safety Follow-up

After discontinuation of study treatment, all subjects will return at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, for scheduled safety follow-up assessments as outlined in Table 6-1. AM03 15Jul15

6.6 Withdrawal of Subjects from Treatment

Subjects will be free to withdraw from treatment at any time, for any reason, or they may be withdrawn/removed, if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects will be avoided.

Subjects may be withdrawn from treatment for any of the following reasons:

- Radiologic disease progression.
- Continued unacceptable toxicities despite optimal treatment or dose reduction.
- Intercurrent illness, at the investigator's discretion.
- Withdrawal of consent.
- Non-compliance/Lost to follow-up.
- Pregnancy.
- Termination of the study by the sponsor.

Following subject withdrawal, every effort will be made to collect safety information on each subject through 30 days following the last dose of study treatment, unless the subject AM03 15Jul15

withdraws consent and refuses to comply with the protocol stipulated safety follow-up or share information obtained after the date of withdrawal of consent.

6.7 Withdrawal of Subjects from Study

Subjects may be withdrawn from the study for any of the following reasons: AM03 15Jul15

- Withdrawal of consent.
- Non-compliance/Lost to follow-up.
- Termination of the study by the sponsor.

6.8 Disease Response Assessments

Imaging endpoints will be determined using the modified RECIST criteria for HCC proposed by Lencioni 2010 mRECIST for HCC is a joint guideline of the American Association for the Study of Liver Diseases and the Journal of the National Cancer Institute.

Lesions which manifest typical imaging characteristics for HCC demonstrate intratumoral arterial contrast on CT and MRI images. mRECIST accounts for newer therapies which may impact tumor vascularity and may not yield a typical cytotoxic decrease in tumor size by incorporating changes in vascularity into the criteria for target lesion response. Diligence in obtaining images during the hepatic arterial contrast enhancement phase is a requirement at baseline and all subsequent scans. The same imaging method must be used at baseline and during follow up.

As in conventional RECIST, overall response is the result of the combined assessment of target, nontarget, and new lesions. There are also specifications for incorporating portal vein thrombosis, portal hepatic lymph nodes, and pleural effusions/ascites into the response assessment. As with conventional RECIST, the appearance of any new lesion overrides any existing lesion response, resulting in classification as progressive disease (PD). Key aspects of mRECIST as adapted for this study are summarized in Appendix 4.

Baseline images will be provided to the BICR for confirmation of radiologic eligibility (measurable disease). Confirmation of radiologic eligibility for the study will be provided to the site by the BICR within 72 hours of receipt of images and will be required for randomization.

Disease assessments and an assessment of α -fetoprotein will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The response assessment will be performed and documented no more than 5 days before the start of the next cycle. All images will be provided to the BICR following each disease assessment.

If disease progression is based only on new lesions or is equivocal, images will be provided to the BICR for confirmation of radiologic disease progression prior to discontinuing study treatment. PR and CR will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

6.8.1 Disease Response Assessments for Subjects in the Extended Access Phase

During the Extended Access phase, subjects will have regular visits for disease assessments at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. Independent radiological review for confirmation of disease progression is not required. AM03 15Jul15

6.9 Treatment after the end of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment AM03 15Jul15

7 Pharmacokinetic, Immunogenicity, Pharmacodynamic and Exploratory Assessments

7.1 Pharmacokinetic Assessments

For determination of mapatumumab concentration, serum samples will be collected as outlined in Table 6-1.

A manual will be provided regarding how to obtain blood samples, process samples, collect serum from the blood samples, and how to store and ship the serum samples. Bioanalysis will be carried out at Human Genome Sciences to determine mapatumumab concentration in each serum sample.

7.2 Immunogenicity

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

7.3 Pharmacodynamic Assessments

Subjects will be given the option to participate in an exploratory biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine and quantify biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The parameters evaluated may include, but may not be limited to, M30, TNFα, sTRAIL, soluble Fas ligand, interferon-α, interferon-γ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, interleukin-12, and FC gamma receptor and interleukin-6 gene polymorphisms. The biomarker sub-study is detailed in Appendix 6.

7.4 Exploratory Assessments (B and T Lymphocyte Subsets)

7.4.1 Rationale for B and T Lymphocyte Analysis

Over 400 subjects have received mapatumumab in doses ranging from 0.01 to 30 mg/kg across multiple Phase 1 and Phase 2 clinical trials in subjects with solid and hematologic malignancies. While there is no evidence to date that mapatumumab exacerbates adverse events associated with chemotherapy, the most commonly observed laboratory abnormality associated with mapatumumab has been lymphopenia. The lymphopenia has been intermittent and reversible and was not associated with infectious events. However, the lymphocyte subpopulation(s) affected have not been characterized.

The evaluation of lymphocytes will include complete blood count/differential and lymphocyte subpopulation analysis (numbers and percentages of T and B cells) by flow cytometry at a central laboratory. Blood samples will be examined by flow cytometry for levels of T helper (CD4+), T cytotoxic (CD8+) and mature B cells (CD19+).

7.4.2 Collection of Samples for B and T Lymphocyte Analysis

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2 as outlined in Table 6-1.

8 Adverse Event Reporting

8.1 Definitions

ADVERSE EVENT (EXPERIENCE) - any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. This includes worsening (eg, increase in frequency or severity) of pre-existing conditions.

SERIOUS ADVERSE EVENT – an adverse event resulting in any of the following outcomes:

- death
- is life threatening (ie, an immediate threat to life)
- inpatient hospitalization
- prolongation of an existing hospitalization
- persistent or significant disability / incapacity
- congenital anomaly / birth defect
- is Medically Important*

*Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

Note: Hospitalizations not associated with an adverse event, for example, for administration of chemotherapy or hydration for chemotherapy administration, are not considered serious adverse events.

UNEXPECTED ADVERSE EVENT - An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means that the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

8.2 Reporting Adverse Events to the Sponsor or Designee

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE. AM03 15Jul15

Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a Human Genome Science product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK CMG.

All adverse events (AEs) that are identified from the start of any study agent administration through the specified study follow-up period (through 30 days following administration of the final study agent dose) will be recorded on the paper/electronic Adverse Event Case Report Form (AE case report form). All data fields on the AE case report form will be completed.

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and emailed to GSK CMG at PPD (fax backup: PPD within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All pages of the SAE Worksheet will be completed, but the SAE worksheet will not be held until all information is available. Additional information and corrections will be provided on subsequent SAE Worksheets as described in the Study Procedure Manual.

8.3 Laboratory Abnormalities as Adverse Events

A laboratory abnormality will be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, additional assessments (excluding follow-up labs), or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical

sequelae are associated with a laboratory abnormality, the diagnosis or medical condition will be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased).

8.4 Other Events Requiring Rapid Reporting

Protocol Specified Events are additional events [toxicities] specifically identified in this protocol that must be reported to GSK CMG or designee in an expedited manner. Protocol Specified Events may or may not be SAEs as defined in this protocol. They are SAEs if they meet one or more of the criteria for an SAE (see Section 8.1). Protocol Specified Events are recorded on SAE Worksheets and sent to GSK CMG within 24 hours of site personnel becoming aware of the event.

The Protocol Specified Events for the study:

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- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transaminase, amylase and lipase abnormalities for which the following criteria apply:
  - Grade 4 elevations in transaminases.
  - Grade 4 elevations in lipase or amylase.
  - Grade 3 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, resulting in chronic damage to the pancreas.
- Any adverse event that results in discontinuation of treatment if that event is assessed as possibly, probably, or definitely related to mapatumumab or sorafenib.

8.5 Reporting a Pregnancy

Any pregnancy in a female participant or a female partner of a male participant must be reported to GSK CMG as soon as the site becomes aware of the pregnancy. All pregnancies are reported up to 30 days following the last study agent treatment. GSK CMG sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. Additional Pregnancy Assessment Forms will be sent to the site every 3 months for reporting of follow-up information. Pregnancy assessment forms must be completed by the investigator until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 8.2.

8.6 Investigator Evaluation of Adverse Events

The Investigator will evaluate all adverse events with respect to seriousness (criteria listed in Section 8.1 above), severity (intensity or grade) and causality (relationship to study agent) according to the following guidelines listed below.

SEVERITY

Severity will be graded using the NCI-CTCAE, Version 4.0. The NCI-CTCAE may be downloaded from the Cancer Treatment Evaluation Program website (http://ctep.info.nih.gov/reporting/ctc.html). In the event that an AE does not have an NCI-CTCAE code, the following severity classifications will be used:

Mild	causing no limitation of usual activities
Moderate	causing some limitation of usual activities
Severe	causing inability to carry out usual activities
Life Threatening*	potentially life threatening or disabling

***Note** – a severity assessment of life threatening is not necessarily the same as life threatening as a "Serious" criterion. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.

CAUSALITY

Definitely Related	reasonable temporal relationship to study agent administration follows a known response pattern (eg, drug is known to cause this AE) there is no alternative etiology
Probably Related	reasonable temporal relationship follows a suspected response pattern (eg, based on similar drugs) no evidence for a more likely alternative etiology
Possibly Related	reasonable temporal relationship little evidence for a more likely alternative etiology
Probably Not Related	does not have a reasonable temporal relationship, OR good evidence for a more likely alternative etiology
Not Related	does not have a temporal relationship, OR definitely due to alternative etiology

ICH guidelines (March, 1995) clarify "reasonable causal relationship" to mean "that there are facts [evidence] or arguments to suggest a causal relationship".

The causality assessment must be made by the investigator based on information available at the time that the SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

***Note -** If there is evidence that mapatumumab/placebo contributed to or exacerbated an event related to sorafenib; the event will be recorded as possibly, probably or definitely related to both sorafenib and mapatumumab.

8.7 Follow-up of Adverse Events

Adverse events that occur during the course of the study are followed until final outcome is known or until the end of the safety follow-up period (30 days following the final dose of any study agent). Adverse events that have not resolved by the end of the safety follow-up period are recorded as ongoing.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for a SAE (eg, the subject is lost to follow up), the reason a final outcome could not be obtained will be documented by the investigator.

8.8 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to Human Genome Science of SAEs and non-serious AEs related to study treatment (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met. AM03 15Jul15

GSK CMG has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK CMG will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Human Genome Science policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK CMG will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.9 Reporting Serious Adverse Events to the Institutional Review Board/Ethics Committee

All SAEs that are considered unexpected and related to the study agent will be reported by GSK CMG or its designee as expedited (ie, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators. Each investigator must notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) responsible for reviewing the study at their site of all expedited reports. In addition, GSK CMG or its designee will follow all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

9 Endpoints and Statistical Analysis

9.1 General Statistical Considerations

Analyses will be applied to a modified intention-to-treat population unless stated otherwise. This population is defined as the set of all randomized subjects who receive at least 1 dose of study treatment (mapatumumab/placebo and/or sorafenib) with subjects analyzed according to the groups they are randomized to, regardless of the treatment they subsequently receive. Additional analyses may be performed on the as-treated population, defined as the set of subjects receiving at least 1 dose of study medication analyzed according to the treatment that they actually receive.

Analyses will be performed using the SAS System™, WinNonlin Enterprise Edition™, StatXact™, and the R statistical package.

9.2 Sample Size Rationale

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

9.3 Efficacy

9.3.1 Primary Efficacy Endpoint

The primary endpoint is time to progression (TTP) defined as the time from randomization to radiologic disease progression based on blinded independent review of imaging scans.

9.3.2 Primary Efficacy Analysis

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with testing the hazard ratio for time to progression at a 1-sided significance level of 0.10 with a Cox proportional hazards model controlling for the factors stratifying the randomization as covariates.

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9.3.3 Secondary Efficacy Endpoints

Secondary endpoints include progression-free survival, overall response, disease control, overall survival, time to response, and duration of response (for responders) as defined below:

- OS: time from randomization to death from any cause.
- PFS: time from randomization to disease progression or death from any cause.
- Objective response (CR+PR according to mRECIST for HCC).
- Disease control (CR+PR+SD according to mRECIST for HCC).
- Time to response: time from randomization to 1st PR or CR in responders only.

- Duration of response: time from 1st PR or CR to disease progression; in responders only.

All secondary endpoints will be based on blinded independent review of imaging scans.

9.3.4 Secondary Efficacy Analyses

Secondary analyses include estimates, using Kaplan Meier methods, of median PFS and median OS along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test).

9.4 Safety

9.4.1 Definition of Safety Variables

The safety parameters assessed are given by the following:

- Frequency, and severity of adverse events (AEs):
  - All AEs will be classified by System Organ Class and Preferred Term under the Medical Dictionary for Regulatory Activities (MedDRA) system of classification with a severity assigned according to the NCI-CTCAE (Version 4.0, 29 May 2009), or the rules specified in Section 8.6.
  - Laboratory parameters as presented in Appendix 7.
  - Laboratory toxicities will be graded based on the NCI-CTCAE (Version 4.0, 29 May 2009).
- Anti-mapatumumab antibody response.
- Vital signs.
- For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

9.4.2 Human Genome Sciences Safety Review Committee

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

9.4.3 Analysis of Safety Variables

The safety analysis will consist of a presentation of rates of AEs observed. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject

listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality observed will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall, as well as categorized by the MedDRA system of classification. AEs will be presented overall, by severity, by relation to mapatumumab/placebo, and by relation to sorafenib.

9.5 Pharmacokinetics

9.5.1 Definition of Pharmacokinetic Evaluation

Serum mapatumumab concentration data obtained from this study will be pooled with data obtained from other studies for use in a population PK analysis, which will be reported separately.

9.5.2 Analysis of Pharmacokinetics

The serum mapatumumab concentration will be determined by enzyme-linked immunosorbent assay. Serum mapatumumab concentration results for this study will be presented using appropriate graphic and tabular summaries.

9.6 Pharmacodynamics

Expression of biomarkers in tumor tissue and peripheral blood will be correlated with clinical outcomes and may be reported separately from the clinical study report.

10 Study Administration

10.1 Informed Consent

A copy of the proposed informed consent document(s) must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with ICH Good Clinical Practices, will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 Data Collection and Management

Data collected for each study subject are recorded electronically on case report forms provided or approved by the sponsor.

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documents related to the study, including any films, tracings, computer discs, or tapes. The investigator must promptly review the completed case report forms for each subject. As the person ultimately responsible for the accuracy of all data, the investigator must sign the Investigator's Statement in each subject's case report form.

The anonymity of participating subjects must be maintained. Subjects are identified by an assigned subject number on case report forms and other documents submitted to the sponsor. Documents that identify the subject beyond subject number are not submitted to the sponsor

(ie, the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Sites enter subject data directly into the electronic data capture (EDC) system and the EDC system automatically generates queries resulting from computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. At study end, each site is provided with a compact disk containing the electronic case report forms for each of their subjects.

Upon completion of the study, or after reaching a pre-specified point in the study, Data Management locks the database and generates the SAS datasets necessary for data analysis and reporting.

10.6 Study Monitoring

The study sponsor, Human Genome Sciences, Inc., or designee, will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review the paper subject diaries and electronic case report forms and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make paper subject diaries and electronic case report forms and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators will promptly notify Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7 Drug Accountability

Upon receipt, the designated unblinded pharmacy personnel at the study site are responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by an unblinded Clinical Research Associate, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by Human Genome Sciences or its designee.

10.8 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated, or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9 Financial Disclosure

The investigator will provide Human Genome Sciences sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10 Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be pooled and analyzed. The investigator acknowledges that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and sponsor's representatives. Neither institution nor principal investigator shall independently publish or present the results of the study prior to the publication of the multi-center study publication. The investigator agrees that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until the entire sponsor's comments on the proposed publication or presentation have been considered and any information determined by sponsor to be confidential information has been removed. If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11 Study or Study Site Termination

If Human Genome Sciences, the investigator, IRB/IEC, or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the

study center should be terminated, this action may be taken after appropriate consultation between Human Genome Sciences and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of Human Genome Sciences to suspend or discontinue testing, evaluation, or development of the product.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to Human Genome Sciences, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

AM03
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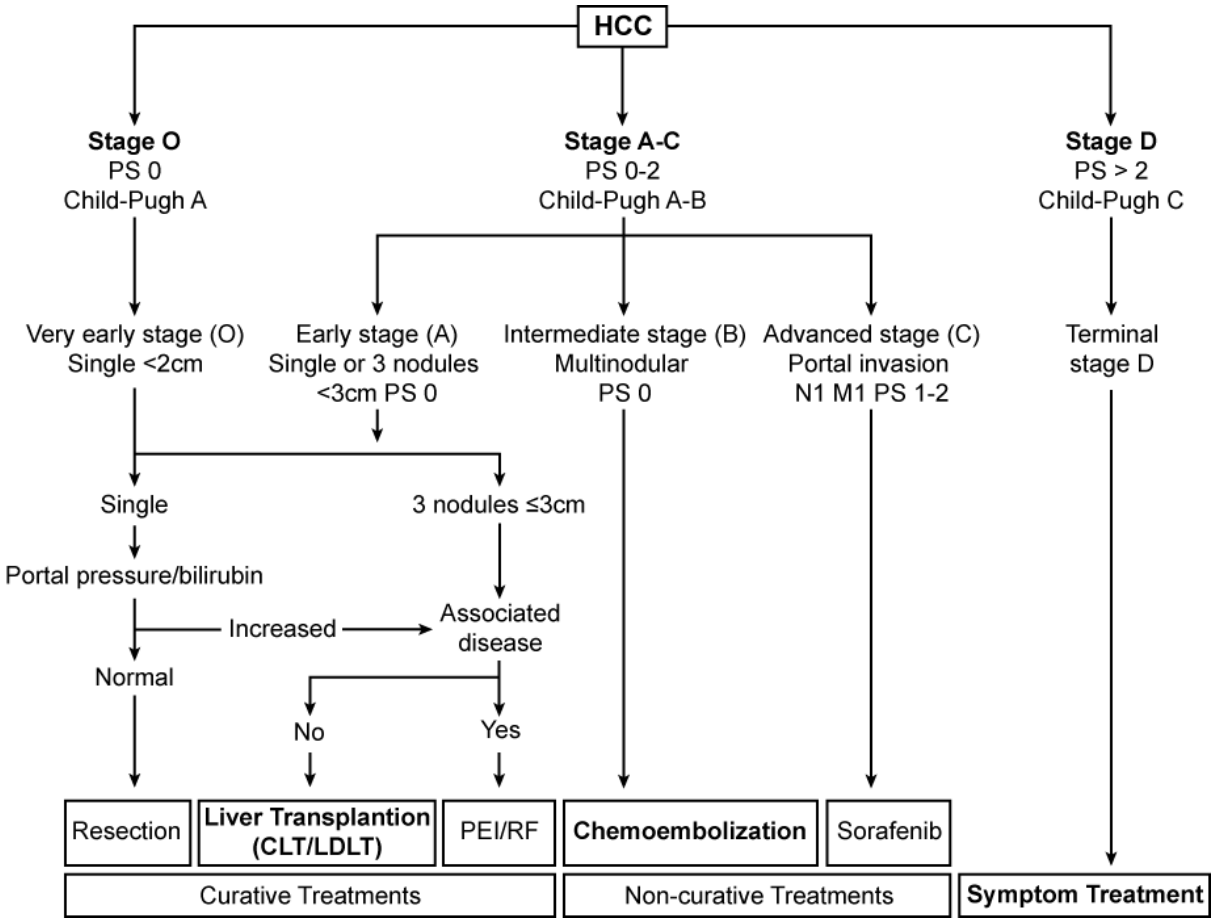
Appendix 1 Child-Pugh Classification

(Zimmermann H and Reichen J, 2000)

	No. of Points		
Factor	**1**	**2**	**3**
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (increased seconds)	1–3	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Minimal	Advanced

Grade	Score
A	5 – 6
B	7 – 9
C	10 – 15

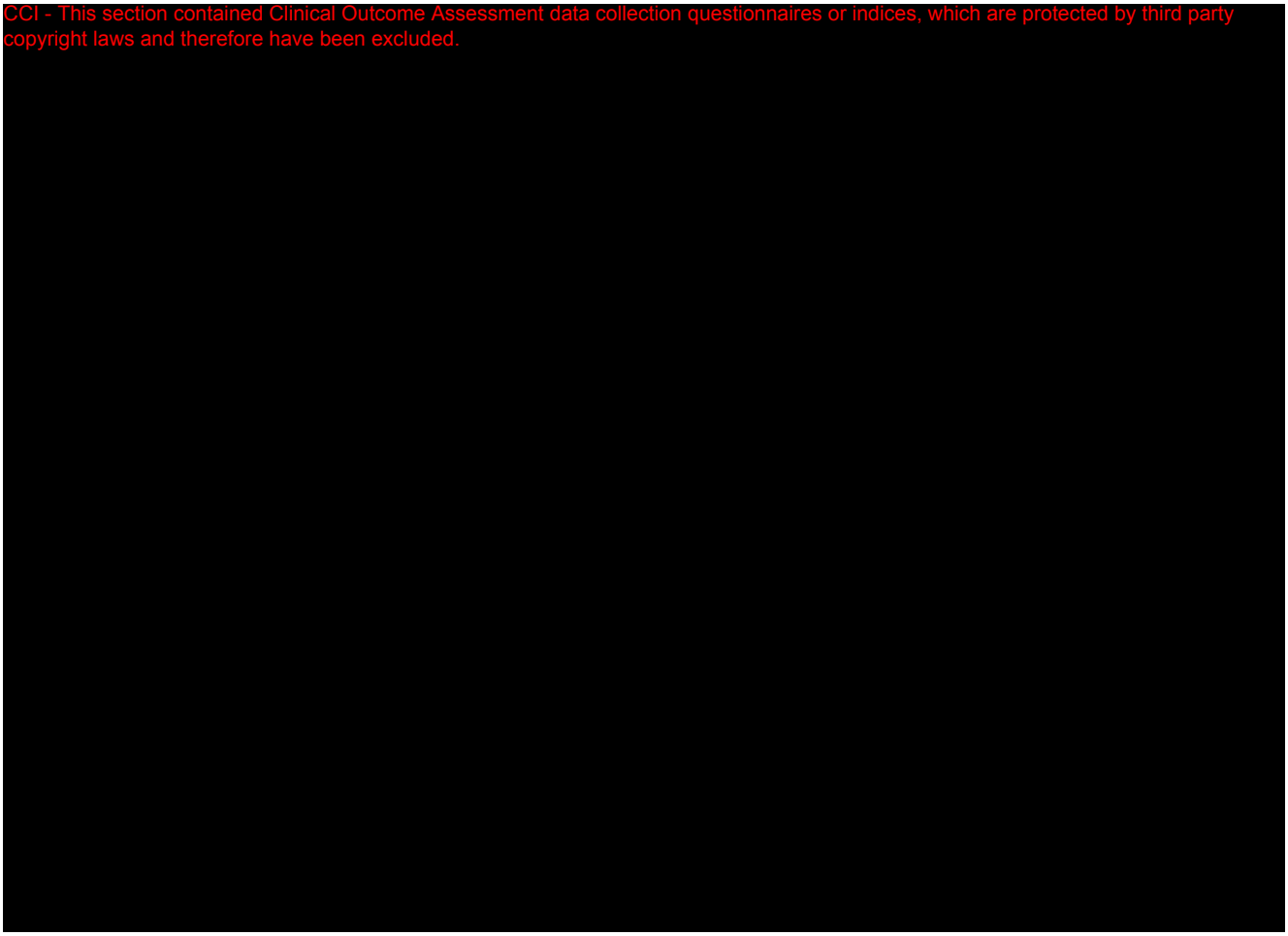
Appendix 2 BCLC Staging and Treatment Strategy



Forner et al, 2010

Appendix 3 Eastern Cooperative Oncology Group (ECOG) Performance Status

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.



Appendix 4 New York Heart Association Classification for Congestive Heart Failure

(The Criteria Committee of the New York Heart Association; Little, Brown & Co. 1994)

Class	New York Heart Association Classification for Congestive Heart Failure
1	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
2	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
3	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
4	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 5 Modified Response Evaluation Criteria in Hepatocellular Carcinoma (mRECIST for HCC)

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(Adapted from Lencioni, 2010 for use in this study)

Measurable disease: The presence of at least 1 target lesion, by contrast enhanced computerized tomography (CT) with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI).

Target lesion: Meets all the following criteria:

- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well-delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

A maximum of 5 target lesions may be selected.

Nontarget lesion: Other lesions, including small lesions (≤ 2 cm in the axial plane). Note that malignant portal vein thrombosis should be considered a nonmeasurable, and therefore nontarget, lesion. Lymph nodes at the portal hepatic can be considered as malignant if the lymph node short axis is at least 2 cm. Selection of effusion, including ascities, as a nontarget lesion is prohibited. Similarly, bone lesions or any other lesion outside the CT or MRI of the abdomen or obtained by other modality, may not be selected as nontarget lesions.

Measurement of lesions: Imaging studies will be by contrast enhanced CT, with use of multislice scanners, or contrast enhanced MRI. The same method must be used at baseline and during follow up. Note that the longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured. The measurement of the viable tumor diameter should not include any major intervening areas of necrosis. (Please see the HGS1012-C1103 Radiographic Data Collection Manual).

Evaluation of target lesions:

Complete Response (CR): Disappearance of 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.

Stable Disease (SD): Any cases that do not qualify for CR, PR or PD.

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.

Evaluation of nontarget lesions:

Complete Response (CR): Disappearance of intratumoral arterial enhancement.

Incomplete Response/Stable Disease (IR/SD): Persistence of intratumoral arterial enhancement in 1 or more nontarget lesions.

Progressive Disease (PD): Unequivocal progression of existing nontarget lesions.

Evaluation of new lesions: A newly detected hepatic nodule will be classified as evidence of progression when its longest diameter is ≥ 1 cm and the nodule shows the hypervascularization in the arterial phase with washout in the portal venous or late venous phase.

Liver lesions ≥ 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least a 1 cm-interval growth in subsequent scans.

An individual radiologic event will be adjudicated in retrospect as progression at the time it was 1st detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

Images by another modality may be obtained, as clinically indicated post-baseline. Sites may conclude that post-baseline images based on another modality that indicate disease are evidence of radiologic progression if: (1) there was no imaging done at baseline; (2) if there was imaging done at baseline showing no disease present at that time; or (3) if there was imagine done at baseline indicating that the on-treatment assessment represents unequivocal worsening. In these cases the disease will be reported as ‘new lesions’.

All images obtained on study will be provided the BICR for the independent efficacy read, or for confirmation of progression if required or requested.

Evaluation of Overall Response: The overall response is determined at each assessment and is a result of the combined assessment of target lesions, nontarget lesions and new lesions.

Overall Response Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response*
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*AFP is not included in assessment of overall response.

Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression. To be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

Appendix 6 Exploratory Biomarker Sub-study

1. Background

Mapatumumab is a targeted therapy. Presently, the relationship between expression of the target, TRAIL-R1, and the anti-tumor activity of the antibody is incompletely understood. Studies conducted with cell lines derived from human tumors have suggested that the relationship between receptor expression and mapatumumab-induced tumor cell death may be complex. However, studies of human tumor cells in vitro and transplanted into animals may not accurately reflect the relationship between receptor expression and response to mapatumumab that may be observed in patients with cancer. One feature of this biomarker study is to compare TRAIL-R1 expression from available biopsy material. This could allow for a greater understanding of patterns of TRAIL-R1 expression in advanced hepatocellular carcinoma.

It is also likely that other factors involved in TRAIL-R1 signaling could critically affect response to mapatumumab treatment. A 2nd goal of this biomarker study is to evaluate biomarkers that may be potential indicators or modifiers of response to mapatumumab. To identify factors that may indicate that a patient is responding to treatment, serum-based markers will be compared before and after treatment. To explore factors that are associated with the outcome of therapy and could be used prior to treatment to predict which patients will respond, somatic (inherited) differences that modify a patient's drug response will be examined.

The information generated from this sub-study will be used solely for research purposes to improve future treatment with mapatumumab. It will not be used to change diagnoses or alter therapy. Participation in this sub-study is optional.

2. Study Objectives and Design

2.1. Indicators of Response

2.1.1. Serum-Based Markers of Response

Induction of cell death in tumor cells can elicit the release of certain biomarkers into the serum. These markers can be quantified to evaluate treatment effect. To assess release of biomarkers associated with cell death, serum-based assays will be conducted, including, but not limited to, assessments of M30, a fragment of cytokeratin 18 that is generated by induction of programmed cell death in epithelial tissues. Other examples of markers of tumor cell death that will be examined include the cytokines TRAIL, TNFα, soluble Fas ligand, interferonα, interferonγ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, and interleukin-12. The levels of these factors will be examined before and after treatment to see if they correlate with response to treatment.

Serum will be isolated and the level of cytokines and other markers like M30 will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2. Modifiers of Response

2.2.1. Neoplastic Modifiers of Response

Historically collected tumor biopsy material, if available, will be collected from subjects during Cycle 1. Samples will also be obtained from subjects who undergo a biopsy during the treatment period. Samples of resected tumor tissue that has been formalin-fixed and embedded in paraffin is acceptable; either tissue blocks or slides may be provided. Frozen samples of tumor tissue may also be provided. Biopsy material collected from fine needle aspirates may be provided; either cell pellets or cytological slides are acceptable.

Levels of TRAIL receptors will be assessed in biopsy material using immunohistochemical techniques if samples are available as formalin-fixed/paraffin-embedded tissue blocks or slides. Historically obtained biopsy material or biopsy material obtained during the treatment period that is in the form of fresh frozen tissue or cell pellet samples will be utilized to isolate RNA for analysis of TRAIL receptor gene expression.

Similar techniques will be used to evaluate other potential biomarkers and factors that may influence mapatumumab response. These may include but are not limited to caspase 8, AKT and Mcl-1.

See the laboratory manual for collection, processing and handling of these samples.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2.2. Somatic Modifiers of Response

Inherited differences in the genes that code for drug targets or components of signaling pathways related to the target can dramatically influence the effect of pharmacotherapy. Variations in genes that could potentially impact mapatumumab's activity, including polymorphic changes in the Fc gamma receptor and interleukin-6 promoter and K-Ras gene mutations, will be examined to see if they correlate with response to treatment.

DNA will be isolated from the blood and polymorphisms and mutations in specific response-related genes will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

3. Statistical Analysis

Associations will be assessed between candidate biomarkers and treatment outcomes captured in the clinical database. Statistical tests to be performed may include Pearson chi-square testing, Fisher's exact test, ANOVA and ANCOVA. Results of the biomarker sub-study may be reported independent of the results of HGS1012-C1103.

4. Subject Selection and Withdrawal

Subjects enrolled in the HGS1012-C1103 research study are given the option to participate in the Biomarkers Sub-study. A subject may withdraw from the sub-study at any time by contacting their Study Investigator, who will contact the sponsor. The sponsor will destroy any remaining sample materials and will send a letter back to the Investigator confirming sample destruction. Any data or analysis generated from the sample prior to the request for destruction will not be destroyed. However, no new information will be generated from the sample and no new analysis will be performed.

5. Confidentiality

Information about sub-study subjects will be kept confidential and managed according to the requirements of local privacy regulations. Information obtained from samples will not be returned to subjects and will not be placed in the subject's medical record.

6. Ethical Considerations

All subjects enrolled in the HGS1012-C1103 research study who agree to participate in the Biomarker Sub-study will be asked to sign a separate Biomarker Informed Consent. Choosing to not participate in this sub-study will not affect the subject's ability to participate in the main clinical trial. The Biomarker Informed Consent will be submitted along with the main research study informed consent for review by the Institutional Review Board/Ethical Committee.

7. Publication of Biomarker Results

Any significant findings, based upon the analysis of aggregate data collected from this sub-study may be published by Human Genome Sciences. Personal identifiers will not be used in any publication resulting from this sub-study.

Appendix 7 Laboratory Tests

CBC with Differential	Chemistry
Total white blood cell (WBC) count differential:	Electrolytes:
Neutrophils	Sodium
Bands	Potassium
Lymphocytes	Magnesium
Monocytes	Chloride
Eosinophils	Carbon dioxide/bicarbonate*
Basophils	Calcium
Hemoglobin	Enzymes:
Hematocrit	SGOT (AST)
Red blood cell count	SGPT (ALT)
Platelet count	Alkaline phosphatase
Absolute Neutrophil Count	Amylase
Total white blood cell count	Lipase
	Gamma glutamyl transferase (GGT)
Prothrombin time (PT)	
Partial thromboplastin time (PTT)	Other:
International normalized ratio (INR)	Creatinine
	Blood Urea Nitrogen
Other:	Total bilirubin
Serum and Urine pregnancy	Total protein
Hepatitis B surface antigen	Albumin
Hepatitis C antibody	
B and T lymphocytes	
HCV RNA	
HBV DNA	
HBsAb	

*To be collected if included in routine automated serum chemistry panel.

Refer to Section 6 (Study Procedures) for laboratory test collection schedule.

Appendix 8 Treatment of Allergic/Hypersensitivity Reactions

In the event of allergic/hypersensitivity reactions to mapatumumab/placebo, investigators will institute treatment measures according to best medical and nursing practice. The grading is based upon the NCI-CTCAE Version 4.0.0.

The following treatment guidelines will be employed:

- If chills and fever occur, the infusion will be interrupted. Subjects may be treated symptomatically and the infusion will be restarted at 50% of the original rate.

Grade 1 allergic/hypersensitivity reaction (transient flushing or rash, drug fever < 38°C):

- Decrease infusion rate by 50% and monitor for worsening condition. If the reaction worsens, stop the infusion.

Grade 2 allergic/hypersensitivity reaction (rash, flushing, urticaria, dyspnea, drug fever < 38°C):

- Stop the infusion.
- Administer bronchodilators, oxygen, acetaminophen, etc as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop the infusion.

Re-treatment following Grade 1 or Grade 2 allergic/hypersensitivity reactions:

- Once the infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions.
- If the subject has a 2nd reaction at the lower infusion rate, the infusion will be stopped and the subject will receive no further treatment with mapatumumab/placebo.
- If the subject experiences a Grade 3 or Grade 4 allergic/hypersensitivity reaction at any time, the subject will receive no further treatment with mapatumumab/placebo.
- If there are questions concerning whether an observed reaction is an allergic/hypersensitivity of Grades 1-4, the medical monitor will be contacted immediately to assist with grading the reaction.

Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- A Grade 3 hypersensitivity reaction consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or asymptomatic hypotension not requiring treatment.
- A Grade 4 hypersensitivity reaction (ie, anaphylaxis) is a life-threatening event characterized by the same symptoms as in a Grade 3 reaction but also complicated by symptomatic hypotension or oxygen saturation of 90% or less.

Treatment of Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- Stop the infusion immediately and disconnect infusion tubing from the subject.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Contact GSK CMG to report an SAE and email SAE worksheet.

Appendix 9 Summary of Modifications and Rationale for Amendment 3

AM03
15Jul15

1. The protocol amendment number and version date have been added to the cover page.
2. A revision chronology page has been added.
3. The protocol has been modified to allow subjects to receive extended access to study drug while receiving the local standard of care for HCC. A new section has been added to clarify assessments required for subjects receiving extended access to study drug.
4. The long term follow up phase of the study has been removed as there is no longer a requirement to follow subjects for long term survival since at least 90% of subjects have met the survival endpoint.
5. The protocol has been updated to comply, where applicable, with the GSK SOP-54825, associated guidance and protocol template v3.1.
6. Reference to contacting Human Genome Science to report Adverse Events has been updated to GSK CMG.

Associated Protocol Modifications:

Text which has been added to the protocol is indicated by **bold typeface** (except if the section is new in its entirety). Text which has been deleted from the protocol is indicated by ~~strike through~~ format.

Cover page:

Formerly:

Protocol Amendment: 02
23 February 2011

Modified to:

Protocol Amendment: 0**3**
15 July 2015

*Added***:** A Revision Chronology page has been added.

Revision Chronology for HGS1012-C1103 (200149)

	Date	**Document***
Global	14 September 2010	Original
Global	21 December 2010	Amendment No 01

	Date	Document*
Global	23 February 2011	Amendment No 02
Global DNG 2013N166298_03	15 July 2015	Amendment No 03

Study Synopsis: Study Design and Schedule, paragraph 3

Formerly:

Subjects will continue to receive study treatment(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiographic progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiographic progression. All subjects will have an end of treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks, starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented) and then every 3 months thereafter for survival until at least 90% of the subjects have met the survival endpoint.

Disease Assessments:

Radiologic disease assessments along with assessment of alpha fetoprotein will be performed at the end of every two 21-day cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The disease assessment will be performed and documented no earlier than 5 days before the start of the next cycle. Clinical responses will be evaluated according to mRECIST for HCC (see Section 6.7 and Appendix 5). The same assessment method will be used throughout the study for each subject. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent, central reader (BICR) for confirmation of disease progression. Partial response (PR) and complete response (CR) will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR). All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

Safety Assessments:

The safety of sorafenib and mapatumumab will be assessed by evaluation of the type, frequency, and severity of adverse events (ie, according to the NCI-CTCAE Version 4.0 grading) and changes in clinical laboratory tests (hematology and clinical chemistry) and immunogenicity over time. In the event that an adverse event does not have an NCI CTCAE Version 4.0 grading, the severity grades in Section 8.6 will be used. Adverse events (including

serious adverse events) will be captured from the start of study agent administration (sorafenib and/or mapatumumab/placebo) through at least 30 days following the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. Laboratory assessments will be performed at screening, and during each study visit outlined in the study calendar found in Section 6.3.

Modified to:

Subjects will continue to receive study treatment(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiographic progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiographic progression. **Subjects who completed more than 24 months of study treatment with sorafenib with or without mapatumumab and who in the opinion of the investigator obtain clinical benefit from treatment, will be allowed to continue treatment with sorafenib with or without unblinded mapatumumab in the clinical trial. This extension of treatment will continue until the subject's disease progresses or they withdraw from study. In addition extension of treatment with mapatumumab will not extend beyond the expiry date of the drug batch (March 2016).**

All subjects will have an end of treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo whichever is later. ~~. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks, starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented) and then every 3 months thereafter for survival until at least 90% of the subjects have met the survival endpoint.~~

During the Extended Access phase, subjects will have regular visits for assessment of disease response at least every 3 months or as per standard of care, whichever is sooner. In addition, BP will be monitored every 6 weeks and recorded in the eCRF. Serious AEs will continue to be collected during this Extended Access phase according to Section 8. Study drug administration and inventory/accountability will continue to be recorded during this period according to Section 5.

Disease Assessments:

Radiologic disease assessments along with assessment of alpha fetoprotein will be performed at the end of every two 21-day cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The disease assessment will be performed and documented no earlier than 5 days before the start of the next cycle. Clinical responses will be evaluated according to mRECIST for HCC (see Section 6.7 and Appendix 5). The same assessment method will be used throughout the study for each subject. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent, central reader (BICR) for confirmation of disease progression. Partial response (PR) and complete response (CR) will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR). All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

During the Extended Access phase, subjects will have regular visits for assessment of disease response at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. Independent radiological review for confirmation of disease progression is not required.

Safety Assessments:

The safety of sorafenib and mapatumumab will be assessed by evaluation of the type, frequency, and severity of adverse events (ie, according to the NCI-CTCAE Version 4.0 grading) and changes in clinical laboratory tests (hematology and clinical chemistry) and immunogenicity over time. In the event that an adverse event does not have an NCI CTCAE Version 4.0 grading, the severity grades in Section 8.6 will be used. Adverse events (including serious adverse events) will be captured from the start of study agent administration (sorafenib and/or mapatumumab/placebo) through at least 30 days following the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. Laboratory assessments will be performed at screening, and during each study visit outlined in the study calendar found in Section 6.3. **During the Extended Access phase, laboratory assessments will be performed as per standard of care; SAEs will continue to be collected according to Section 8.**

Section 3.1 Basic Design Characteristics

Formerly:

Estimated Study Duration:

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib with or without mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Estimated median length of subject treatment is 6-8 months. All subjects will have an End of Treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented). Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

Modified to:

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib with or without mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Estimated median length of subject treatment is 6-8 months. **Subjects who completed more than 24 months of study treatment with mapatumumab and/or sorafenib and who in the opinion of the investigator obtain clinical benefit from treatment, will be allowed to continue treatment with unblinded mapatumumab and/or sorafenib in the clinical trial. This extension of treatment will continue until the subject's disease progresses or they withdraw from study. In addition extension of**

treatment with mapatumumab will not extend beyond the expiry date of the drug batch (March 2016).

All subjects will have an End of Treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, whichever is later **for scheduled safety follow-up assessments.** ~~After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented). Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.~~

During the Extended Access phase, subjects will have regular visits for disease assessments according to local standard of care. The response assessment will be performed and documented at 12 week intervals (± 6 days). In addition BP will be monitored every 6 weeks and recorded in the eCRF. Serious AEs will continue to be collected during this Extended Access phase according to Section 8. Study drug administration and inventory/accountability will continue to be recorded during this period according to Section 5.

Section 6.3 On-treatment Study Procedures

Formerly:

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Informed consent		X															
Laboratory																	
CBC with differential; Coagulation parameters	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy	2	X	X														
Hepatitis	1	X															
B and T lymphocyte subsets	3		X				X	X			X						
Immunogenicity	4		X					X				X				X	
Pharmacokinetics	5		X			X		X				X				X	
Biomarkers	6		X	X	X	X	X	X	X	X	X						
Study Agent Admin																	
Sorafenib	7		Twice daily														
Mapatumumab/ Placebo	7		X					X				X					
Physical/Clinical																	
Med Hx / Phys.Exam	-	X															
Vital signs	8	X	X			X	X	X		X	X	X					
Body weight	9	X	X					X				X					
Performance Status	10	X	X					X				X				X	
Record AEs/ Conmeds	11	X	<----------Throughout the study---------->														

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Disease Assessments	12	X	Performed at the end of every 2 cycles (ie, Cycles 2, 4, 6) and every 2 cycles thereafter until radiologic PD is documented.														X
α – Fetoprotein (AFP)	12	X	Performed at the end of every 2 cycles (ie Cycles 2, 4, 6) and every 2 cycles thereafter until radiographic PD is documented.														X
ECG	-	X	Repeat as clinically indicated														
Survival	13																X

AE = adverse event; CBC = complete blood count; CT = computerized tomography; ECG -= electrocardiogram; PD = progressive disease.

1 Safety Labs: Day 1 (complete blood count with differential, coagulation parameters [INR, PT, PTT] and chemistry) must be performed within 3 days prior to dosing on Day 1 of each cycle. See Appendix 7 for a detailed list of required laboratory assessments.

2 Pregnancy: Serum test at screening, urine test pre-dose Cycle 1 Day 1; must be negative to receive treatment.

3 B and T lymphocyte subsets: Blood samples for quantification of B and T lymphocytes will be obtained in Cycles 1 and 2 only. Samples will be obtained on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

4 Immunogenicity: Obtain prior to dosing on Day 1 of Cycles 1, 2, 4, 6, every 2 cycles thereafter and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

5 Pharmacokinetics: Blood specimens will be collected for determination of serum mapatumumab concentrations from subjects as follows: Cycle 1 (on Day 1 prior to the administration mapatumumab/placebo and at the completion of the mapatumumab/placebo infusion, and on Day 8), Cycles 2, 4 and 6 and thereafter on each even cycle (prior to dosing on Day 1), on the day of each disease assessment, and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

6 Biomarkers: For subjects participating in the optional biomarker sub-study, historical biopsy samples will be collected, if available, and samples will be collected if obtained during the treatment period in Cycle 1 Days 1 (pre-dose mapatumumab), 2, 3, 8 and 15 and Cycle 2 Days 1 (pre-dose mapatumumab), 3, 8 and 15. In addition, blood samples will be obtained as follows: blood for isolation of DNA will be collected once, preferably in Cycle 1. Blood for isolation of serum will be collected in Cycles 1 and 2 (pre-dose on the day of mapatumumab/placebo dosing). Further details on the biomarker sub-study are outlined in Appendix 6.

7 Study Agent Administration: Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, sorafenib should be taken at the same time as any other calendar day.

8 Vital Signs: Blood pressure will be monitored weekly for the first 6 weeks. Vital signs will be obtained within 30 minutes prior to administration of mapatumumab/placebo and at the end of infusion on Day 1 of each cycle.

9 Body Weight: To be obtained on the day of or within 3 days before dosing on Day 1 of each cycle.

10 Performance Status: Obtained prior to dosing on Day 1 of each cycle.

11 Adverse Events: AE collection begins with the start of 1st study agent administration. Concurrent medications will be recorded within 28 days prior to Cycle 1 Day 1.

[12] Disease and α – Fetoprotein (AFP) Assessments: Radiologic and AFP assessments will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6, etc). For subjects discontinuing treatment prior to documentation of radiologic disease progression, disease assessments will be performed every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on study, until radiologic disease progression is documented. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent reader for confirmation of disease progression. All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

[13] Survival**:** Contact will be made with the subject every 3 months to document survival until at least 90% of subjects have met the survival endpoint.

[14] Subjects who discontinue mapatumumab/placebo will complete the current cycle assessments per the study calendar. Subsequently, subjects receiving sorafenib alone will return at least every 21 days and on additional days as clinically indicated for safety labs (CBC with differential, chemistry and coagulation parameters) for the duration of treatment. Disease assessments must be performed every 6 weeks until radiologic disease progression. Adverse events and concomitant medications will be recorded throughout the study.

(concluded)

Modified to:

Table 6-1 Study calendar

AM03
15Jul15

			Cycle 1					Cycle 2				Additional Cycles[13]			Extended Access Phase	Safety Follow-up Phase
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15		≥ 30 days following last dose
Informed consent		X													X	
Laboratory																
CBC with differential; Coagulation parameters	1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry	1	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pregnancy	2	X	X													
Hepatitis	1	X														
B and T lymphocyte subsets	3		X				X	X			X					
Immunogenicity	4		X					X				X				
Pharmacokinetics	5		X			X		X				X				
Biomarkers	6		X	X	X	X	X	X	X	X	X					
Study Agent Admin																
Sorafenib	7		Twice daily												X	
Mapatumumab/ Placebo	7		X					X				X			X	
Physical/Clinical																
Med Hx / Phys.Exam	-	X														
Vital signs	8	X	X			X	X	X		X	X	X			X	
Body weight	9	X	X					X				X				
Performance Status	10	X	X					X				X				
Record AEs/ Conmeds	11	X	<----------Throughout the study---------->													
Disease Assessments	12	X	Performed at the end of every 2 cycles (ie, Cycles 2, 4, 6) and every 2 cycles thereafter												X	

Table 6-1 Study calendar

AM03
15Jul15

			Cycle 1					Cycle 2				Additional Cycles[13]			Extended Access Phase	Safety Follow-up Phase
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15		≥ 30 days following last dose
			until radiologic PD is documented.													
α – Fetoprotein (AFP)	12	X	Performed at the end of every 2 cycles (ie Cycles 2, 4, 6) and every 2 cycles thereafter until radiographic PD is documented.													
ECG	-	X	Repeat as clinically indicated													

AE = adverse event; CBC = complete blood count; CT = computerized tomography; ECG -= electrocardiogram; PD = progressive disease.

1 Safety Labs: Day 1 (complete blood count with differential, coagulation parameters [INR, PT, PTT] and chemistry) must be performed within 3 days prior to dosing on Day 1 of each cycle. See Appendix 7 for a detailed list of required laboratory assessments.

2 Pregnancy: Serum test at screening, urine test pre-dose Cycle 1 Day 1; must be negative to receive treatment.

3 B and T lymphocyte subsets: Blood samples for quantification of B and T lymphocytes will be obtained in Cycles 1 and 2 only. Samples will be obtained on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

4 Immunogenicity: Obtain prior to dosing on Day 1 of Cycles 1, 2, 4, 6, every 2 cycles thereafter and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

5 Pharmacokinetics: Blood specimens will be collected for determination of serum mapatumumab concentrations from subjects as follows: Cycle 1 (on Day 1 prior to the administration mapatumumab/placebo and at the completion of the mapatumumab/placebo infusion, and on Day 8), Cycles 2, 4 and 6 and thereafter on each even cycle (prior to dosing on Day 1), on the day of each disease assessment, and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

6 Biomarkers: For subjects participating in the optional biomarker sub-study, historical biopsy samples will be collected, if available, and samples will be collected if obtained during the treatment period in Cycle 1 Days 1 (pre-dose mapatumumab), 2, 3, 8 and 15 and Cycle 2 Days 1 (pre-dose mapatumumab), 3, 8 and 15. In addition, blood samples will be obtained as follows: blood for isolation of DNA will be collected once, preferably in Cycle 1. Blood for isolation of serum will be collected in Cycles 1 and 2 (pre-dose on the day of mapatumumab/placebo dosing). Further details on the biomarker sub-study are outlined in Appendix 6.

7 Study Agent Administration: Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, sorafenib should be taken at the same time as any other calendar day.

8 Vital Signs: Blood pressure will be monitored weekly for the first 6 weeks. Vital signs will be obtained within 30 minutes prior to administration of mapatumumab/placebo and at the end of infusion on Day 1 of each cycle. **For subjects in the Extended Access Phase, only BP is required to be monitored and this should be performed every 6 weeks (± 3 days).**

9 Body Weight: To be obtained on the day of or within 3 days before dosing on Day 1 of each cycle.

10 Performance Status: Obtained prior to dosing on Day 1 of each cycle.

[11] Adverse Events: (S)AE collection begins with the start of 1st study agent administration. Concurrent medications will be recorded within 28 days prior to Cycle 1 Day 1**. For subjects in the Extended Access Phase, only SAEs will be recorded.**

[12] Disease and α – Fetoprotein (AFP) Assessments: Radiologic and AFP assessments will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6, etc). For subjects discontinuing treatment prior to documentation of radiologic disease progression, disease assessments will be performed every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on study, until radiologic disease progression is documented. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent reader for confirmation of disease progression. All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee. **For subjects in the Extended Access Phase, disease assessments will be performed as at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. Independent radiological review of response or for confirmation of disease progression is not required**.

[13] Subjects who discontinue mapatumumab/placebo will complete the current cycle assessments per the study calendar. **Subsequently, for subjects in the Extended Access Phase, subjects receiving sorafenib alone will be assessed as per local standard of care and will return at least every 6 weeks for BP monitoring. Serious adverse events will be recorded throughout the study**

(concluded)

Section 6 Study Procedures

Added:

Section 6.4 Extended Access to Study Drug

Subjects who completed more than 24 months of study treatment sorafenib with or without mapatumumab and who in the opinion of the investigator obtain clinical benefit from treatment, will be allowed to continue treatment with sorafenib with or without unblinded mapatumumab in the clinical trial. Prior to continuing into the Extended Access phase, subjects will be re-consented to agree to the study assessments and a local re-review of their pathology/cytology. This extension of treatment will continue until the subject's disease progresses (Section 6.8) or they withdraw from study (Section 6.7). In addition extension of treatment with mapatumumab will not extend beyond the expiry date of the drug batch (March 2016).

During the Extended Access phase, subjects will have regular visits for disease assessments at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. In addition BP will be monitored every 6 weeks and recorded in the eCRF. Serious AEs will continue to be collected during this Extended Access phase according to Section 8. Study drug administration and inventory/accountability will continue to be recorded during this period according to Section 5. Laboratory assessments will be performed as per the standard of care.

Section 6.4 Follow-up Procedures, header

Deleted

Section 6.4.1 Safety Follow-up, header

Formerly:

After discontinuation of study treatment, all subjects will return 1 day after cycle completion (approximately Day 22) and at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, for scheduled safety follow-up assessments as outlined in Table 6-1.

Modified to:

Section 6.5 Safety Follow-up

After discontinuation of study treatment, all subjects will return ~~1 day after cycle completion (approximately Day 22)~~ at least 30 days after the last dose of sorafenib and/or mapatumumab, for scheduled safety follow-up assessments as outlined in Table 6-1.

Section 6.4.2 Long-term Follow-up

Formerly:

For subjects discontinuing treatment prior to documentation of radiologic disease progression, and for subjects who experience stable disease or a response (PR, CR) but are no longer receiving treatment, radiologic disease assessments will be performed at 6 week intervals (± 3 days), starting 6 weeks after the previous radiologic disease assessment while on treatment, until radiologic disease progression is documented. Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

Deleted.

Section 6.5 Withdrawal of Subjects from Treatment, paragraph 3

Formerly:

Subjects who withdraw are to be followed for radiologic progression as outlined in Section 6.4.2. In addition, every effort will be made to collect safety information on each subject through 30 days following the last dose of study treatment, unless the subject withdraws consent and refuses to comply with the protocol stipulated safety follow-up and radiologic disease progression assessments, or share information obtained after the date of withdrawal of consent.

Modified to:

~~Subjects who withdraw are to be followed for radiologic progression as outlined in Section 6.4.2. In addition~~ **Following subject withdrawal**, every effort will be made to collect safety information on each subject through 30 days following the last dose of study treatment, unless the subject withdraws consent and refuses to comply with the protocol stipulated safety follow-up ~~and radiologic disease progression assessments,~~ or share information obtained after the date of withdrawal of consent.

Section 6.6 Withdrawal of Subjects from Study, paragraph 2

Formerly:

Every effort will be made to collect follow-up information on subjects in the long-term follow-up period of the study, unless the subject withdraws consent and refuses to share information obtained during the long-term follow-up period obtained after the date of withdrawal of consent.

Deleted

Section 6.7 Disease Response Assessments

Modified to:

Section 6.8 Disease Response Assessments

Added:

Section 6.8.1. Disease Response Assessments for Subjects in the Extended Access Phase

During the Extended Access phase, subjects will have regular visits for disease assessments at least every 3 months or as per standard of care, whichever is sooner, until disease progression is documented. Independent radiological review for confirmation of disease progression is not required.

Section 6.9 Treatment after the end of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment

Section 8.2 Reporting Adverse Events to the Sponsor or Designee

Added:

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a Human Genome Science product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK CMG.

Formerly:

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and sent to HGS within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All pages of the SAE Worksheet will be completed, but the SAE worksheet will not be held until all information is available. Additional information and corrections will be provided on subsequent SAE Worksheets as described in the Study Procedure Manual. SAE Worksheets

will be sent by facsimile to the Drug Safety Department at HGS using the fax number listed below.

FAX #: PPD

Modified to:

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and ~~sent to HGS~~ **emailed to GSK CMG at** PPD **(fax backup:** PPD within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All pages of the SAE Worksheet will be completed, but the SAE worksheet will not be held until all information is available. Additional information and corrections will be provided on subsequent SAE Worksheets as described in the Study Procedure Manual. ~~SAE Worksheets will be sent by facsimile to the Drug Safety Department at HGS using the fax number listed below.~~

~~FAX #:~~ PPD

Section 8.8 Serious Adverse Events Assessed During Long-term Follow-up

Formerly:

SAEs that occur after the safety follow-up period (30 days following the final dose of study agent) that are assessed by the investigator as possibly, probably, or definitely related to study agent must be reported to Human Genome Sciences on an SAE worksheet, as described in Section 8.2. Post-study SAEs will not be documented on the AE case report form.

Deleted.

Section 8.8 Serious Adverse Events Assessed During Long-Term Follow-up

Section Deleted.

Added:

Section 8.8 Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to Human Genome Science of SAEs and non-serious AEs related to study treatment (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK CMG has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK CMG will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Human Genome Science policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK CMG will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

HUMAN GENOME SCIENCES

CLINICAL PROTOCOL HGS1012-C1103
Protocol Amendment: 02
Date: 23 February 2011

AM02
23Feb11

TITLE OF STUDY:

A RANDOMIZED, MULTI-CENTER, BLINDED, PLACEBO-CONTROLLED STUDY OF MAPATUMUMAB ([HGS1012], A FULLY-HUMAN MONOCLONAL ANTIBODY TO TRAIL-R1) IN COMBINATION WITH SORAFENIB AS A FIRST-LINE THERAPY IN SUBJECTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

STUDY SPONSOR: Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850

EudraCT Number: 2010-020798-17

Confidentiality

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator:

_____

Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

Study Synopsis

Study Number: HGS1012-C1103

Title of the Study: A Randomized, Multi-Center, Blinded, Placebo-Controlled Study of Mapatumumab ([HGS1012], a Fully-Human Monoclonal Antibody to TRAIL-R1) in Combination with Sorafenib as a First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma

Clinical Development Phase: 2

Objectives:

Primary:

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

Secondary:

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

Diagnosis & Inclusion Criteria:

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
   - Located in the liver.
   - Can be accurately measured in at least 1 dimension.
   - Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
   - Suitable for repeat measurement.
   - Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be confirmed by the blinded, independent, central read (BICR) prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x 10^9 /L or ≥ 1500 /mm^3.
   - Platelet count ≥ 50 x 10^9 /L or ≥ 50,000 /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal.
   - Serum albumin ≥ 2.8 g/dL or ≥ 28 g/L. AM01 21Dec10
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

Exclusion Criteria:

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. History of organ allograft. AM02 23Feb11
4. Previously received mapatumumab and/or sorafenib.
5. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.
6. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
7. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
8. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
9. Hepatic encephalopathy, per the investigator's evaluation.

10. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
11. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
12. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
13. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
14. Known human immunodeficiency virus infection.
15. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
16. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
17. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
18. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
19. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
20. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
21. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
22. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
23. Hepatitis B virus DNA levels > 2,000 IU/mL.

Study Design and Schedule:

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma. In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive 30 mg/kg mapatumumab or placebo.

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Approximately 100 advanced HCC subjects will be randomized/enrolled.

Study Treatment:

Mapatumumab will be supplied in open label vials and third party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent but independent of all other study activities. All other study personnel, the subject, the Sponsor will remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle.

Arm B: Sorafenib 400 mg orally twice daily continuously + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle.

Subjects will continue to receive study treatment(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiographic progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiographic progression. All subjects will have an end of treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks, starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented) and then every 3 months thereafter for survival until at least 90% of the subjects have met the survival endpoint.

Disease Assessments:

Radiologic disease assessments along with assessment of alpha fetoprotein will be performed at the end of every two 21-day cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The disease assessment will be performed and documented no earlier than 5 days before the start of the next cycle. Clinical responses will be evaluated according to mRECIST for HCC (see Section 6.7 and Appendix 5). The same assessment method will be used throughout the study for each subject. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent, central reader (BICR) for confirmation of disease progression. Partial response (PR) and complete response (CR) will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR). All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

Safety Assessments:

The safety of sorafenib and mapatumumab will be assessed by evaluation of the type, frequency, and severity of adverse events (ie, according to the NCI-CTCAE Version 4.0 grading) and changes in clinical laboratory tests (hematology and clinical chemistry) and immunogenicity over time. In the event that an adverse event does not have an NCI-CTCAE Version 4.0 grading, the severity grades in Section 8.6 will be used. Adverse events (including serious adverse events) will be captured from the start of study agent administration (sorafenib and/or mapatumumab/placebo) through at least 30 days following the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. Laboratory assessments will be performed at screening, and during each study visit outlined in the study calendar found in Section 6.3.

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

Immunogenicity:

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

Dose Modification/Delay:

Dose modifications will not be allowed for mapatumumab/placebo. Dose modifications of sorafenib for toxicity will be made according to the guidelines provided in the treatment section (Section 5.2.3) of the protocol.

Details regarding pre-treatment and management of hypersensitivity reactions related to mapatumumab are provided in Section 5.1.5 and Appendix 8.

Pharmacokinetics:

Multiple blood specimens will be obtained from subjects for serum mapatumumab concentration determinations as outlined in Table 6-1.

Pharmacodynamics:

Subjects will be given the option to participate in a biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and several blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The biomarker sub-study is detailed in Appendix 6.

Exploratory Assessments:

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

Study Endpoints:

The following will be evaluated (these endpoints and the respective analyses are defined in Section 9):

Primary:

- Time to progression (TTP).

Secondary:

- Overall survival.
- Progression-free survival.
- Objective response (complete response [CR] + partial response [PR]).
- Disease control (CR + PR + stable disease [SD]).
- Response duration and time to response in responders.
- Frequency and severity of treatment-emergent adverse events.
- Laboratory parameters.
- Serum mapatumumab concentrations for use in a population pharmacokinetic analysis.

Statistical Methods:

Sample Size:

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

Statistical Analysis:

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with testing the hazard ratio for time to progression at a 1-sided significance level of 0.10 with a Cox

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proportional hazards model controlling for the factors stratifying the randomization as covariates. Secondary analyses include estimates, using Kaplan Meier methods, of median progression-free survival (PFS) and median overall survival (OS) along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test). For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

Study Calendar:

The study calendar is located in Section 6.3 of the protocol.

Table of Contents

List of Tables

List of Abbreviations

AE	adverse event
AFP	α - fetoprotein
ALT	alanine transaminase
AST	aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central read
CR	complete response
CT	computerized tomography
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
Fc	heavy chain constant region or fragment of antibody
GGT	gamma-glutamyl transpeptidase
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGS	Human Genome Sciences
HGSRC	Human Genome Sciences Review Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IR	incomplete response
IRB	Institutional Review Board
kg	kilogram
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mRECIST	modified RECIST assessment for HCC
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ng	nanogram
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease
PK	pharmacokinetics
PPT	partial thromboplastin time
PR	partial response
PS	performance status
PT	prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TRAIL-R1	TRAIL receptor 1
TRAIL-R2	TRAIL receptor 2
TTP	time to progression

1 Background

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma is the 5th most common cancer worldwide accounting for 2% of all malignancies. It is the 3rd leading cause of cancer-related death globally with 1 million new cases a year (WHO, 2007; IACR, 2002; Ferlay et al, 2004; Lopez et al, 2006).

Hepatocellular carcinoma is more prevalent in males with a male:female ratio as high as 8:1. Depending on the endemic risk factors, hepatocellular carcinoma is diagnosed during the 4th through 6th decades of life. The reported incidence of hepatocellular carcinoma is increasing because of a better ability to diagnose the disease and because of the long-term consequences of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection (Reis et al, 2006). Worldwide the most common cause of hepatocellular carcinoma is chronic HBV infection (El-Serag et al, 2003). Endemic areas thus include China, South Asia and South Africa where the incidence of hepatocellular carcinoma can be as high as 120 cases per 100,000. In the United States, where HCV and alcohol are the main risk factors, the age-adjusted incidence rates have increased from 1.4 cases per 100,000 in 1980 to a current incidence of 4 cases per 100,000. This equates to about 8500-11,000 new cases diagnosed each year (IACR, 2002; Ferlay et al, 2004; Pawlik et al, 2004; Edwards, et al, 2005; Jemal et al, 2007; Bosch et al, 2004).

1.2 Treatment Options for Patients with Hepatocellular Carcinoma

Surgery, including transplantation, is the only curative modality for hepatocellular carcinoma (Venook, 1994; Cha et al, 2003). The 5-year survival rate for patients with unresectable hepatocellular carcinoma is 11% in the US (ACS, 2007), < 8% in Europe (Capocaccia et al, 2007), and < 10% in Asia (Teo and Fock, 2001). Symptomatic hepatocellular carcinoma has a very poor prognosis with a median survival of 1–8 months (Former et al, 2006; Llovet et al, 1999a, b).

Sorafenib, a multikinase inhibitor, is the 1st systemic therapy to significantly impact survival in patients with advanced hepatocellular carcinoma, as demonstrated in an international, multicenter Phase 3, placebo-controlled trial (Llovet et al, 2007). Sorafenib was approved in the United States and European Union for the 1st-line treatment of advanced hepatocellular carcinoma in late 2007 and the 2008 National Comprehensive Cancer Network guidelines have been updated with the addition of sorafenib as a treatment option for hepatocellular carcinoma patients. The updated Barcelona Clinic Liver Cancer (BCLC) guidelines recommend sorafenib for hepatocellular carcinoma patients with BCLC Advanced Stage (C) (Forner et al, 2010).

1.3 The Role of the TRAIL Pathway in HCC

1.3.1 TRAIL and TRAIL Receptors

TRAIL is a member of the tumor necrosis factor (TNF) ligand superfamily, with homology to Fas/Apo1 ligand (Pitti et al, 1996; Wiley et al, 1995). TRAIL induces programmed cell death primarily in tumor cells through activation of TRAIL death receptors, TRAIL-R1 (death receptor 4) or TRAIL-R2 (death receptor 5) (Ashkenazi et al, 1999; Evdokiou et al,

2002; Kothny-Wilkes et al, 1998; Lawrence et al, 2001; Pitti et al, 1996; Walczak et al, 1999; Wiley et al, 1995).

TRAIL-R1, the target of mapatumumab, is detectable on tumor cells derived from colon, lung, liver, gastric, pancreas, uterus and esophagus and in tissue sections from various tumors of the colon, lung, pancreas, liver and stomach without significant expression in parallel normal tissues (Halpern et al, 2004; Roach et al, 2004).

1.3.2 TRAIL and HBV/HCV Infection

Acutely infected tissues, including the liver, utilize the TRAIL pathway to eliminate virally and bacterially infected cells (Herr et al, 2007). In viral hepatitis, TRAIL and 1 of its receptors, TRAIL-R2, are upregulated and contribute to the elimination of infected hepatocytes associated with viral hepatitis (Bantel and Schulze-Osthoff, 2003; Lin et al, 2002; Matsuda et al, 2005). In addition to HBV and HCV infection, steatosis, exposure to bile acids and chronic alcohol exposure induce increased expression of TRAIL and TRAIL-R2, but not TRAIL-R1, in human hepatocytes (Dunn et al, 2007; Mundt et al, 2005). Cell surface expression of TRAIL-R2, but not TRAIL-R1, was altered and responsible for sensitization to TRAIL in hepatocytes exposed to bile acids (Higuchi et al, 2001; Malhi et al, 2007). These findings have been reproduced in preclinical models. Non-virally infected hepatocytes are refractory to TRAIL and TRAIL-R agonists but exposure of HCV-infected hepatocytes to TRAIL leads to a significant level of apoptosis (Volkmann et al, 2007). Inhibition of the TRAIL pathway may protect infected cells from apoptosis and allow for chronic infection (Mundt et al, 2003). Recent non-clinical observations demonstrated that natural killer cells expressing the ligand TRAIL, are enriched in the livers of patients with chronic HBV infection, and TRAIL is overexpressed in the livers of patients with HCV-associated steatosis (Mundt et al, 2005).

In summary, preclinical data suggest that mapatumumab may promote apoptosis of cancer cells, including hepatocellular carcinoma cells. Whether viral infection, including HBV or HCV infection, will attenuate or modulate the effects of mapatumumab on hepatocytes is not yet known, but experience to date in a Phase 1b trial of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody indicates that the safety experience is consistent with underlying disease and known sorafenib toxicities (see Section 1.2).

1.4 Mapatumumab

1.4.1 Mapatumumab Pharmacology

Mapatumumab is a fully human, agonist monoclonal antibody that activates the cell death pathway in tumor cells by specifically binding to TRAIL-R1 with high affinity. Mapatumumab efficiently induces apoptosis in human cancer cell lines expressing the TRAIL-R1 protein on the cell surface. Nonclinical studies have demonstrated that mapatumumab can induce cytotoxicity in multiple tumor cell lines representing both solid and hematological malignancies, including cancers of the biliary tract, colon, lung, breast, pancreas, esophagus, ovary, kidney, uterus, as well as lymphoma and various leukemias. Mapatumumab has also demonstrated anti-tumor activity as a single agent, preventing

tumor growth and in some cases causing regression of tumors in xenograft tumor models of multiple human malignancies, including lung, colon, kidney, and uterus (Camidge, 2007; Georgakis et al, 2005; Jin et al, 2007; Humphreys, 2004; Marini et al, 2006; Menoret et al, 2006; Pukac et al, 2005).

The relationship between receptor expression and response to therapy with mapatumumab remains unclear. In vitro studies of cell lines have shown that TRAIL-R1 expression level is not a consistent predictor of response to mapatumumab. Although both TRAIL-R1 expression and apoptosis in response to mapatumumab are increased in many tumor cell lines as compared with normal diploid cells, there are examples of mapatumumab cytotoxicity on cell lines with very low levels of detectable receptor, and conversely, mapatumumab resistant cell lines that have relatively high levels of TRAIL-R1 cell surface expression.

Tumor cell cytotoxic activity can be enhanced when mapatumumab is administered in combination with chemotherapeutics or other anti-neoplastic agents. Enhanced apoptotic signaling, in vitro cell killing and in vivo anti-tumor activity have been observed when mapatumumab has been combined with various types of therapeutic agents and treatments including microtubule poisons, anti metabolites, topoisomerase inhibitors, proteosome inhibitors, platinum agents and radiation. Both the level and spectrum of activity of mapatumumab is enhanced in in vitro cytotoxicity and in vivo xenograft studies in combination with various chemotherapeutic and anti-neoplastic agents, including a xenograft model of hepatocellular carcinoma in combination with cisplatin and gemcitabine (Camidge, 2007; Pukac et al, 2005; Georgakis et al, 2005; Humphreys, 2004; Jin et al, 2007; Human Genome Sciences data on file).

Please refer to the mapatumumab Investigator's Brochure for detailed information regarding the nonclinical pharmacology, toxicology, and PK of mapatumumab.

1.4.2 Non-Clinical Mapatumumab Safety Studies

To assess the nonclinical safety of mapatumumab, a 6-month toxicity study, with a 4-month recovery period, was conducted in chimpanzees. Mapatumumab was administered intravenously at up to 40 mg/kg every 10 days. No mapatumumab-specific toxicity was identified and no anti-mapatumumab antibodies were detected.

To assess its off-target effects, mapatumumab was administered intravenously weekly to cynomolgus monkeys, whose TRAIL R1 homolog does not bind mapatumumab. Mapatumumab was well tolerated at doses of up to 50 mg/kg and was not highly immunogenic: of the 40 monkeys treated, 1 developed anti-mapatumumab antibodies. The positive response was observed in an animal in the high dose (50 mg/kg) group.

In vitro, mapatumumab was found to decrease viability of normal human hepatocytes, although the observed effect was less than that observed with TRAIL. This effect was variable across donors and did not amplify with increasing concentrations of mapatumumab. It should be noted that in clinical studies, plasma mapatumumab concentrations have been achieved that are > 1100–fold greater than the minimum exposure resulting in reduced in vitro hepatocyte viability. Despite this, the clinical results do not reveal evidence of hepatotoxicity in those

studies. Hence it appears that the in vitro hepatocyte viability assay is not predictive of mapatumumab effects in vivo.

1.4.3 Clinical Experience with Mapatumumab

Over 400 subjects have received mapatumumab in clinical trials to date. Preliminary clinical data are available from 218 subjects who received mapatumumab as a single agent at doses ranging from 0.01 to 20 mg/kg across 6 clinical trials.

Based on available data, mapatumumab appears to be well tolerated and no significant safety issues have been observed. Adverse events have generally been mild to moderate in severity, manageable, and do not appear related to dose. The most frequently reported treatment-related adverse events occurring in > 10% of subjects were fatigue, hypotension, nausea and pyrexia. Severe events have been uncommon and generally judged not related to mapatumumab. Severe events judged at least possibly related to mapatumumab have been observed and a complete list can be found in the mapatumumab Investigator's Brochure. Grade 3 or Grade 4 hematologic, renal, or hepatic laboratory abnormalities also have been relatively uncommon with no significant trend or dose-response evident. Lymphopenia was the most commonly observed laboratory abnormality, but tended to be intermittent and reversible and was not associated with infectious events.

In subjects with solid tumors, stable disease has been the best response observed with mapatumumab as a single-agent. However, 2 complete responses (CRs) and 1 partial response (PR) were observed in subjects with follicular lymphoma.

In addition, preliminary clinical data are available from 234 subjects who received mapatumumab at doses ranging from 1 to 30 mg/kg every 21 days in combination with chemotherapy in 5 clinical trials (carboplatin/paclitaxel [N = 100], gemcitabine/cisplatin [N = 49], bortezomib [n = 69], or sorafenib [n = 16]. Mapatumumab has been generally well tolerated; adverse events and laboratory abnormalities have been consistent with those expected with underlying disease or chemotherapy. A listing of severe events considered at least possibly related to mapatumumab can be found in the mapatumumab Investigator's Brochure. The most commonly occurring laboratory abnormalities have been hematologic (ie, anemia, neutropenia, thrombocytopenia, and leukopenia), as expected with chemotherapy. Grade 3/4 laboratory abnormalities have been relatively uncommon. Higher frequencies of Grade 3/4 neutropenia, leukopenia, lymphopenia, and thrombocytopenia have been observed. Data from randomized Phase 2 studies in combination with chemotherapy suggest that mapatumumab may increase rates of lymphopenia.

One subject receiving mapatumumab in combination with carboplatin/paclitaxel has achieved a CR. Twenty-two subjects receiving mapatumumab in combination with paclitaxel/carboplatin and 12 subjects receiving mapatumumab in combination with gemcitabine/cisplatin have achieved PRs. Three subjects receiving mapatumumab in combination with bortezomib achieved CRs; 25 subjects receiving mapatumumab in combination with bortezomib achieved a PR.

1.5 Rationale for the Evaluation of Mapatumumab in Combination with Sorafenib in Hepatocellular Carcinoma

Sorafenib is the standard of care for treatment of patients with advanced hepatocellular carcinoma. Sorafenib is a multikinase inhibitor that targets the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway, blocks tumor angiogenesis and induces apoptosis (Panka et al, 2006; Rahmani et al, 205; Yu et al, 2005; Wilhelm et al, 2004). Sorafenib was approved by the European Medicines Agency and the Food and Drug Administration in 2007 for treatment of patients with hepatocellular carcinoma based on the demonstration of improved overall survival in the 602 patient randomized, placebo-controlled, Phase 3 "Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol" (SHARP) trial. Approximately half the 602 patients had either hepatitis C virus or hepatitis B virus as underlying etiology and 26% had alcohol-related cirrhosis. The median overall survival was 10.7 months for patients in the sorafenib arm compared with 7.0 months for patients in the placebo arm (hazard ratio in the sorafenib group, 0.69 95% confidence interval, 0.55 to 0.87; $p < 0.001$). The median time to radiologic progression was 5.5 months in the sorafenib arm, compared with 2.8 months in the placebo arm ($p < 0.0001$) (Llovet et al, 2008). Seven patients in the sorafenib group (2%) and 2 patients in the placebo group (1%) had a PR; no patients had a CR.

A 2nd randomized, placebo-controlled Phase 3 trial was conducted in the Asia-Pacific region (Cheng et al, 2009). The 226 patients randomly assigned to sorafenib or placebo in this trial appeared to have more advanced disease than those in the SHARP trial, with a higher frequency of extrahepatic spread, poorer ECOG PS, and higher levels of AFP, but still showed a benefit from treatment with sorafenib. The majority (73%) had hepatitis B virus as an underlying etiology. The median overall survival was 6.5 months for patients in the sorafenib arm, compared with 4.2 months in the placebo group (hazard ratio, 0.68, 95% confidence interval, 0.50-0.93; $p = 0.014$). The median time to progression was 2.8 months in the sorafenib group, compared with 1.4 months in the placebo group (hazard ratio, 0.57, 95% confidence interval 0.42-0.79; $p = 0.0005$).

The mechanisms of sorafenib and mapatumumab action suggest that these agents could interact synergistically. Sorafenib sensitizes human cancer cell lines, including cell lines derived from hepatocellular carcinoma, to apoptotic stimuli by reducing expression of apoptotic regulatory proteins; Mcl-1, Bcl-xL, and FLIP (Kim et al,2008; Koehler et al, 2009; Rosato et al, 2007; Liu et al, 2006; Rahmani et al, 2005; Yu et al, 2005). Mcl-1, Bcl-xL and FLIP have also been shown to mediate sensitivity of a wide range of tumor cell lines to TRAIL receptor agonists (Meng et al, 2007; Rosato et al, 2007; Llobet et al 2010; Blechacz et al, 2009; Katz et al, 2009; Huang and Sincrope, 2010; and Menoret et al, 2006). Recent studies demonstrated the combination of sorafenib with TRAIL or TRAIL receptor antibodies has significant activity in hepatocellular carcinoma cell lines (Koehler et al, 2009) and colon tumor xenografts (Ricci et al, 2007) that were resistant to TRAIL and an antibody against TRAIL-R2.

Mapatumumab activity has been evaluated preclinically in hepatocellular carcinoma cell lines by in vitro cytotoxicity assays both as a single agent and in combination with doxorubicin, cisplatin, gemcitabine or sorafenib. Single agent mapatumumab activity was observed in 4 of

10 hepatocellular carcinoma cell lines. Increased in vitro cytotoxicity, including examples of synergy, were observed in 8 of 10 cell lines when mapatumumab was combined with doxorubicin or cisplatin or the combination of cisplatin and gemcitabine (Humphreys et al, 2008). Two of these hepatocellular carcinoma cell lines were evaluated for in vitro cytotoxicity of mapatumumab in combination with sorafenib. One displayed an increase in cytotoxicity from 30% to 60% when treated with a combination of sorafenib and mapatumumab. Importantly, treatment of a primary human hepatocyte cell line did not induce any apoptosis at doses of mapatumumab that were cytotoxic to hepatocellular carcinoma cell lines (PPD and PPD [personal communication], 2008; Abdulghani et al, 2008). Therefore, collectively, the expression of TRAIL-R1 in hepatocellular carcinoma and preclinical activity observed with combinations of mapatumumab with chemotherapy or sorafenib supports the rationale that this combination may be able to effectively target hepatocellular carcinoma.

1.6 Rationale for Dose Selection

As of June 2010, mapatumumab has been administered with chemotherapy (ie, carboplatin/paclitaxel, gemcitabine/cisplatin, bortezomib, or sorafenib) to 234 subjects, including 61 subjects who received 20 mg/kg and 50 subjects who received 30 mg/kg mapatumumab. Based on available data, mapatumumab in combination with chemotherapy is generally well tolerated at dose levels up to and including 30 mg/kg, and no significant safety issues have been observed in the course of the clinical trials even at the higher doses.

Preliminary PK data are available for subjects who received 1, 10, 20 or 30 mg/kg mapatumumab in combination with gemcitabine and cisplatin (n = 49), 10 or 30 mg/kg mapatumumab in combination with paclitaxel and carboplatin (n = 73), and 3, 10, or 30 mg/kg mapatumumab in combination with sorafenib (n = 17). Serum or plasma mapatumumab concentrations are consistently within the range of expected concentrations predicted from Phase 1 study results in solid tumor patients administered mapatumumab as monotherapy. Mapatumumab PK is linear and not affected by the addition of therapeutic agents. As expected, the observed peak and trough levels of mapatumumab at 30 mg/kg are 2 to 3 times higher than those observed at 10 mg/kg. Exposure appears to increase in proportion to dose and exposures for a given dose are similar across studies.

A Phase 1b dose escalation study of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody is being conducted. Safety observations have been consistent with the underlying disease and known sorafenib toxicities. As of June 2010, 6 subjects have received 3 mg/kg, 9 subjects have received 10 mg/kg, and 1 subject has received 30 mg/kg mapatumumab. The number of cycles completed ranges from 1 to 20; 4/16 (25.0%) of subjects have completed 11 or more cycles. Adverse events have generally been consistent with published reports of the toxicities associated with sorafenib and previous experience with mapatumumab, as well as underlying disease. The most frequently occurring treatment-emergent adverse events, regardless of severity or attribution of causality, include diarrhea (10/16, 62.5%), fatigue (9/16, 56.3%), nausea (9/16, 56.3%), and vomiting (7/16, 43.8%). Serious adverse events, regardless of attribution of causality, include hypertension, upper respiratory tract infection, atrial fibrillation, hyperbilirubinemia,

hypoglycemia, and hepatic pain. Severe adverse events considered at least possibly related to mapatumumab or its interaction with sorafenib include elevated lipase (3/16, 18.8%), hepatic pain (1/16, 6.3%), and thrombocytopenia (1/16, 6.3%). Laboratory abnormalities have generally been mild or moderate in severity, manageable, and/or consistent with those expected with chemotherapy or the underlying disease. The most frequent Grade 3 or Grade 4 laboratory abnormalities include elevated total bilirubin (Grade 3, 4/16, 25.0%; Grade 4, 1/16, 6.3%) and lymphopenia (Grade 3, 3/16, 18.8%; Grade 4, 2/16, 12.5%). Additional information on the safety experience can be found in the mapatumumab Investigators' Brochure.

Based on the information currently available, the safety profile continues to be favorable, supporting continued evaluation of mapatumumab in combination with chemotherapy, including sorafenib. The maximum tolerated dose has not been reached in any of the Phase 1 or Phase 2 trials conducted to date. Thus, further evaluation of the 30 mg/kg dose is warranted.

The dose of sorafenib for this study, 400 mg twice daily, is the approved dose for the treatment of unresectable hepatocellular carcinoma.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

2.2 Secondary Objective

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

3 Study Design

3.1 Basic Design Characteristics

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio: 30 mg/kg mapatumumab or placebo.

Mapatumumab will be supplied in open label vials and 3rd party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent, but independent of all other study activities. All other study site personnel, the subject, and the Sponsor will remain blinded to the study agent

received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Number of Subjects:

Approximately 100 subjects with advanced HCC will be randomized/enrolled.

Treatment Groups:

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle

Arm B: Sorafenib 400 mg orally twice daily continuously in each cycle + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle

Randomization

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Estimated Study Duration:

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib with or without mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Estimated median length of subject treatment is 6-8 months. All subjects will have an End of Treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented). Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced

dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be must be confirmed by the BICR prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x 10^9 /L or ≥ 1500 /mm^3.
   - Platelet count ≥ 50 x 10^9 /L or ≥ 50,000 /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal. AM01 21Dec10
   - Serum albumin ≥ 2.8 g/dL or ≥ 28 g/L.
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

4.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. History of organ allograft. AM02 23Feb11
4. Previously received mapatumumab or sorafenib.
5. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.

6. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
7. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
8. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
9. Hepatic encephalopathy, per the investigator's evaluation.
10. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
11. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
12. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
13. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
14. Known human immunodeficiency virus infection.
15. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
16. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
17. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
18. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
19. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
20. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
21. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
22. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
23. Hepatitis B virus DNA levels > 2,000 IU/mL.

5 Study Treatment Regimen

Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, the sorafenib should be taken at the same time as any other calendar day.

5.1 Mapatumumab and Placebo

5.1.1 Formulation

Mapatumumab will be supplied as a lyophilized formulation in sterile, single-use 10 mL vials containing 100 mg mapatumumab. Upon reconstitution with 5.0 mL of sterile water for injection, each vial will contain 20 mg/mL mapatumumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 19 mg/mL glycine, 5 mg/mL sucrose, 0.2 mg/mL polysorbate 80, pH 6.5.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

5.1.2 Packaging, Labeling, Preparation, and Storage

The Pharmacy Manual will provide instructions for preparation and storage of study agent. The product will be securely stored at 2-8ºC.

The study agent label will contain, at a minimum, the following information:

- Product name
- Concentration
- Lot number
- Storage instructions
- Investigational drug statement
- Manufacturer's name and address

Study agent inventory/accountability forms will be examined and reconciled by the unblinded study monitor or designee. At the end of the study, all used and unused investigational study agent will be accounted for on a study agent accountability form provided to the investigator by the Sponsor or designee. Please refer to the HGS1012-C1103 Pharmacy Manual for more details regarding storage, handling and drug accountability.

5.1.3 Mapatumumab/Placebo Dose, Route of Administration and Schedule

The dose of mapatumumab is 30 mg/kg. Mapatumumab dose calculations will be based upon the subject's weight measured on Day 1 or within 3 days before Day 1 of each cycle. The planned duration of each treatment cycle will be 21 days. Mapatumumab/placebo will be administered on Day 1 of each cycle.

After reconstitution with sterile water for injection, the calculated mapatumumab dose to be administered to the subject will be further diluted in normal saline to a total volume of 250 mL for intravenous infusion. After adding the reconstituted product, the bag will be gently inverted to mix the solution. Following reconstitution and/or dilution in normal saline, mapatumumab will be stored at 2-8ºC. The product will be administered to the subject within 8 hours of reconstitution. Refer to the HGS1012-C1103 Pharmacy Manual for instructions on admixing and administering study agent.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

Mapatumumab/placebo will be infused at a constant rate over 1 hour.

Infusion and hypersensitivity reactions may occur. A suggested pre-medication regimen for mapatumumab/placebo consists of diphenhydramine and acetaminophen administered within 1 hour prior to the start of the mapatumumab/placebo dose. Use of a pre-medication regimen and alternatives to this regimen are at the investigator's discretion.

Subjects will be monitored closely during and after infusion for any sign of acute adverse reaction. If an allergic reaction occurs, see Section 5.1.5 and Appendix 8 for suggested medical management.

5.1.4 Mapatumumab/Placebo Dose Toxicity/Delay

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Mapatumumab/placebo will be discontinued for Grade 4 transaminase elevations of any duration if they are considered related to mapatumumab.

Mapatumumab/placebo may be delayed up to 2 weeks for toxicities considered related to mapatumumab as described below or if the investigator believes that a delay in dosing is warranted in the interest of subject safety.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0) will be used to grade AEs.

- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transient transaminase, amylase and lipase abnormalities for which the following criteria will apply:
  - Grade 3 or Grade 4 elevations in transaminases that do not resolve to baseline or Grade 1 before the next cycle.
  - Grade 3 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, or resulting in chronic damage to the pancreas.
  - Any Grade 4 elevations in lipase or amylase for > 4 consecutive days.

If mapatumumab/placebo is delayed for toxicity and the toxicity does not resolve (≤ Grade 1) or return to baseline within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from further treatment with

mapatumumab/placebo. If mapatumumab/placebo is delayed because the investigator believes a delay is warranted in the interest of subject safety and dosing of mapatumumab/placebo is not resumed within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from future treatment with mapatumumab/placebo. Sorafenib dosing will continue while mapatumumab/placebo dosing is held. The subject will continue receiving sorafenib until radiologic progressive disease or an unacceptable toxicity occurs, at the discretion of the Investigator.

Doses of mapatumumab may not be altered.

5.1.5 Management of Allergic/Hypersensitivity Reactions to Mapatumumab/Placebo

The administration of any recombinant protein has the potential to induce local or system immunologic reactions; subjects could experience, for example, acute allergic reactions. To date, 2 such SAEs have been reported which were considered related to mapatumumab (hypersensitivity and angioedema/facial edema). In the event of allergic/hypersensitivity reactions, investigators will institute treatment measures according to best medical and nursing practice. Guidelines for treatment are provided in Appendix 8.

For a NCI-CTCAE Version 4.0 Grade 3 or Grade 4 hypersensitivity reaction, treatment with mapatumumab/placebo will be discontinued.

If mapatumumab/placebo is discontinued for Grade 3 or Grade 4 hypersensitivity reactions, the subject will continue to receive sorafenib, until radiologic progression or unacceptable toxicity.

5.2 Sorafenib

5.2.1 Packaging, Labeling, Preparation, and Storage

Sorafenib is supplied as tablets, each containing 274 mg sorafenib tosylate, equivalent to 200 mg of sorafenib.

The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken orally twice daily without food (at least 1 hour before or 2 hours after a meal).

Sorafenib will be stored at room temperature (15-30°C, 59-86°F) in a dry place.

For country-specific formulation and packaging information, please refer to the instructions provided in the sorafenib product labeling.

Supplier: Commercially available.

5.2.2 Anticipated Toxicities with Sorafenib

Toxicities anticipated with the use of sorafenib include the following:

- Cardiac: Cardiac ischemia and/or infarction, hypertension.

- Dermatologic: Hand-foot skin reaction, rash/desquamation.
- Hemorrhagic: Increased risk of bleeding.
- Gastrointestinal: Gastrointestinal perforation.
- Other: Wound-healing complications, fatigue, weight-loss, alopecia, pruritis, dry skin, diarrhea, anorexia, nausea, vomiting, constipation, liver dysfunction and abdominal pain.

Laboratory abnormalities observed in hepatocellular carcinoma patients treated with sorafenib include hypophosphatemia, lipase elevations, amylase elevations, hypoalbuminemia, international normalized ratio elevations, lymphopenia and thrombocytopenia.

Refer to the product labeling accompanying the product for information approved in your country.

5.2.3 Alteration of Sorafenib Dose/Schedule Due to Toxicity

Sorafenib may be reduced or delayed for toxicities considered related to sorafenib as described below, or if the investigator believes that a reduction in dose is warranted in the interest of subject safety. When a dose reduction is necessary, sorafenib dose may be reduced to 400 mg once daily. If an additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day (see Table 5-1). A maximum of 2 dose reductions of sorafenib will be allowed per subject. Additional dose reductions not mentioned in Table 5-1 will need to be discussed with the medical monitor.

Table 5-1 Sorafenib dose levels

Dose Levels	Sorafenib
0	400 mg twice daily
-1	400 mg once daily
-2	400 mg once every other day

Skin toxicity and hypertension are associated with sorafenib. Guidelines for the management of these events are provided in Table 5-2 and Table 5-3, respectively.

Skin Toxicity

Hand-foot skin reaction and rash are common in subjects treated with sorafenib. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, or in severe or persistent cases, permanent discontinuation. Skin toxicities will be managed according to Table 5-2.

Table 5-2 Dose modifications of sorafenib for skin toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, parethesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subject'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 subject'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 1 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 subject 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 1 dose level (400 mg daily or 400 mg every other day).
	3rd occurrence	Discontinue sorafenib treatment.

Hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Subjects will have their blood pressure monitored and recorded. If the subject's blood pressure is elevated at any time (> 150/100 mmHg), even outside clinic visits, they will contact their study investigator. Guidelines for the management of hypertension are provided in Table 5-3.

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (suggest dihydropyridine calcium channel blocker)	Increase frequency and monitor by a health professional every 2 days until stabilized.	No change
Grade 2 (symptomatic/ persistent) **OR** diastolic BP > 110 mm Hg **OR** Grade 3	Add agent(s): calcium channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor by health professional every 2 days until stabilized; continue monitoring every 2 days to stabilization after dosing restarted.	Hold* sorafenib until symptoms resolve and diastolic BP < 100 mm/Hg Resume treatment at 1 dose level lower**

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 4	Discontinue sorafenib	Discontinue sorafenib	Discontinue sorafenib

*Subjects requiring a delay of > 21 days will discontinue sorafenib, unless in the study investigator's opinion, the subject may benefit from continued treatment.

**Subjects requiring > 2 dose reductions will discontinue sorafenib.

BP = Blood pressure.

Refer to NCI-CTCAE v4.0 for grade definitions.

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Guidelines for the management of other non-hematologic and hematologic sorafenib-associated toxicities are provided in Table 5-4. Those toxicities that are at least possibly related to an interaction with mapatumumab/placebo will have the mapatumumab toxicity guidelines in Section 5.1.4 applied.

Table 5-4 Dose modifications of sorafenib for sorafenib-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 1, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.
Hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 2, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.

See Table 5-2 and Table 5-3 for dose modifications due to skin toxicity and hypertension respectively.

*Subjects who develop Grade 3 fever/chills, Grade 3 elevation of hepatic transaminases with ALT and AST < 10X upper limit of normal, Grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, Grade 3 leukopenia, or Grade 3/Grade 4 lymphopenia may continue sorafenib treatment without interruption at the discretion of the investigator.

Sorafenib Discontinuation

Temporary or permanent discontinuation of sorafenib will be considered in subjects who develop cardiac ischemia and/or infarction or severe or persistent hypertension despite institution of antihypertensive therapy. If a subject experiences a bleeding event that necessitates medical intervention or a gastrointestinal perforation, sorafenib will be

permanently discontinued. Subjects, who undergo a surgical procedure or intervention to decrease portal hypertension, including transjugular intrahepatic portosystemic shunt, will discontinue sorafenib.

If the subject is withdrawn from further treatment with sorafenib, the subject may continue to receive mapatumumab/placebo alone every 21 days until radiologic progression or unacceptable toxicity.

5.3 Concurrent Medications and Therapies

5.3.1 Allowable Regimens

Subjects may continue their baseline medication(s). The daily dose of each medication will be maintained throughout the study if possible. If for any reason deemed necessary by the investigator, a subject requires additional medication(s), the medication(s) route of administration and the indication for which it was given must be recorded in the source documents. All concomitant medications will be recorded on the appropriate case report form. AM01 21Dec10

Systemic, inhaled and topical steroids used as part of an antiemetic regimen or maintenance-dose for non-cancerous disease are permitted.

5.3.2 Prohibited Medications

Subjects who require the use of strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) are not eligible for this study and use of these agents is prohibited as long as the subject is receiving sorafenib in this study.

Subjects will not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies), immunotherapy or any locoregional therapy (such as embolization, RFA or percutaneous ethanol injection) to treat hepatocellular carcinoma during the treatment period. Alternative anticancer therapies may be administered after radiologic disease progression has been documented, but will be avoided if possible during the 30 day safety follow up period after the last dose of study agent (mapatumumab/placebo and/or sorafenib) whichever is last. These medications are allowed in the long-term follow-up period after the 30 day safety follow-up period and documentation of radiologic disease progression. AM02 23Feb11

5.3.3 Prohibited Therapies

Subjects will not undergo major or elective surgery during the treatment period of the study; if surgery is required, the subject will be withdrawn from study treatment.

6 Study Procedures

6.1 Screening Procedures

The nature of this study and the potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent (including

consent for the use and disclosure of research-related health information) must be obtained before any screening procedures are performed that are not considered standard of care.

All of the following assessments must be performed within 28 days prior to enrollment:

- Obtain written informed consent for participation in the study.
- Obtain informed consent for participation in the optional biomarker sub-study.
  - If consented, obtain tissue block/slides or cell pellet from diagnostic histologic/ cytologic sample.
- Record demographics.
- Obtain medical history, to include history of all treatments used to treat the current cancer and all prior cancer treatments.
- Perform baseline complete physical examination including body weight and height.
- Assess vital signs (blood pressure, heart rate, respiratory rate and temperature).
- Evaluate performance status (ECOG scale; see Appendix 3).
- Draw blood for laboratory tests (see Appendix 7): complete blood count with differential, chemistry**,** hepatitis B surface antigen, Hepatitis B virus DNA, hepatitis C antibody and testing for serum pregnancy (all females with an intact uterus [unless amenorrheic for the previous 24 months] regardless of age).
- Obtain radiologic disease and AFP assessments. The method of disease assessment, as per mRECIST for HCC (see Appendix 5), will be consistent throughout the study.
- Obtain electrocardiogram.
- Record medications used within 28 days before enrollment.
- Confirm that subject meets all inclusion/exclusion criteria.

6.2 Study Enrollment/Randomization Procedures

Subjects that meet the eligibility criteria will be randomly assigned treatment by a central interactive voice response system in a 1:1 ratio to 1 of 2 treatment arms. The randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2). The 1st planned dose of sorafenib and mapatumumab/placebo will be administered no more than 3 days following randomization and not prior to randomization. All study site personnel (with the exception of the unblinded site pharmacist or unblinded designee), the subject, and the Sponsor will remain blinded to the study agent received.

6.3 On-treatment Study Procedures

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Informed consent		X															
Laboratory																	
CBC with differential; Coagulation parameters	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy	2	X	X														
Hepatitis	1	X															
B and T lymphocyte subsets	3		X				X	X			X						
Immunogenicity	4		X					X				X				X	
Pharmacokinetics	5		X			X		X				X				X	
Biomarkers	6		X	X	X	X	X	X	X	X	X						
Study Agent Admin																	
Sorafenib	7		Twice daily														
Mapatumumab/ Placebo	7		X					X				X					
Physical/Clinical																	
Med Hx / Phys.Exam	-	X															
Vital signs	8	X	X			X	X	X		X	X	X					
Body weight	9	X	X					X				X					
Performance Status	10	X	X					X				X				X	

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Record AEs/ Conmeds	11	X	<----------Throughout the study---------->														
Disease Assessments	12	X	Performed at the end of every 2 cycles (ie, Cycles 2, 4, 6) and every 2 cycles thereafter until radiologic PD is documented.														X
α – Fetoprotein (AFP)	12	X	Performed at the end of every 2 cycles (ie Cycles 2, 4, 6) and every 2 cycles thereafter until radiographic PD is documented.														X
ECG	-	X	Repeat as clinically indicated														
Survival	13																X

AE = adverse event; CBC = complete blood count; CT = computerized tomography; ECG -= electrocardiogram; PD = progressive disease.

[1] Safety Labs: Day 1 (complete blood count with differential, coagulation parameters [INR, PT, PTT] and chemistry) must be performed within 3 days prior to dosing on Day 1 of each cycle. See Appendix 7 for a detailed list of required laboratory assessments.

[2] Pregnancy: Serum test at screening, urine test pre-dose Cycle 1 Day 1; must be negative to receive treatment.

[3] B and T lymphocyte subsets: Blood samples for quantification of B and T lymphocytes will be obtained in Cycles 1 and 2 only. Samples will be obtained on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

[4] Immunogenicity: Obtain prior to dosing on Day 1 of Cycles 1, 2, 4, 6, every 2 cycles thereafter and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

[5] Pharmacokinetics: Blood specimens will be collected for determination of serum mapatumumab concentrations from subjects as follows: Cycle 1 (on Day 1 prior to the administration mapatumumab/placebo and at the completion of the mapatumumab/placebo infusion, and on Day 8), Cycles 2, 4 and 6 and thereafter on each even cycle (prior to dosing on Day 1), on the day of each disease assessment, and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

[6] Biomarkers: For subjects participating in the optional biomarker sub-study, historical biopsy samples will be collected, if available, and samples will be collected if obtained during the treatment period in Cycle 1 Days 1 (pre-dose mapatumumab), 2, 3, 8 and 15 and Cycle 2 Days 1 (pre-dose mapatumumab), 3, 8 and 15. In addition, blood samples will be obtained as follows: blood for isolation of DNA will be collected once, preferably in Cycle 1. Blood for isolation of serum will be collected in Cycles 1 and 2 (pre-dose on the day of mapatumumab/placebo dosing). Further details on the biomarker sub-study are outlined in Appendix 6.

[7] Study Agent Administration: Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, sorafenib should be taken at the same time as any other calendar day.

[8] Vital Signs: Blood pressure will be monitored weekly for the first 6 weeks. Vital signs will be obtained within 30 minutes prior to administration of mapatumumab/placebo and at the end of infusion on Day 1 of each cycle.

[9] Body Weight: To be obtained on the day of or within 3 days before dosing on Day 1 of each cycle.

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	

[10] Performance Status: Obtained prior to dosing on Day 1 of each cycle.

[11] Adverse Events: AE collection begins with the start of 1st study agent administration. Concurrent medications will be recorded within 28 days prior to Cycle 1 Day 1.

[12] Disease and α – Fetoprotein (AFP) Assessments: Radiologic and AFP assessments will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6, etc). For subjects discontinuing treatment prior to documentation of radiologic disease progression, disease assessments will be performed every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on study, until radiologic disease progression is documented. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent reader for confirmation of disease progression. All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

[13] Survival**:** Contact will be made with the subject every 3 months to document survival until at least 90% of subjects have met the survival endpoint.

[14] Subjects who discontinue mapatumumab/placebo will complete the current cycle assessments per the study calendar. Subsequently, subjects receiving sorafenib alone will return at least every 21 days and on additional days as clinically indicated for safety labs (CBC with differential, chemistry and coagulation parameters) for the duration of treatment. Disease assessments must be performed every 6 weeks until radiologic disease progression. Adverse events and concomitant medications will be recorded throughout the study.

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6.4 Follow-up Procedures

6.4.1 Safety Follow-up

After discontinuation of study treatment, all subjects will return 1 day after cycle completion (approximately Day 22) and at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, for scheduled safety follow-up assessments as outlined in Table 6-1.

6.4.2 Long-term Follow-up

For subjects discontinuing treatment prior to documentation of radiologic disease progression, and for subjects who experience stable disease or a response (PR, CR) but are no longer receiving treatment, radiologic disease assessments will be performed at 6 week intervals (± 3 days), starting 6 weeks after the previous radiologic disease assessment while on treatment, until radiologic disease progression is documented. Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

6.5 Withdrawal of Subjects from Treatment

Subjects will be free to withdraw from treatment at any time, for any reason, or they may be withdrawn/removed, if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects will be avoided.

Subjects may be withdrawn from treatment for any of the following reasons:

- Radiologic disease progression.
- Continued unacceptable toxicities despite optimal treatment or dose reduction.
- Intercurrent illness, at the investigator's discretion.
- Withdrawal of consent.
- Non-compliance/Lost to follow-up.
- Pregnancy.
- Termination of the study by the sponsor.

Subjects who withdraw are to be followed for radiologic progression as outlined in Section 6.4.2. In addition, every effort will be made to collect safety information on each subject through 30 days following the last dose of study treatment, unless the subject withdraws consent and refuses to comply with the protocol stipulated safety follow-up and radiologic disease progression assessments, or share information obtained after the date of withdrawal of consent.

6.6 Withdrawal of Subjects from Study

Subjects may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent.

- Non-compliance/Lost to follow-up.
- Termination of the study by the sponsor.

Every effort will be made to collect follow-up information on subjects in the long-term follow-up period of the study, unless the subject withdraws consent and refuses to share information obtained during the long-term follow-up period obtained after the date of withdrawal of consent.

6.7 Disease Response Assessments

Imaging endpoints will be determined using the modified RECIST criteria for HCC proposed by Lencioni and Llovet (2010; mRECIST). mRECIST for HCC is a joint guideline of the American Association for the Study of Liver Diseases and the Journal of the National Cancer Institute.

Lesions which manifest typical imaging characteristics for HCC demonstrate intratumoral arterial contrast on CT and MRI images. mRECIST accounts for newer therapies which may impact tumor vascularity and may not yield a typical cytotoxic decrease in tumor size by incorporating changes in vascularity into the criteria for target lesion response. Diligence in obtaining images during the hepatic arterial contrast enhancement phase is a requirement at baseline and all subsequent scans. The same imaging method must be used at baseline and during follow up.

As in conventional RECIST, overall response is the result of the combined assessment of target, nontarget, and new lesions. There are also specifications for incorporating portal vein thrombosis, portal hepatic lymph nodes, and pleural effusions/ascites into the response assessment. As with conventional RECIST, the appearance of any new lesion overrides any existing lesion response, resulting in classification as progressive disease (PD). Key aspects of mRECIST as adapted for this study are summarized in Appendix 4.

Baseline images will be provided to the BICR for confirmation of radiologic eligibility (measurable disease). Confirmation of radiologic eligibility for the study will be provided to the site by the BICR within 72 hours of receipt of images and will be required for randomization.

Disease assessments and an assessment of α -fetoprotein will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The response assessment will be performed and documented no more than 5 days before the start of the next cycle. All images will be provided to the BICR following each disease assessment.

If disease progression is based only on new lesions or is equivocal, images will be provided to the BICR for confirmation of radiologic disease progression prior to discontinuing study treatment. PR and CR will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

7 Pharmacokinetic, Immunogenicity, Pharmacodynamic and Exploratory Assessments

7.1 Pharmacokinetic Assessments

For determination of mapatumumab concentration, serum samples will be collected as outlined in Table 6-1.

A manual will be provided regarding how to obtain blood samples, process samples, collect serum from the blood samples, and how to store and ship the serum samples. Bioanalysis will be carried out at Human Genome Sciences to determine mapatumumab concentration in each serum sample.

7.2 Immunogenicity

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

7.3 Pharmacodynamic Assessments

Subjects will be given the option to participate in an exploratory biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine and quantify biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The parameters evaluated may include, but may not be limited to, M30, TNFα, sTRAIL, soluble Fas ligand, interferon-α, interferon-γ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, interleukin-12, and FC gamma receptor and interleukin-6 gene polymorphisms. The biomarker sub-study is detailed in Appendix 6.

7.4 Exploratory Assessments (B and T Lymphocyte Subsets)

7.4.1 Rationale for B and T Lymphocyte Analysis

Over 400 subjects have received mapatumumab in doses ranging from 0.01 to 30 mg/kg across multiple Phase 1 and Phase 2 clinical trials in subjects with solid and hematologic malignancies. While there is no evidence to date that mapatumumab exacerbates adverse events associated with chemotherapy, the most commonly observed laboratory abnormality associated with mapatumumab has been lymphopenia. The lymphopenia has been intermittent and reversible and was not associated with infectious events. However, the lymphocyte subpopulation(s) affected have not been characterized.

The evaluation of lymphocytes will include complete blood count/differential and lymphocyte subpopulation analysis (numbers and percentages of T and B cells) by flow cytometry at a central laboratory. Blood samples will be examined by flow cytometry for levels of T helper (CD4+), T cytotoxic (CD8+) and mature B cells (CD19+).

7.4.2 Collection of Samples for B and T Lymphocyte Analysis

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2 as outlined in Table 6-1.

8 Adverse Event Reporting

8.1 Definitions

ADVERSE EVENT (EXPERIENCE) - any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. This includes worsening (eg, increase in frequency or severity) of pre-existing conditions.

SERIOUS ADVERSE EVENT – an adverse event resulting in any of the following outcomes:

- death
- is life threatening (ie, an immediate threat to life)
- inpatient hospitalization
- prolongation of an existing hospitalization
- persistent or significant disability / incapacity
- congenital anomaly / birth defect
- is Medically Important*

*Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

Note: Hospitalizations not associated with an adverse event, for example, for administration of chemotherapy or hydration for chemotherapy administration, are not considered serious adverse events.

UNEXPECTED ADVERSE EVENT - An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means that the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

8.2 Reporting Adverse Events to the Sponsor or Designee

All adverse events (AEs) that are identified from the start of any study agent administration through the specified study follow-up period (through 30 days following administration of the

final study agent dose) will be recorded on the paper/electronic Adverse Event Case Report Form (AE case report form). All data fields on the AE case report form will be completed.

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and sent to HGS within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All pages of the SAE Worksheet will be completed, but the SAE worksheet will not be held until all information is available. Additional information and corrections will be provided on subsequent SAE Worksheets as described in the Study Procedure Manual. SAE Worksheets will be sent by facsimile to the Drug Safety Department at HGS using the fax number listed below.

FAX #: PPD

8.3 Laboratory Abnormalities as Adverse Events

A laboratory abnormality will be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, additional assessments (excluding follow-up labs), or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition will be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased).

8.4 Other Events Requiring Rapid Reporting

Protocol Specified Events are additional events [toxicities] specifically identified in this protocol that must be reported to Human Genome Sciences or designee in an expedited manner. Protocol Specified Events may or may not be SAEs as defined in this protocol. They are SAEs if they meet one or more of the criteria for an SAE (see Section 8.1). Protocol Specified Events are recorded on SAE Worksheets and sent to Human Genome Sciences within 24 hours of site personnel becoming aware of the event.

The Protocol Specified Events for the study:

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- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transaminase, amylase and lipase abnormalities for which the following criteria apply:
  - Grade 4 elevations in transaminases.
  - Grade 4 elevations in lipase or amylase.
  - Grade 3 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, resulting in chronic damage to the pancreas.
- Any adverse event that results in discontinuation of treatment if that event is assessed as possibly, probably, or definitely related to mapatumumab or sorafenib.

8.5 Reporting a Pregnancy

Any pregnancy in a female participant or a female partner of a male participant must be reported to Human Genome Sciences Drug Safety as soon as the site becomes aware of the pregnancy. All pregnancies are reported up to 30 days following the last study agent treatment. Human Genome Sciences Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. Additional Pregnancy Assessment Forms will be sent to the site every 3 months for reporting of follow-up information. Pregnancy assessment forms must be completed by the investigator until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 8.2.

8.6 Investigator Evaluation of Adverse Events

The Investigator will evaluate all adverse events with respect to seriousness (criteria listed in Section 8.1 above), severity (intensity or grade) and causality (relationship to study agent) according to the following guidelines listed below.

SEVERITY

Severity will be graded using the NCI-CTCAE, Version 4.0. The NCI-CTCAE may be downloaded from the Cancer Treatment Evaluation Program website (http://ctep.info.nih.gov/reporting/ctc.html). In the event that an AE does not have an NCI-CTCAE code, the following severity classifications will be used:

Mild	causing no limitation of usual activities
Moderate	causing some limitation of usual activities
Severe	causing inability to carry out usual activities
Life Threatening*	potentially life threatening or disabling

***Note** – a severity assessment of life threatening is not necessarily the same as life threatening as a "Serious" criterion. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.

CAUSALITY	
Definitely Related	reasonable temporal relationship to study agent administration follows a known response pattern (eg, drug is known to cause this AE) there is no alternative etiology
Probably Related	reasonable temporal relationship follows a suspected response pattern (eg, based on similar drugs) no evidence for a more likely alternative etiology
Possibly Related	reasonable temporal relationship little evidence for a more likely alternative etiology
Probably Not Related	does not have a reasonable temporal relationship, OR good evidence for a more likely alternative etiology
Not Related	does not have a temporal relationship, OR definitely due to alternative etiology

ICH guidelines (March, 1995) clarify "reasonable causal relationship" to mean "that there are facts [evidence] or arguments to suggest a causal relationship".

The causality assessment must be made by the investigator based on information available at the time that the SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

***Note -** If there is evidence that mapatumumab/placebo contributed to or exacerbated an event related to sorafenib; the event will be recorded as possibly, probably or definitely related to both sorafenib and mapatumumab.

8.7 Follow-up of Adverse Events

Adverse events that occur during the course of the study are followed until final outcome is known or until the end of the safety follow-up period (30 days following the final dose of any study agent). Adverse events that have not resolved by the end of the safety follow-up period are recorded as ongoing.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for a SAE (eg, the subject is lost to follow up), the reason a final outcome could not be obtained will be documented by the investigator.

8.8 Serious Adverse Events Assessed During Long-Term Follow-up

SAEs that occur after the safety follow-up period (30 days following the final dose of study agent) that are assessed by the investigator as possibly, probably, or definitely related to study agent must be reported to Human Genome Sciences on an SAE worksheet, as described in Section 8.2. Post-study SAEs will not be documented on the AE case report form.

8.9 Reporting Serious Adverse Events to the Institutional Review Board/Ethics Committee

All SAEs that are considered unexpected and related to the study agent will be reported by Human Genome Sciences or its designee as expedited (ie, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators. Each investigator must notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) responsible for reviewing the study at their site of all expedited reports. In addition, Human Genome Sciences or its designee will follow all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

9 Endpoints and Statistical Analysis

9.1 General Statistical Considerations

Analyses will be applied to a modified intention-to-treat population unless stated otherwise. This population is defined as the set of all randomized subjects who receive at least 1 dose of study treatment (mapatumumab/placebo and/or sorafenib) with subjects analyzed according to the groups they are randomized to, regardless of the treatment they subsequently receive. Additional analyses may be performed on the as-treated population, defined as the set of subjects receiving at least 1 dose of study medication analyzed according to the treatment that they actually receive.

Analyses will be performed using the SAS System™, WinNonlin Enterprise Edition™, StatXact™, and the R statistical package.

9.2 Sample Size Rationale

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

9.3 Efficacy

9.3.1 Primary Efficacy Endpoint

The primary endpoint is time to progression (TTP) defined as the time from randomization to radiologic disease progression based on blinded independent review of imaging scans.

9.3.2 Primary Efficacy Analysis

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with testing the hazard

ratio for time to progression at a 1-sided significance level of 0.10 with a Cox proportional hazards model controlling for the factors stratifying the randomization as covariates. AM01 21Dec10

9.3.3 Secondary Efficacy Endpoints

Secondary endpoints include progression-free survival, overall response, disease control, overall survival, time to response, and duration of response (for responders) as defined below:

- OS: time from randomization to death from any cause.
- PFS: time from randomization to disease progression or death from any cause.
- Objective response (CR+PR according to mRECIST for HCC).
- Disease control (CR+PR+SD according to mRECIST for HCC).
- Time to response: time from randomization to 1st PR or CR in responders only.
- Duration of response: time from 1st PR or CR to disease progression; in responders only.

All secondary endpoints will be based on blinded independent review of imaging scans.

9.3.4 Secondary Efficacy Analyses

Secondary analyses include estimates, using Kaplan Meier methods, of median PFS and median OS along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test).

9.4 Safety

9.4.1 Definition of Safety Variables

The safety parameters assessed are given by the following:

- Frequency, and severity of adverse events (AEs):
  - All AEs will be classified by System Organ Class and Preferred Term under the Medical Dictionary for Regulatory Activities (MedDRA) system of classification with a severity assigned according to the NCI-CTCAE (Version 4.0, 29 May 2009), or the rules specified in Section 8.6.
  - Laboratory parameters as presented in Appendix 7.
  - Laboratory toxicities will be graded based on the NCI-CTCAE (Version 4.0, 29 May 2009).
- Anti-mapatumumab antibody response.
- Vital signs.
- For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

9.4.2 Human Genome Sciences Safety Review Committee

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

9.4.3 Analysis of Safety Variables

The safety analysis will consist of a presentation of rates of AEs observed. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality observed will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall, as well as categorized by the MedDRA system of classification. AEs will be presented overall, by severity, by relation to mapatumumab/placebo, and by relation to sorafenib.

9.5 Pharmacokinetics

9.5.1 Definition of Pharmacokinetic Evaluation

Serum mapatumumab concentration data obtained from this study will be pooled with data obtained from other studies for use in a population PK analysis, which will be reported separately.

9.5.2 Analysis of Pharmacokinetics

The serum mapatumumab concentration will be determined by enzyme-linked immunosorbent assay. Serum mapatumumab concentration results for this study will be presented using appropriate graphic and tabular summaries.

9.6 Pharmacodynamics

Expression of biomarkers in tumor tissue and peripheral blood will be correlated with clinical outcomes and may be reported separately from the clinical study report.

10 Study Administration

10.1 Informed Consent

A copy of the proposed informed consent document(s) must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with ICH Good Clinical Practices, will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 Data Collection and Management

Data collected for each study subject are recorded electronically on case report forms provided or approved by the sponsor.

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documents related to the study, including any films, tracings, computer discs, or tapes. The investigator must promptly review the completed case report forms for each subject. As the person ultimately responsible for the accuracy of all data, the investigator must sign the Investigator's Statement in each subject's case report form.

The anonymity of participating subjects must be maintained. Subjects are identified by an assigned subject number on case report forms and other documents submitted to the sponsor. Documents that identify the subject beyond subject number are not submitted to the sponsor (ie, the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Sites enter subject data directly into the electronic data capture (EDC) system and the EDC system automatically generates queries resulting from computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. At study end, each site is provided with a compact disk containing the electronic case report forms for each of their subjects.

Upon completion of the study, or after reaching a pre-specified point in the study, Data Management locks the database and generates the SAS datasets necessary for data analysis and reporting.

10.6 Study Monitoring

The study sponsor, Human Genome Sciences, Inc., or designee, will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review the paper subject diaries and electronic case report forms and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make paper subject diaries and electronic case report forms and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators will promptly notify Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7 Drug Accountability

Upon receipt, the designated unblinded pharmacy personnel at the study site are responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this

inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by an unblinded Clinical Research Associate, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by Human Genome Sciences or its designee.

10.8 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated, or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9 Financial Disclosure

The investigator will provide Human Genome Sciences sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10 Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be pooled and analyzed. The investigator acknowledges that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and sponsor's representatives. Neither institution nor principal investigator shall independently publish or present the results of the study prior to the publication of the multi-center study publication. The investigator agrees that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until the entire sponsor's comments on the proposed publication or presentation have been considered and any information determined by sponsor to be confidential information has been removed.

If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11 Study or Study Site Termination

If Human Genome Sciences, the investigator, IRB/IEC, or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between Human Genome Sciences and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of Human Genome Sciences to suspend or discontinue testing, evaluation, or development of the product.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to Human Genome Sciences, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

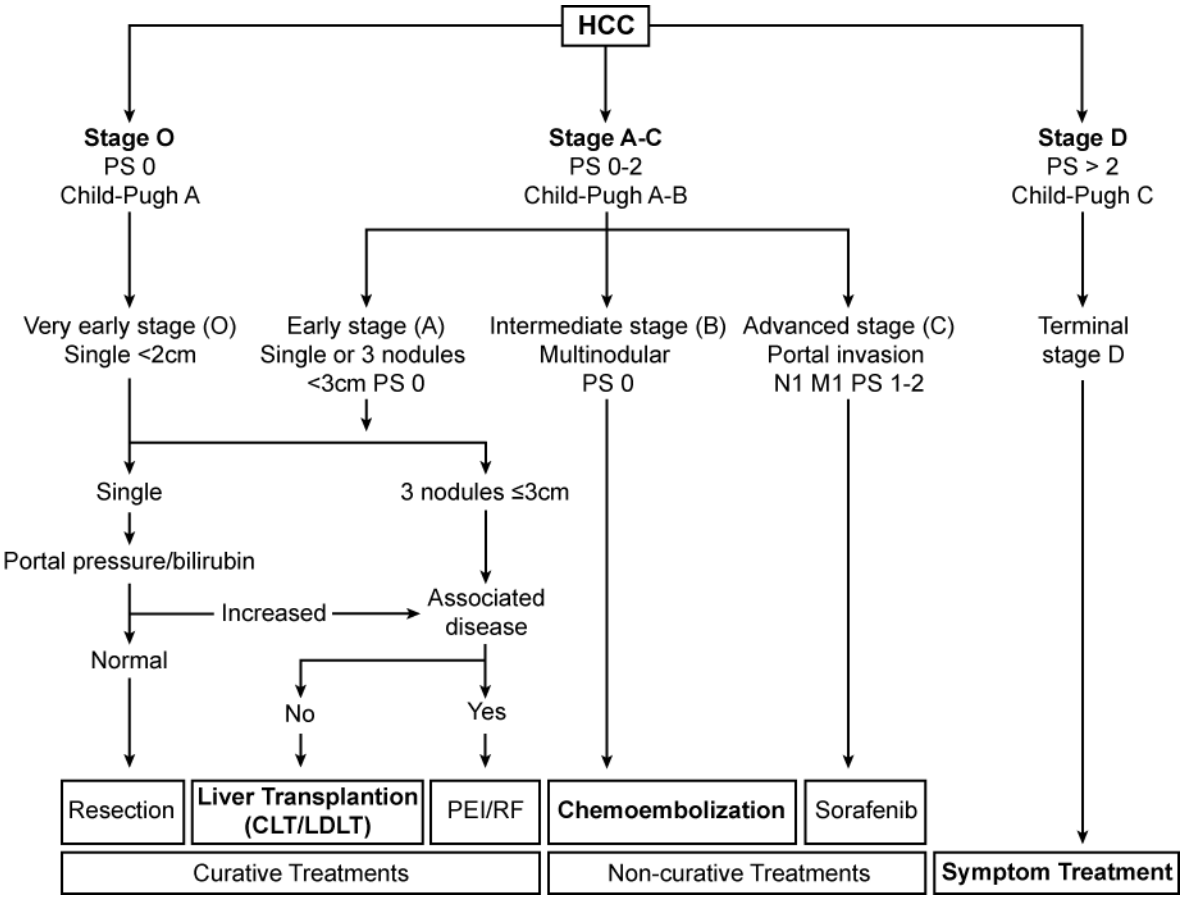
Appendix 1 Child-Pugh Classification

(Zimmerman H and Reichen J, 2000)

	No. of Points		
Factor	**1**	**2**	**3**
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (increased seconds)	1–3	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Minimal	Advanced

Grade	Score
A	5 – 6
B	7 – 9
C	10 – 15

Appendix 2 BCLC Staging and Treatment Strategy



Forner et al, 2010

Appendix 3 Eastern Cooperative Oncology Group (ECOG) Performance Status

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix 4 New York Heart Association Classification for Congestive Heart Failure

(The Criteria Committee of the New York Heart Association; Little, Brown & Co. 1994)

Class	New York Heart Association Classification for Congestive Heart Failure
1	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
2	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
3	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
4	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 5 Modified Response Evaluation Criteria in Hepatocellular Carcinoma (mRECIST for HCC)

AM01
21Dec10

(Adapted from Lencioni and Llovet, 2010 for use in this study)

Measurable disease: The presence of at least 1 target lesion, by contrast enhanced computerized tomography (CT) with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI).

Target lesion: Meets all the following criteria:

- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well-delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

A maximum of 5 target lesions may be selected.

Nontarget lesion: Other lesions, including small lesions (≤ 2 cm in the axial plane). Note that malignant portal vein thrombosis should be considered a nonmeasurable, and therefore nontarget, lesion. Lymph nodes at the portal hepatic can be considered as malignant if the lymph node short axis is at least 2 cm. Selection of effusion, including ascities, as a nontarget lesion is prohibited. Similarly, bone lesions or any other lesion outside the CT or MRI of the abdomen or obtained by other modality, may not be selected as nontarget lesions.

Measurement of lesions: Imaging studies will be by contrast enhanced CT, with use of multislice scanners, or contrast enhanced MRI. The same method must be used at baseline and during follow up. Note that the longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured. The measurement of the viable tumor diameter should not include any major intervening areas of necrosis. (Please see the HGS1012-C1103 Radiographic Data Collection Manual).

Evaluation of target lesions:

Complete Response (CR): Disappearance of 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.

Stable Disease (SD): Any cases that do not qualify for CR, PR or PD.

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.

Evaluation of nontarget lesions:

Complete Response (CR): Disappearance of intratumoral arterial enhancement.

Incomplete Response/Stable Disease (IR/SD): Persistence of intratumoral arterial enhancement in 1 or more nontarget lesions.

Progressive Disease (PD): Unequivocal progression of existing nontarget lesions.

Evaluation of new lesions: A newly detected hepatic nodule will be classified as evidence of progression when its longest diameter is ≥ 1 cm and the nodule shows the hypervascularization in the arterial phase with washout in the portal venous or late venous phase.

Liver lesions ≥ 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least a 1 cm-interval growth in subsequent scans.

An individual radiologic event will be adjudicated in retrospect as progression at the time it was 1st detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

Images by another modality may be obtained, as clinically indicated post-baseline. Sites may conclude that post-baseline images based on another modality that indicate disease are evidence of radiologic progression if: (1) there was no imaging done at baseline; (2) if there was imaging done at baseline showing no disease present at that time; or (3) if there was imagine done at baseline indicating that the on-treatment assessment represents unequivocal worsening. In these cases the disease will be reported as ‘new lesions’.

All images obtained on study will be provided the BICR for the independent efficacy read, or for confirmation of progression if required or requested.

Evaluation of Overall Response: The overall response is determined at each assessment and is a result of the combined assessment of target lesions, nontarget lesions and new lesions.

Overall Response Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response*
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*AFP is not included in assessment of overall response.

Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression. To be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

Appendix 6 Exploratory Biomarker Sub-study

1. Background

Mapatumumab is a targeted therapy. Presently, the relationship between expression of the target, TRAIL-R1, and the anti-tumor activity of the antibody is incompletely understood. Studies conducted with cell lines derived from human tumors have suggested that the relationship between receptor expression and mapatumumab-induced tumor cell death may be complex. However, studies of human tumor cells in vitro and transplanted into animals may not accurately reflect the relationship between receptor expression and response to mapatumumab that may be observed in patients with cancer. One feature of this biomarker study is to compare TRAIL-R1 expression from available biopsy material. This could allow for a greater understanding of patterns of TRAIL-R1 expression in advanced hepatocellular carcinoma.

It is also likely that other factors involved in TRAIL-R1 signaling could critically affect response to mapatumumab treatment. A 2nd goal of this biomarker study is to evaluate biomarkers that may be potential indicators or modifiers of response to mapatumumab. To identify factors that may indicate that a patient is responding to treatment, serum-based markers will be compared before and after treatment. To explore factors that are associated with the outcome of therapy and could be used prior to treatment to predict which patients will respond, somatic (inherited) differences that modify a patient's drug response will be examined.

The information generated from this sub-study will be used solely for research purposes to improve future treatment with mapatumumab. It will not be used to change diagnoses or alter therapy. Participation in this sub-study is optional.

2. Study Objectives and Design

2.1. Indicators of Response

2.1.1. Serum-Based Markers of Response

Induction of cell death in tumor cells can elicit the release of certain biomarkers into the serum. These markers can be quantified to evaluate treatment effect. To assess release of biomarkers associated with cell death, serum-based assays will be conducted, including, but not limited to, assessments of M30, a fragment of cytokeratin 18 that is generated by induction of programmed cell death in epithelial tissues. Other examples of markers of tumor cell death that will be examined include the cytokines TRAIL, TNFα, soluble Fas ligand, interferonα, interferonγ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, and interleukin-12. The levels of these factors will be examined before and after treatment to see if they correlate with response to treatment.

Serum will be isolated and the level of cytokines and other markers like M30 will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2. Modifiers of Response

2.2.1. Neoplastic Modifiers of Response

Historically collected tumor biopsy material, if available, will be collected from subjects during Cycle 1. Samples will also be obtained from subjects who undergo a biopsy during the treatment period. Samples of resected tumor tissue that has been formalin-fixed and embedded in paraffin is acceptable; either tissue blocks or slides may be provided. Frozen samples of tumor tissue may also be provided. Biopsy material collected from fine needle aspirates may be provided; either cell pellets or cytological slides are acceptable.

Levels of TRAIL receptors will be assessed in biopsy material using immunohistochemical techniques if samples are available as formalin-fixed/paraffin-embedded tissue blocks or slides. Historically obtained biopsy material or biopsy material obtained during the treatment period that is in the form of fresh frozen tissue or cell pellet samples will be utilized to isolate RNA for analysis of TRAIL receptor gene expression.

Similar techniques will be used to evaluate other potential biomarkers and factors that may influence mapatumumab response. These may include but are not limited to caspase 8, AKT and Mcl-1.

See the laboratory manual for collection, processing and handling of these samples.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2.2. Somatic Modifiers of Response

Inherited differences in the genes that code for drug targets or components of signaling pathways related to the target can dramatically influence the effect of pharmacotherapy. Variations in genes that could potentially impact mapatumumab's activity, including polymorphic changes in the Fc gamma receptor and interleukin-6 promoter and K-Ras gene mutations, will be examined to see if they correlate with response to treatment.

DNA will be isolated from the blood and polymorphisms and mutations in specific response-related genes will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

3. Statistical Analysis

Associations will be assessed between candidate biomarkers and treatment outcomes captured in the clinical database. Statistical tests to be performed may include Pearson chi-square testing, Fisher's exact test, ANOVA and ANCOVA. Results of the biomarker sub-study may be reported independent of the results of HGS1012-C1103.

4. Subject Selection and Withdrawal

Subjects enrolled in the HGS1012-C1103 research study are given the option to participate in the Biomarkers Sub-study. A subject may withdraw from the sub-study at any time by contacting their Study Investigator, who will contact the sponsor. The sponsor will destroy any remaining sample materials and will send a letter back to the Investigator confirming sample destruction. Any data or analysis generated from the sample prior to the request for destruction will not be destroyed. However, no new information will be generated from the sample and no new analysis will be performed.

5. Confidentiality

Information about sub-study subjects will be kept confidential and managed according to the requirements of local privacy regulations. Information obtained from samples will not be returned to subjects and will not be placed in the subject's medical record.

6. Ethical Considerations

All subjects enrolled in the HGS1012-C1103 research study who agree to participate in the Biomarker Sub-study will be asked to sign a separate Biomarker Informed Consent. Choosing to not participate in this sub-study will not affect the subject's ability to participate in the main clinical trial. The Biomarker Informed Consent will be submitted along with the main research study informed consent for review by the Institutional Review Board/Ethical Committee.

7. Publication of Biomarker Results

Any significant findings, based upon the analysis of aggregate data collected from this sub-study may be published by Human Genome Sciences. Personal identifiers will not be used in any publication resulting from this sub-study.

Appendix 7 Laboratory Tests

CBC with Differential	Chemistry
Total white blood cell (WBC) count differential:	Electrolytes:
Neutrophils	Sodium
Bands	Potassium
Lymphocytes	Magnesium
Monocytes	Chloride
Eosinophils	Carbon dioxide/bicarbonate*
Basophils	Calcium
Hemoglobin	Enzymes:
Hematocrit	SGOT (AST)
Red blood cell count	SGPT (ALT)
Platelet count	Alkaline phosphatase
Absolute Neutrophil Count	Amylase
Total white blood cell count	Lipase
	Gamma glutamyl transferase (GGT)
Prothrombin time (PT)	
Partial thromboplastin time (PTT)	Other:
International normalized ratio (INR)	Creatinine
	Blood Urea Nitrogen
Other:	Total bilirubin
Serum and Urine pregnancy	Total protein
Hepatitis B surface antigen	Albumin
Hepatitis C antibody	
B and T lymphocytes	
HCV RNA	
HBV DNA	
HBsAb	

*To be collected if included in routine automated serum chemistry panel.

Refer to Section 6 (Study Procedures) for laboratory test collection schedule.

Appendix 8 Treatment of Allergic/Hypersensitivity Reactions

In the event of allergic/hypersensitivity reactions to mapatumumab/placebo, investigators will institute treatment measures according to best medical and nursing practice. The grading is based upon the NCI-CTCAE Version 4.0.0.

The following treatment guidelines will be employed:

- If chills and fever occur, the infusion will be interrupted. Subjects may be treated symptomatically and the infusion will be restarted at 50% of the original rate.

Grade 1 allergic/hypersensitivity reaction (transient flushing or rash, drug fever < 38°C):

- Decrease infusion rate by 50% and monitor for worsening condition. If the reaction worsens, stop the infusion.

Grade 2 allergic/hypersensitivity reaction (rash, flushing, urticaria, dyspnea, drug fever < 38°C):

- Stop the infusion.
- Administer bronchodilators, oxygen, acetaminophen, etc as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop the infusion.

Re-treatment following Grade 1 or Grade 2 allergic/hypersensitivity reactions:

- Once the infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions.
- If the subject has a 2nd reaction at the lower infusion rate, the infusion will be stopped and the subject will receive no further treatment with mapatumumab/placebo.
- If the subject experiences a Grade 3 or Grade 4 allergic/hypersensitivity reaction at any time, the subject will receive no further treatment with mapatumumab/placebo.
- If there are questions concerning whether an observed reaction is an allergic/hypersensitivity of Grades 1-4, the medical monitor will be contacted immediately to assist with grading the reaction.

Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- A Grade 3 hypersensitivity reaction consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or asymptomatic hypotension not requiring treatment.
- A Grade 4 hypersensitivity reaction (ie, anaphylaxis) is a life-threatening event characterized by the same symptoms as in a Grade 3 reaction but also complicated by symptomatic hypotension or oxygen saturation of 90% or less.

Treatment of Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- Stop the infusion immediately and disconnect infusion tubing from the subject.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Contact Human Genome Sciences to report an SAE and fax SAE worksheet.

Protocol Amendment 02, 23 February 2011
Protocol Number: HGS1012-C1103-02

Protocol Title: A Randomized, Multi-Center, Blinded, Placebo-Controlled Study of Mapatumumab ([HGS1012], A Fully-Human Monoclonal Antibody To TRAIL-R1) In Combination with Sorafenib As A First Line Therapy In Subjects With Advanced Hepatocellular Carcinoma

Summary of Modifications and Rationale

1. Subjects with a history of organ allograft will be excluded from participating as they were also not eligible in the registration trial for sorafenib.
2. The prohibited medications section has been clarified to include any locoregional therapy including embolization, RFA or percutaneous ethanol injection.

Associated Protocol Modifications:

Title Page

Formerly:

Protocol Amendment 01 Date 21 December 2010

Modified to:

Protocol Amendment 02 Date 23 February 2011

Study Synopsis Exclusion Criteria
Section 4.2 Exclusion Criteria

Addition:

3. History of organ allograft.

Section 5.3.2 Prohibited Medications

Formerly:

Subjects will not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies) or immunotherapy to treat hepatocellular carcinoma during the treatment period. Alternative anticancer therapies may be administered after radiologic disease progression has been documented, but will be avoided if possible during the 30 day safety follow up period after the last dose of study agent (mapatumumab/placebo and/or sorafenib) whichever is last. These medications are allowed in the long-term follow-up period after the 30 day safety follow-up period and documentation of radiologic disease progression.

Modified to:

Subjects will not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies), immunotherapy or any locoregional therapy (such as embolization, RFA or percutaneous ethanol injection) to treat hepatocellular carcinoma during the treatment period. Alternative anticancer therapies may be administered after radiologic disease progression has been documented, but will be avoided if possible during the 30 day safety follow up period after the last dose of study agent (mapatumumab/placebo and/or sorafenib) whichever is last. These medications are allowed in the long-term follow-up period after the 30 day safety follow-up period and documentation of radiologic disease progression.

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HUMAN GENOME SCIENCES

CLINICAL PROTOCOL HGS1012-C1103
Protocol Amendment: 01
Date: 21 December 2010

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21Dec10

TITLE OF STUDY:

A RANDOMIZED, MULTI-CENTER, BLINDED, PLACEBO-CONTROLLED STUDY OF MAPATUMUMAB ([HGS1012], A FULLY-HUMAN MONOCLONAL ANTIBODY TO TRAIL-R1) IN COMBINATION WITH SORAFENIB AS A FIRST-LINE THERAPY IN SUBJECTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

STUDY SPONSOR: Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850

EudraCT Number: 2010-020798-17

Confidentiality

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator:

Signature *Date*

Name (please type or print)

Institution

Address

Study Synopsis

Study Number: HGS1012-C1103

Title of the Study: A Randomized, Multi-Center, Blinded, Placebo-Controlled Study of Mapatumumab ([HGS1012], a Fully-Human Monoclonal Antibody to TRAIL-R1) in Combination with Sorafenib as a First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma

Clinical Development Phase: 2

Objectives:

Primary:

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

Secondary:

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

Diagnosis & Inclusion Criteria:

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
   - Located in the liver.
   - Can be accurately measured in at least 1 dimension.
   - Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
   - Suitable for repeat measurement.
   - Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be confirmed by the blinded, independent, central read (BICR) prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x 10^9 /L or ≥ 1500 /mm^3.
   - Platelet count ≥ 50 x 10^9 /L or ≥ 50,000 /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal.
   - Serum albumin ≥ 2.8 g/dL or ≥ 28 g/L. AM01 21Dec10
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

Exclusion Criteria:

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. Previously received mapatumumab and/or sorafenib.
4. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.
5. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
6. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
7. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
8. Hepatic encephalopathy, per the investigator's evaluation.

9. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
10. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
11. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
12. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
13. Known human immunodeficiency virus infection.
14. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
15. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
16. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
17. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
18. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
19. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
20. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
21. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
22. Hepatitis B virus DNA levels > 2,000 IU/mL.

Study Design and Schedule:

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma. In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive 30 mg/kg mapatumumab or placebo.

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Approximately 100 advanced HCC subjects will be randomized/enrolled.

Study Treatment:

Mapatumumab will be supplied in open label vials and third party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent but independent of all other study activities. All other study personnel, the subject, the Sponsor will remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle.

Arm B: Sorafenib 400 mg orally twice daily continuously + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle.

Subjects will continue to receive study treatment(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiographic progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiographic progression. All subjects will have an end of treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks, starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented) and then every 3 months thereafter for survival until at least 90% of the subjects have met the survival endpoint.

Disease Assessments:

Radiologic disease assessments along with assessment of alpha fetoprotein will be performed at the end of every two 21-day cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The disease assessment will be performed and documented no earlier than 5 days before the start of the next cycle. Clinical responses will be evaluated according to mRECIST for HCC (see Section 6.7 and Appendix 5). The same assessment method will be used throughout the study for each subject. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent, central reader (BICR) for confirmation of disease progression. Partial response (PR) and complete response (CR) will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR). All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

Safety Assessments:

The safety of sorafenib and mapatumumab will be assessed by evaluation of the type, frequency, and severity of adverse events (ie, according to the NCI-CTCAE Version 4.0 grading) and changes in clinical laboratory tests (hematology and clinical chemistry) and immunogenicity over time. In the event that an adverse event does not have an NCI-CTCAE Version 4.0 grading, the severity grades in Section 8.6 will be used. Adverse events (including serious adverse events) will be captured from the start of study agent administration (sorafenib and/or mapatumumab/placebo) through at least 30 days following the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. Laboratory assessments will be performed at screening, and during each study visit outlined in the study calendar found in Section 6.3.

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

Immunogenicity:

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

Dose Modification/Delay:

Dose modifications will not be allowed for mapatumumab/placebo. Dose modifications of sorafenib for toxicity will be made according to the guidelines provided in the treatment section (Section 5.2.3) of the protocol.

Details regarding pre-treatment and management of hypersensitivity reactions related to mapatumumab are provided in Section 5.1.5 and Appendix 8.

Pharmacokinetics:

Multiple blood specimens will be obtained from subjects for serum mapatumumab concentration determinations as outlined in Table 6-1.

Pharmacodynamics:

Subjects will be given the option to participate in a biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and several blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The biomarker sub-study is detailed in Appendix 6.

Exploratory Assessments:

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

Study Endpoints:

The following will be evaluated (these endpoints and the respective analyses are defined in Section 9):

Primary:

- Time to progression (TTP).

Secondary:

- Overall survival.
- Progression-free survival.
- Objective response (complete response [CR] + partial response [PR]).
- Disease control (CR + PR + stable disease [SD]).
- Response duration and time to response in responders.
- Frequency and severity of treatment-emergent adverse events.
- Laboratory parameters.
- Serum mapatumumab concentrations for use in a population pharmacokinetic analysis.

Statistical Methods:

Sample Size:

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

Statistical Analysis:

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with testing the hazard ratio for time to progression at a 1-sided significance level of 0.10 with a Cox

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proportional hazards model controlling for the factors stratifying the randomization as covariates. Secondary analyses include estimates, using Kaplan Meier methods, of median progression-free survival (PFS) and median overall survival (OS) along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test). For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

Study Calendar:

The study calendar is located in Section 6.3 of the protocol.

Table of Contents

List of Tables

List of Abbreviations

AE	adverse event
AFP	α - fetoprotein
ALT	alanine transaminase
AST	aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central read
CR	complete response
CT	computerized tomography
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
Fc	heavy chain constant region or fragment of antibody
GGT	gamma-glutamyl transpeptidase
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGS	Human Genome Sciences
HGSRC	Human Genome Sciences Review Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IR	incomplete response
IRB	Institutional Review Board
kg	kilogram
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mRECIST	modified RECIST assessment for HCC
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ng	nanogram
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease
PK	pharmacokinetics
PPT	partial thromboplastin time
PR	partial response
PS	performance status
PT	prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TRAIL-R1	TRAIL receptor 1
TRAIL-R2	TRAIL receptor 2
TTP	time to progression

1 Background

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma is the 5th most common cancer worldwide accounting for 2% of all malignancies. It is the 3rd leading cause of cancer-related death globally with 1 million new cases a year (WHO, 2007; IACR, 2002; Ferlay et al, 2004; Lopez et al, 2006).

Hepatocellular carcinoma is more prevalent in males with a male:female ratio as high as 8:1. Depending on the endemic risk factors, hepatocellular carcinoma is diagnosed during the 4th through 6th decades of life. The reported incidence of hepatocellular carcinoma is increasing because of a better ability to diagnose the disease and because of the long-term consequences of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection (Reis et al, 2006). Worldwide the most common cause of hepatocellular carcinoma is chronic HBV infection (El-Serag et al, 2003). Endemic areas thus include China, South Asia and South Africa where the incidence of hepatocellular carcinoma can be as high as 120 cases per 100,000. In the United States, where HCV and alcohol are the main risk factors, the age-adjusted incidence rates have increased from 1.4 cases per 100,000 in 1980 to a current incidence of 4 cases per 100,000. This equates to about 8500-11,000 new cases diagnosed each year (IACR, 2002; Ferlay et al, 2004; Pawlik et al, 2004; Edwards, et al, 2005; Jemal et al, 2007; Bosch et al, 2004).

1.2 Treatment Options for Patients with Hepatocellular Carcinoma

Surgery, including transplantation, is the only curative modality for hepatocellular carcinoma (Venook, 1994; Cha et al, 2003). The 5-year survival rate for patients with unresectable hepatocellular carcinoma is 11% in the US (ACS, 2007), < 8% in Europe (Capocaccia et al, 2007), and < 10% in Asia (Teo and Fock, 2001). Symptomatic hepatocellular carcinoma has a very poor prognosis with a median survival of 1–8 months (Former et al, 2006; Llovet et al, 1999a, b).

Sorafenib, a multikinase inhibitor, is the 1st systemic therapy to significantly impact survival in patients with advanced hepatocellular carcinoma, as demonstrated in an international, multicenter Phase 3, placebo-controlled trial (Llovet et al, 2007). Sorafenib was approved in the United States and European Union for the 1st-line treatment of advanced hepatocellular carcinoma in late 2007 and the 2008 National Comprehensive Cancer Network guidelines have been updated with the addition of sorafenib as a treatment option for hepatocellular carcinoma patients. The updated Barcelona Clinic Liver Cancer (BCLC) guidelines recommend sorafenib for hepatocellular carcinoma patients with BCLC Advanced Stage (C) (Forner et al, 2010).

1.3 The Role of the TRAIL Pathway in HCC

1.3.1 TRAIL and TRAIL Receptors

TRAIL is a member of the tumor necrosis factor (TNF) ligand superfamily, with homology to Fas/Apo1 ligand (Pitti et al, 1996; Wiley et al, 1995). TRAIL induces programmed cell death primarily in tumor cells through activation of TRAIL death receptors, TRAIL-R1 (death receptor 4) or TRAIL-R2 (death receptor 5) (Ashkenazi et al, 1999; Evdokiou et al,

2002; Kothny-Wilkes et al, 1998; Lawrence et al, 2001; Pitti et al, 1996; Walczak et al, 1999; Wiley et al, 1995).

TRAIL-R1, the target of mapatumumab, is detectable on tumor cells derived from colon, lung, liver, gastric, pancreas, uterus and esophagus and in tissue sections from various tumors of the colon, lung, pancreas, liver and stomach without significant expression in parallel normal tissues (Halpern et al, 2004; Roach et al, 2004).

1.3.2 TRAIL and HBV/HCV Infection

Acutely infected tissues, including the liver, utilize the TRAIL pathway to eliminate virally and bacterially infected cells (Herr et al, 2007). In viral hepatitis, TRAIL and 1 of its receptors, TRAIL-R2, are upregulated and contribute to the elimination of infected hepatocytes associated with viral hepatitis (Bantel and Schulze-Osthoff, 2003; Lin et al, 2002; Matsuda et al, 2005). In addition to HBV and HCV infection, steatosis, exposure to bile acids and chronic alcohol exposure induce increased expression of TRAIL and TRAIL-R2, but not TRAIL-R1, in human hepatocytes (Dunn et al, 2007; Mundt et al, 2005). Cell surface expression of TRAIL-R2, but not TRAIL-R1, was altered and responsible for sensitization to TRAIL in hepatocytes exposed to bile acids (Higuchi et al, 2001; Malhi et al, 2007). These findings have been reproduced in preclinical models. Non-virally infected hepatocytes are refractory to TRAIL and TRAIL-R agonists but exposure of HCV-infected hepatocytes to TRAIL leads to a significant level of apoptosis (Volkmann et al, 2007). Inhibition of the TRAIL pathway may protect infected cells from apoptosis and allow for chronic infection (Mundt et al, 2003). Recent non-clinical observations demonstrated that natural killer cells expressing the ligand TRAIL, are enriched in the livers of patients with chronic HBV infection, and TRAIL is overexpressed in the livers of patients with HCV-associated steatosis (Mundt et al, 2005).

In summary, preclinical data suggest that mapatumumab may promote apoptosis of cancer cells, including hepatocellular carcinoma cells. Whether viral infection, including HBV or HCV infection, will attenuate or modulate the effects of mapatumumab on hepatocytes is not yet known, but experience to date in a Phase 1b trial of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody indicates that the safety experience is consistent with underlying disease and known sorafenib toxicities (see Section 1.2).

1.4 Mapatumumab

1.4.1 Mapatumumab Pharmacology

Mapatumumab is a fully human, agonist monoclonal antibody that activates the cell death pathway in tumor cells by specifically binding to TRAIL-R1 with high affinity. Mapatumumab efficiently induces apoptosis in human cancer cell lines expressing the TRAIL-R1 protein on the cell surface. Nonclinical studies have demonstrated that mapatumumab can induce cytotoxicity in multiple tumor cell lines representing both solid and hematological malignancies, including cancers of the biliary tract, colon, lung, breast, pancreas, esophagus, ovary, kidney, uterus, as well as lymphoma and various leukemias. Mapatumumab has also demonstrated anti-tumor activity as a single agent, preventing

tumor growth and in some cases causing regression of tumors in xenograft tumor models of multiple human malignancies, including lung, colon, kidney, and uterus (Camidge, 2007; Georgakis et al, 2005; Jin et al, 2007; Humphreys, 2004; Marini et al, 2006; Menoret et al, 2006; Pukac et al, 2005).

The relationship between receptor expression and response to therapy with mapatumumab remains unclear. In vitro studies of cell lines have shown that TRAIL-R1 expression level is not a consistent predictor of response to mapatumumab. Although both TRAIL-R1 expression and apoptosis in response to mapatumumab are increased in many tumor cell lines as compared with normal diploid cells, there are examples of mapatumumab cytotoxicity on cell lines with very low levels of detectable receptor, and conversely, mapatumumab resistant cell lines that have relatively high levels of TRAIL-R1 cell surface expression.

Tumor cell cytotoxic activity can be enhanced when mapatumumab is administered in combination with chemotherapeutics or other anti-neoplastic agents. Enhanced apoptotic signaling, in vitro cell killing and in vivo anti-tumor activity have been observed when mapatumumab has been combined with various types of therapeutic agents and treatments including microtubule poisons, anti metabolites, topoisomerase inhibitors, proteosome inhibitors, platinum agents and radiation. Both the level and spectrum of activity of mapatumumab is enhanced in in vitro cytotoxicity and in vivo xenograft studies in combination with various chemotherapeutic and anti-neoplastic agents, including a xenograft model of hepatocellular carcinoma in combination with cisplatin and gemcitabine (Camidge, 2007; Pukac et al, 2005; Georgakis et al, 2005; Humphreys, 2004; Jin et al, 2007; Human Genome Sciences data on file).

Please refer to the mapatumumab Investigator's Brochure for detailed information regarding the nonclinical pharmacology, toxicology, and PK of mapatumumab.

1.4.2 Non-Clinical Mapatumumab Safety Studies

To assess the nonclinical safety of mapatumumab, a 6-month toxicity study, with a 4-month recovery period, was conducted in chimpanzees. Mapatumumab was administered intravenously at up to 40 mg/kg every 10 days. No mapatumumab-specific toxicity was identified and no anti-mapatumumab antibodies were detected.

To assess its off-target effects, mapatumumab was administered intravenously weekly to cynomolgus monkeys, whose TRAIL R1 homolog does not bind mapatumumab. Mapatumumab was well tolerated at doses of up to 50 mg/kg and was not highly immunogenic: of the 40 monkeys treated, 1 developed anti-mapatumumab antibodies. The positive response was observed in an animal in the high dose (50 mg/kg) group.

In vitro, mapatumumab was found to decrease viability of normal human hepatocytes, although the observed effect was less than that observed with TRAIL. This effect was variable across donors and did not amplify with increasing concentrations of mapatumumab. It should be noted that in clinical studies, plasma mapatumumab concentrations have been achieved that are > 1100–fold greater than the minimum exposure resulting in reduced in vitro hepatocyte viability. Despite this, the clinical results do not reveal evidence of hepatotoxicity in those

studies. Hence it appears that the in vitro hepatocyte viability assay is not predictive of mapatumumab effects in vivo.

1.4.3 Clinical Experience with Mapatumumab

Over 400 subjects have received mapatumumab in clinical trials to date. Preliminary clinical data are available from 218 subjects who received mapatumumab as a single agent at doses ranging from 0.01 to 20 mg/kg across 6 clinical trials.

Based on available data, mapatumumab appears to be well tolerated and no significant safety issues have been observed. Adverse events have generally been mild to moderate in severity, manageable, and do not appear related to dose. The most frequently reported treatment-related adverse events occurring in > 10% of subjects were fatigue, hypotension, nausea and pyrexia. Severe events have been uncommon and generally judged not related to mapatumumab. Severe events judged at least possibly related to mapatumumab have been observed and a complete list can be found in the mapatumumab Investigator's Brochure. Grade 3 or Grade 4 hematologic, renal, or hepatic laboratory abnormalities also have been relatively uncommon with no significant trend or dose-response evident. Lymphopenia was the most commonly observed laboratory abnormality, but tended to be intermittent and reversible and was not associated with infectious events.

In subjects with solid tumors, stable disease has been the best response observed with mapatumumab as a single-agent. However, 2 complete responses (CRs) and 1 partial response (PR) were observed in subjects with follicular lymphoma.

In addition, preliminary clinical data are available from 234 subjects who received mapatumumab at doses ranging from 1 to 30 mg/kg every 21 days in combination with chemotherapy in 5 clinical trials (carboplatin/paclitaxel [N = 100], gemcitabine/cisplatin [N = 49], bortezomib [n = 69], or sorafenib [n = 16]. Mapatumumab has been generally well tolerated; adverse events and laboratory abnormalities have been consistent with those expected with underlying disease or chemotherapy. A listing of severe events considered at least possibly related to mapatumumab can be found in the mapatumumab Investigator's Brochure. The most commonly occurring laboratory abnormalities have been hematologic (ie, anemia, neutropenia, thrombocytopenia, and leukopenia), as expected with chemotherapy. Grade 3/4 laboratory abnormalities have been relatively uncommon. Higher frequencies of Grade 3/4 neutropenia, leukopenia, lymphopenia, and thrombocytopenia have been observed. Data from randomized Phase 2 studies in combination with chemotherapy suggest that mapatumumab may increase rates of lymphopenia.

One subject receiving mapatumumab in combination with carboplatin/paclitaxel has achieved a CR. Twenty-two subjects receiving mapatumumab in combination with paclitaxel/carboplatin and 12 subjects receiving mapatumumab in combination with gemcitabine/cisplatin have achieved PRs. Three subjects receiving mapatumumab in combination with bortezomib achieved CRs; 25 subjects receiving mapatumumab in combination with bortezomib achieved a PR.

1.5 Rationale for the Evaluation of Mapatumumab in Combination with Sorafenib in Hepatocellular Carcinoma

Sorafenib is the standard of care for treatment of patients with advanced hepatocellular carcinoma. Sorafenib is a multikinase inhibitor that targets the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway, blocks tumor angiogenesis and induces apoptosis (Panka et al, 2006; Rahmani et al, 205; Yu et al, 2005; Wilhelm et al, 2004). Sorafenib was approved by the European Medicines Agency and the Food and Drug Administration in 2007 for treatment of patients with hepatocellular carcinoma based on the demonstration of improved overall survival in the 602 patient randomized, placebo-controlled, Phase 3 "Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol" (SHARP) trial. Approximately half the 602 patients had either hepatitis C virus or hepatitis B virus as underlying etiology and 26% had alcohol-related cirrhosis. The median overall survival was 10.7 months for patients in the sorafenib arm compared with 7.0 months for patients in the placebo arm (hazard ratio in the sorafenib group, 0.69 95% confidence interval, 0.55 to 0.87; $p < 0.001$). The median time to radiologic progression was 5.5 months in the sorafenib arm, compared with 2.8 months in the placebo arm ($p < 0.0001$) (Llovet et al, 2008). Seven patients in the sorafenib group (2%) and 2 patients in the placebo group (1%) had a PR; no patients had a CR.

A 2nd randomized, placebo-controlled Phase 3 trial was conducted in the Asia-Pacific region (Cheng et al, 2009). The 226 patients randomly assigned to sorafenib or placebo in this trial appeared to have more advanced disease than those in the SHARP trial, with a higher frequency of extrahepatic spread, poorer ECOG PS, and higher levels of AFP, but still showed a benefit from treatment with sorafenib. The majority (73%) had hepatitis B virus as an underlying etiology. The median overall survival was 6.5 months for patients in the sorafenib arm, compared with 4.2 months in the placebo group (hazard ratio, 0.68, 95% confidence interval, 0.50-0.93; $p = 0.014$). The median time to progression was 2.8 months in the sorafenib group, compared with 1.4 months in the placebo group (hazard ratio, 0.57, 95% confidence interval 0.42-0.79; $p = 0.0005$).

The mechanisms of sorafenib and mapatumumab action suggest that these agents could interact synergistically. Sorafenib sensitizes human cancer cell lines, including cell lines derived from hepatocellular carcinoma, to apoptotic stimuli by reducing expression of apoptotic regulatory proteins; Mcl-1, Bcl-xL, and FLIP (Kim et al,2008; Koehler et al, 2009; Rosato et al, 2007; Liu et al, 2006; Rahmani et al, 2005; Yu et al, 2005). Mcl-1, Bcl-xL and FLIP have also been shown to mediate sensitivity of a wide range of tumor cell lines to TRAIL receptor agonists (Meng et al, 2007; Rosato et al, 2007; Llobet et al 2010; Blechacz et al, 2009; Katz et al, 2009; Huang and Sincrope, 2010; and Menoret et al, 2006). Recent studies demonstrated the combination of sorafenib with TRAIL or TRAIL receptor antibodies has significant activity in hepatocellular carcinoma cell lines (Koehler et al, 2009) and colon tumor xenografts (Ricci et al, 2007) that were resistant to TRAIL and an antibody against TRAIL-R2.

Mapatumumab activity has been evaluated preclinically in hepatocellular carcinoma cell lines by in vitro cytotoxicity assays both as a single agent and in combination with doxorubicin, cisplatin, gemcitabine or sorafenib. Single agent mapatumumab activity was observed in 4 of

10 hepatocellular carcinoma cell lines. Increased in vitro cytotoxicity, including examples of synergy, were observed in 8 of 10 cell lines when mapatumumab was combined with doxorubicin or cisplatin or the combination of cisplatin and gemcitabine (Humphreys et al, 2008). Two of these hepatocellular carcinoma cell lines were evaluated for in vitro cytotoxicity of mapatumumab in combination with sorafenib. One displayed an increase in cytotoxicity from 30% to 60% when treated with a combination of sorafenib and mapatumumab. Importantly, treatment of a primary human hepatocyte cell line did not induce any apoptosis at doses of mapatumumab that were cytotoxic to hepatocellular carcinoma cell lines (PPD and PPD [personal communication], 2008; Abdulghani et al, 2008). Therefore, collectively, the expression of TRAIL-R1 in hepatocellular carcinoma and preclinical activity observed with combinations of mapatumumab with chemotherapy or sorafenib supports the rationale that this combination may be able to effectively target hepatocellular carcinoma.

1.6 Rationale for Dose Selection

As of June 2010, mapatumumab has been administered with chemotherapy (ie, carboplatin/paclitaxel, gemcitabine/cisplatin, bortezomib, or sorafenib) to 234 subjects, including 61 subjects who received 20 mg/kg and 50 subjects who received 30 mg/kg mapatumumab. Based on available data, mapatumumab in combination with chemotherapy is generally well tolerated at dose levels up to and including 30 mg/kg, and no significant safety issues have been observed in the course of the clinical trials even at the higher doses.

Preliminary PK data are available for subjects who received 1, 10, 20 or 30 mg/kg mapatumumab in combination with gemcitabine and cisplatin (n = 49), 10 or 30 mg/kg mapatumumab in combination with paclitaxel and carboplatin (n = 73), and 3, 10, or 30 mg/kg mapatumumab in combination with sorafenib (n = 17). Serum or plasma mapatumumab concentrations are consistently within the range of expected concentrations predicted from Phase 1 study results in solid tumor patients administered mapatumumab as monotherapy. Mapatumumab PK is linear and not affected by the addition of therapeutic agents. As expected, the observed peak and trough levels of mapatumumab at 30 mg/kg are 2 to 3 times higher than those observed at 10 mg/kg. Exposure appears to increase in proportion to dose and exposures for a given dose are similar across studies.

A Phase 1b dose escalation study of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody is being conducted. Safety observations have been consistent with the underlying disease and known sorafenib toxicities. As of June 2010, 6 subjects have received 3 mg/kg, 9 subjects have received 10 mg/kg, and 1 subject has received 30 mg/kg mapatumumab. The number of cycles completed ranges from 1 to 20; 4/16 (25.0%) of subjects have completed 11 or more cycles. Adverse events have generally been consistent with published reports of the toxicities associated with sorafenib and previous experience with mapatumumab, as well as underlying disease. The most frequently occurring treatment-emergent adverse events, regardless of severity or attribution of causality, include diarrhea (10/16, 62.5%), fatigue (9/16, 56.3%), nausea (9/16, 56.3%), and vomiting (7/16, 43.8%). Serious adverse events, regardless of attribution of causality, include hypertension, upper respiratory tract infection, atrial fibrillation, hyperbilirubinemia,

hypoglycemia, and hepatic pain. Severe adverse events considered at least possibly related to mapatumumab or its interaction with sorafenib include elevated lipase (3/16, 18.8%), hepatic pain (1/16, 6.3%), and thrombocytopenia (1/16, 6.3%). Laboratory abnormalities have generally been mild or moderate in severity, manageable, and/or consistent with those expected with chemotherapy or the underlying disease. The most frequent Grade 3 or Grade 4 laboratory abnormalities include elevated total bilirubin (Grade 3, 4/16, 25.0%; Grade 4, 1/16, 6.3%) and lymphopenia (Grade 3, 3/16, 18.8%; Grade 4, 2/16, 12.5%). Additional information on the safety experience can be found in the mapatumumab Investigators' Brochure.

Based on the information currently available, the safety profile continues to be favorable, supporting continued evaluation of mapatumumab in combination with chemotherapy, including sorafenib. The maximum tolerated dose has not been reached in any of the Phase 1 or Phase 2 trials conducted to date. Thus, further evaluation of the 30 mg/kg dose is warranted.

The dose of sorafenib for this study, 400 mg twice daily, is the approved dose for the treatment of unresectable hepatocellular carcinoma.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

2.2 Secondary Objective

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

3 Study Design

3.1 Basic Design Characteristics

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio: 30 mg/kg mapatumumab or placebo.

Mapatumumab will be supplied in open label vials and 3rd party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent, but independent of all other study activities. All other study site personnel, the subject, and the Sponsor will remain blinded to the study agent

received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Number of Subjects:

Approximately 100 subjects with advanced HCC will be randomized/enrolled.

Treatment Groups:

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle

Arm B: Sorafenib 400 mg orally twice daily continuously in each cycle + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle

Randomization

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Estimated Study Duration:

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib with or without mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Estimated median length of subject treatment is 6-8 months. All subjects will have an End of Treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented). Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced

dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be must be confirmed by the BICR prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x 10^9 /L or ≥ 1500 /mm^3.
   - Platelet count ≥ 50 x 10^9 /L or ≥ 50,000 /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal. AM01 21Dec10
   - Serum albumin ≥ 2.8 g/dL or ≥ 28 g/L.
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

4.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. Previously received mapatumumab or sorafenib.
4. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.

5. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
6. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
7. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
8. Hepatic encephalopathy, per the investigator's evaluation.
9. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
10. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
11. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
12. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
13. Known human immunodeficiency virus infection.
14. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
15. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
16. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
17. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
18. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
19. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
20. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
21. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
22. Hepatitis B virus DNA levels > 2,000 IU/mL.

5 Study Treatment Regimen

Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, the sorafenib should be taken at the same time as any other calendar day.

5.1 Mapatumumab and Placebo

5.1.1 Formulation

Mapatumumab will be supplied as a lyophilized formulation in sterile, single-use 10 mL vials containing 100 mg mapatumumab. Upon reconstitution with 5.0 mL of sterile water for injection, each vial will contain 20 mg/mL mapatumumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 19 mg/mL glycine, 5 mg/mL sucrose, 0.2 mg/mL polysorbate 80, pH 6.5.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

5.1.2 Packaging, Labeling, Preparation, and Storage

The Pharmacy Manual will provide instructions for preparation and storage of study agent. The product will be securely stored at 2-8ºC.

The study agent label will contain, at a minimum, the following information:

- Product name
- Concentration
- Lot number
- Storage instructions
- Investigational drug statement
- Manufacturer's name and address

Study agent inventory/accountability forms will be examined and reconciled by the unblinded study monitor or designee. At the end of the study, all used and unused investigational study agent will be accounted for on a study agent accountability form provided to the investigator by the Sponsor or designee. Please refer to the HGS1012-C1103 Pharmacy Manual for more details regarding storage, handling and drug accountability.

5.1.3 Mapatumumab/Placebo Dose, Route of Administration and Schedule

The dose of mapatumumab is 30 mg/kg. Mapatumumab dose calculations will be based upon the subject's weight measured on Day 1 or within 3 days before Day 1 of each cycle. The planned duration of each treatment cycle will be 21 days. Mapatumumab/placebo will be administered on Day 1 of each cycle.

After reconstitution with sterile water for injection, the calculated mapatumumab dose to be administered to the subject will be further diluted in normal saline to a total volume of 250 mL for intravenous infusion. After adding the reconstituted product, the bag will be gently inverted to mix the solution. Following reconstitution and/or dilution in normal saline, mapatumumab will be stored at 2-8ºC. The product will be administered to the subject within 8 hours of reconstitution. Refer to the HGS1012-C1103 Pharmacy Manual for instructions on admixing and administering study agent.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

Mapatumumab/placebo will be infused at a constant rate over 1 hour.

Infusion and hypersensitivity reactions may occur. A suggested pre-medication regimen for mapatumumab/placebo consists of diphenhydramine and acetaminophen administered within 1 hour prior to the start of the mapatumumab/placebo dose. Use of a pre-medication regimen and alternatives to this regimen are at the investigator's discretion.

Subjects will be monitored closely during and after infusion for any sign of acute adverse reaction. If an allergic reaction occurs, see Section 5.1.5 and Appendix 8 for suggested medical management.

5.1.4 Mapatumumab/Placebo Dose Toxicity/Delay

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Mapatumumab/placebo will be discontinued for Grade 4 transaminase elevations of any duration if they are considered related to mapatumumab.

Mapatumumab/placebo may be delayed up to 2 weeks for toxicities considered related to mapatumumab as described below or if the investigator believes that a delay in dosing is warranted in the interest of subject safety.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0) will be used to grade AEs.

- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transient transaminase, amylase and lipase abnormalities for which the following criteria will apply:
  - Grade 3 or Grade 4 elevations in transaminases that do not resolve to baseline or Grade 1 before the next cycle.
  - Grade 3 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, or resulting in chronic damage to the pancreas.
  - Any Grade 4 elevations in lipase or amylase for > 4 consecutive days.

If mapatumumab/placebo is delayed for toxicity and the toxicity does not resolve (≤ Grade 1) or return to baseline within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from further treatment with

mapatumumab/placebo. If mapatumumab/placebo is delayed because the investigator believes a delay is warranted in the interest of subject safety and dosing of mapatumumab/placebo is not resumed within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from future treatment with mapatumumab/placebo. Sorafenib dosing will continue while mapatumumab/placebo dosing is held. The subject will continue receiving sorafenib until radiologic progressive disease or an unacceptable toxicity occurs, at the discretion of the Investigator.

Doses of mapatumumab may not be altered.

5.1.5 Management of Allergic/Hypersensitivity Reactions to Mapatumumab/Placebo

The administration of any recombinant protein has the potential to induce local or system immunologic reactions; subjects could experience, for example, acute allergic reactions. To date, 2 such SAEs have been reported which were considered related to mapatumumab (hypersensitivity and angioedema/facial edema). In the event of allergic/hypersensitivity reactions, investigators will institute treatment measures according to best medical and nursing practice. Guidelines for treatment are provided in Appendix 8.

For a NCI-CTCAE Version 4.0 Grade 3 or Grade 4 hypersensitivity reaction, treatment with mapatumumab/placebo will be discontinued.

If mapatumumab/placebo is discontinued for Grade 3 or Grade 4 hypersensitivity reactions, the subject will continue to receive sorafenib, until radiologic progression or unacceptable toxicity.

5.2 Sorafenib

5.2.1 Packaging, Labeling, Preparation, and Storage

Sorafenib is supplied as tablets, each containing 274 mg sorafenib tosylate, equivalent to 200 mg of sorafenib.

The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken orally twice daily without food (at least 1 hour before or 2 hours after a meal).

Sorafenib will be stored at room temperature (15-30°C, 59-86°F) in a dry place.

For country-specific formulation and packaging information, please refer to the instructions provided in the sorafenib product labeling.

Supplier: Commercially available.

5.2.2 Anticipated Toxicities with Sorafenib

Toxicities anticipated with the use of sorafenib include the following:

- Cardiac: Cardiac ischemia and/or infarction, hypertension.

- Dermatologic: Hand-foot skin reaction, rash/desquamation.
- Hemorrhagic: Increased risk of bleeding.
- Gastrointestinal: Gastrointestinal perforation.
- Other: Wound-healing complications, fatigue, weight-loss, alopecia, pruritis, dry skin, diarrhea, anorexia, nausea, vomiting, constipation, liver dysfunction and abdominal pain.

Laboratory abnormalities observed in hepatocellular carcinoma patients treated with sorafenib include hypophosphatemia, lipase elevations, amylase elevations, hypoalbuminemia, international normalized ratio elevations, lymphopenia and thrombocytopenia.

Refer to the product labeling accompanying the product for information approved in your country.

5.2.3 Alteration of Sorafenib Dose/Schedule Due to Toxicity

Sorafenib may be reduced or delayed for toxicities considered related to sorafenib as described below, or if the investigator believes that a reduction in dose is warranted in the interest of subject safety. When a dose reduction is necessary, sorafenib dose may be reduced to 400 mg once daily. If an additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day (see Table 5-1). A maximum of 2 dose reductions of sorafenib will be allowed per subject. Additional dose reductions not mentioned in Table 5-1 will need to be discussed with the medical monitor.

Table 5-1 Sorafenib dose levels

Dose Levels	Sorafenib
0	400 mg twice daily
-1	400 mg once daily
-2	400 mg once every other day

Skin toxicity and hypertension are associated with sorafenib. Guidelines for the management of these events are provided in Table 5-2 and Table 5-3, respectively.

Skin Toxicity

Hand-foot skin reaction and rash are common in subjects treated with sorafenib. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, or in severe or persistent cases, permanent discontinuation. Skin toxicities will be managed according to Table 5-2.

Table 5-2 Dose modifications of sorafenib for skin toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, parethesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subject'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 subject'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 1 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 subject 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 1 dose level (400 mg daily or 400 mg every other day).
	3rd occurrence	Discontinue sorafenib treatment.

Hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Subjects will have their blood pressure monitored and recorded. If the subject's blood pressure is elevated at any time (> 150/100 mmHg), even outside clinic visits, they will contact their study investigator. Guidelines for the management of hypertension are provided in Table 5-3.

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (suggest dihydropyridine calcium channel blocker)	Increase frequency and monitor by a health professional every 2 days until stabilized.	No change
Grade 2 (symptomatic/ persistent) **OR** diastolic BP > 110 mm Hg **OR** Grade 3	Add agent(s): calcium channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor by health professional every 2 days until stabilized; continue monitoring every 2 days to stabilization after dosing restarted.	Hold* sorafenib until symptoms resolve <u>and</u> diastolic BP < 100 mm/Hg Resume treatment at 1 dose level lower**

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 4	Discontinue sorafenib	Discontinue sorafenib	Discontinue sorafenib

*Subjects requiring a delay of > 21 days will discontinue sorafenib, unless in the study investigator's opinion, the subject may benefit from continued treatment.

**Subjects requiring > 2 dose reductions will discontinue sorafenib.

BP = Blood pressure.

Refer to NCI-CTCAE v4.0 for grade definitions.

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Guidelines for the management of other non-hematologic and hematologic sorafenib-associated toxicities are provided in Table 5-4. Those toxicities that are at least possibly related to an interaction with mapatumumab/placebo will have the mapatumumab toxicity guidelines in Section 5.1.4 applied.

Table 5-4 Dose modifications of sorafenib for sorafenib-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 1, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.
Hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 2, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.

See Table 5-2 and Table 5-3 for dose modifications due to skin toxicity and hypertension respectively.

*Subjects who develop Grade 3 fever/chills, Grade 3 elevation of hepatic transaminases with ALT and AST < 10X upper limit of normal, Grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, Grade 3 leukopenia, or Grade 3/Grade 4 lymphopenia may continue sorafenib treatment without interruption at the discretion of the investigator.

Sorafenib Discontinuation

Temporary or permanent discontinuation of sorafenib will be considered in subjects who develop cardiac ischemia and/or infarction or severe or persistent hypertension despite institution of antihypertensive therapy. If a subject experiences a bleeding event that necessitates medical intervention or a gastrointestinal perforation, sorafenib will be

permanently discontinued. Subjects, who undergo a surgical procedure or intervention to decrease portal hypertension, including transjugular intrahepatic portosystemic shunt, will discontinue sorafenib.

If the subject is withdrawn from further treatment with sorafenib, the subject may continue to receive mapatumumab/placebo alone every 21 days until radiologic progression or unacceptable toxicity.

5.3 Concurrent Medications and Therapies

5.3.1 Allowable Regimens

Subjects may continue their baseline medication(s). The daily dose of each medication will be maintained throughout the study if possible. If for any reason deemed necessary by the investigator, a subject requires additional medication(s), the medication(s) route of administration and the indication for which it was given must be recorded in the source documents. All concomitant medications will be recorded on the appropriate case report form. AM01 21Dec10

Systemic, inhaled and topical steroids used as part of an antiemetic regimen or maintenance-dose for non-cancerous disease are permitted.

5.3.2 Prohibited Medications

Subjects who require the use of strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) are not eligible for this study and use of these agents is prohibited as long as the subject is receiving sorafenib in this study.

Subjects will not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies) or immunotherapy to treat hepatocellular carcinoma during the treatment period. Alternative anticancer therapies may be administered after radiologic disease progression has been documented, but will be avoided if possible during the 30 day safety follow up period after the last dose of study agent (mapatumumab/placebo and/or sorafenib) whichever is last. These medications are allowed in the long-term follow-up period after the 30 day safety follow-up period and documentation of radiologic disease progression.

5.3.3 Prohibited Therapies

Subjects will not undergo major or elective surgery during the treatment period of the study; if surgery is required, the subject will be withdrawn from study treatment.

6 Study Procedures

6.1 Screening Procedures

The nature of this study and the potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent (including consent for the use and disclosure of research-related health information) must be obtained before any screening procedures are performed that are not considered standard of care.

All of the following assessments must be performed within 28 days prior to enrollment:

- Obtain written informed consent for participation in the study.
- Obtain informed consent for participation in the optional biomarker sub-study.
  - If consented, obtain tissue block/slides or cell pellet from diagnostic histologic/ cytologic sample.
- Record demographics.
- Obtain medical history, to include history of all treatments used to treat the current cancer and all prior cancer treatments.
- Perform baseline complete physical examination including body weight and height.
- Assess vital signs (blood pressure, heart rate, respiratory rate and temperature).
- Evaluate performance status (ECOG scale; see Appendix 3).
- Draw blood for laboratory tests (see Appendix 7): complete blood count with differential, chemistry**,** hepatitis B surface antigen, Hepatitis B virus DNA, hepatitis C antibody and testing for serum pregnancy (all females with an intact uterus [unless amenorrheic for the previous 24 months] regardless of age).
- Obtain radiologic disease and AFP assessments. The method of disease assessment, as per mRECIST for HCC (see Appendix 5), will be consistent throughout the study.
- Obtain electrocardiogram.
- Record medications used within 28 days before enrollment.
- Confirm that subject meets all inclusion/exclusion criteria.

6.2 Study Enrollment/Randomization Procedures

Subjects that meet the eligibility criteria will be randomly assigned treatment by a central interactive voice response system in a 1:1 ratio to 1 of 2 treatment arms. The randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2). The 1st planned dose of sorafenib and mapatumumab/placebo will be administered no more than 3 days following randomization and not prior to randomization. All study site personnel (with the exception of the unblinded site pharmacist or unblinded designee), the subject, and the Sponsor will remain blinded to the study agent received.

6.3 On-treatment Study Procedures

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Informed consent		X															
Laboratory																	
CBC with differential; Coagulation parameters	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy	2	X	X														
Hepatitis	1	X															
B and T lymphocyte subsets	3		X				X	X			X						
Immunogenicity	4		X					X				X				X	
Pharmacokinetics	5		X			X		X				X				X	
Biomarkers	6		X	X	X	X	X	X	X	X	X						
Study Agent Admin																	
Sorafenib	7		Twice daily														
Mapatumumab/ Placebo	7		X					X				X					
Physical/Clinical																	
Med Hx / Phys.Exam	-	X															
Vital signs	8	X	X			X	X	X		X	X	X					
Body weight	9	X	X					X				X					
Performance Status	10	X	X					X				X				X	

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Record AEs/ Conmeds	11	X	<----------Throughout the study---------->														
Disease Assessments	12	X	Performed at the end of every 2 cycles (ie, Cycles 2, 4, 6) and every 2 cycles thereafter until radiologic PD is documented.														X
α – Fetoprotein (AFP)	12	X	Performed at the end of every 2 cycles (ie Cycles 2, 4, 6) and every 2 cycles thereafter until radiographic PD is documented.														X
ECG	-	X	Repeat as clinically indicated														
Survival	13																X

AE = adverse event; CBC = complete blood count; CT = computerized tomography; ECG -= electrocardiogram; PD = progressive disease.

[1] Safety Labs: Day 1 (complete blood count with differential, coagulation parameters [INR, PT, PTT] and chemistry) must be performed within 3 days prior to dosing on Day 1 of each cycle. See Appendix 7 for a detailed list of required laboratory assessments.

[2] Pregnancy: Serum test at screening, urine test pre-dose Cycle 1 Day 1; must be negative to receive treatment.

[3] B and T lymphocyte subsets: Blood samples for quantification of B and T lymphocytes will be obtained in Cycles 1 and 2 only. Samples will be obtained on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

[4] Immunogenicity: Obtain prior to dosing on Day 1 of Cycles 1, 2, 4, 6, every 2 cycles thereafter and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

[5] Pharmacokinetics: Blood specimens will be collected for determination of serum mapatumumab concentrations from subjects as follows: Cycle 1 (on Day 1 prior to the administration mapatumumab/placebo and at the completion of the mapatumumab/placebo infusion, and on Day 8), Cycles 2, 4 and 6 and thereafter on each even cycle (prior to dosing on Day 1), on the day of each disease assessment, and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

[6] Biomarkers: For subjects participating in the optional biomarker sub-study, historical biopsy samples will be collected, if available, and samples will be collected if obtained during the treatment period in Cycle 1 Days 1 (pre-dose mapatumumab), 2, 3, 8 and 15 and Cycle 2 Days 1 (pre-dose mapatumumab), 3, 8 and 15. In addition, blood samples will be obtained as follows: blood for isolation of DNA will be collected once, preferably in Cycle 1. Blood for isolation of serum will be collected in Cycles 1 and 2 (pre-dose on the day of mapatumumab/placebo dosing). Further details on the biomarker sub-study are outlined in Appendix 6.

[7] Study Agent Administration: Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, sorafenib should be taken at the same time as any other calendar day.

[8] Vital Signs: Blood pressure will be monitored weekly for the first 6 weeks. Vital signs will be obtained within 30 minutes prior to administration of mapatumumab/placebo and at the end of infusion on Day 1 of each cycle.

[9] Body Weight: To be obtained on the day of or within 3 days before dosing on Day 1 of each cycle.

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	

[10] Performance Status: Obtained prior to dosing on Day 1 of each cycle.

[11] Adverse Events: AE collection begins with the start of 1st study agent administration. Concurrent medications will be recorded within 28 days prior to Cycle 1 Day 1.

[12] Disease and α – Fetoprotein (AFP) Assessments: Radiologic and AFP assessments will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6, etc). For subjects discontinuing treatment prior to documentation of radiologic disease progression, disease assessments will be performed every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on study, until radiologic disease progression is documented. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent reader for confirmation of disease progression. All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

[13] Survival**:** Contact will be made with the subject every 3 months to document survival until at least 90% of subjects have met the survival endpoint.

[14] Subjects who discontinue mapatumumab/placebo will complete the current cycle assessments per the study calendar. Subsequently, subjects receiving sorafenib alone will return at least every 21 days and on additional days as clinically indicated for safety labs (CBC with differential, chemistry and coagulation parameters) for the duration of treatment. Disease assessments must be performed every 6 weeks until radiologic disease progression. Adverse events and concomitant medications will be recorded throughout the study.

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6.4 Follow-up Procedures

6.4.1 Safety Follow-up

After discontinuation of study treatment, all subjects will return 1 day after cycle completion (approximately Day 22) and at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, for scheduled safety follow-up assessments as outlined in Table 6-1.

6.4.2 Long-term Follow-up

For subjects discontinuing treatment prior to documentation of radiologic disease progression, and for subjects who experience stable disease or a response (PR, CR) but are no longer receiving treatment, radiologic disease assessments will be performed at 6 week intervals (± 3 days), starting 6 weeks after the previous radiologic disease assessment while on treatment, until radiologic disease progression is documented. Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

6.5 Withdrawal of Subjects from Treatment

Subjects will be free to withdraw from treatment at any time, for any reason, or they may be withdrawn/removed, if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects will be avoided.

Subjects may be withdrawn from treatment for any of the following reasons:

- Radiologic disease progression.
- Continued unacceptable toxicities despite optimal treatment or dose reduction.
- Intercurrent illness, at the investigator's discretion.
- Withdrawal of consent.
- Non-compliance/Lost to follow-up.
- Pregnancy.
- Termination of the study by the sponsor.

Subjects who withdraw are to be followed for radiologic progression as outlined in Section 6.4.2. In addition, every effort will be made to collect safety information on each subject through 30 days following the last dose of study treatment, unless the subject withdraws consent and refuses to comply with the protocol stipulated safety follow-up and radiologic disease progression assessments, or share information obtained after the date of withdrawal of consent.

6.6 Withdrawal of Subjects from Study

Subjects may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent.

- Non-compliance/Lost to follow-up.
- Termination of the study by the sponsor.

Every effort will be made to collect follow-up information on subjects in the long-term follow-up period of the study, unless the subject withdraws consent and refuses to share information obtained during the long-term follow-up period obtained after the date of withdrawal of consent.

6.7 Disease Response Assessments

Imaging endpoints will be determined using the modified RECIST criteria for HCC proposed by Lencioni and Llovet (2010; mRECIST). mRECIST for HCC is a joint guideline of the American Association for the Study of Liver Diseases and the Journal of the National Cancer Institute.

Lesions which manifest typical imaging characteristics for HCC demonstrate intratumoral arterial contrast on CT and MRI images. mRECIST accounts for newer therapies which may impact tumor vascularity and may not yield a typical cytotoxic decrease in tumor size by incorporating changes in vascularity into the criteria for target lesion response. Diligence in obtaining images during the hepatic arterial contrast enhancement phase is a requirement at baseline and all subsequent scans. The same imaging method must be used at baseline and during follow up.

As in conventional RECIST, overall response is the result of the combined assessment of target, nontarget, and new lesions. There are also specifications for incorporating portal vein thrombosis, portal hepatic lymph nodes, and pleural effusions/ascites into the response assessment. As with conventional RECIST, the appearance of any new lesion overrides any existing lesion response, resulting in classification as progressive disease (PD). Key aspects of mRECIST as adapted for this study are summarized in Appendix 4.

Baseline images will be provided to the BICR for confirmation of radiologic eligibility (measurable disease). Confirmation of radiologic eligibility for the study will be provided to the site by the BICR within 72 hours of receipt of images and will be required for randomization.

Disease assessments and an assessment of α -fetoprotein will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The response assessment will be performed and documented no more than 5 days before the start of the next cycle. All images will be provided to the BICR following each disease assessment.

If disease progression is based only on new lesions or is equivocal, images will be provided to the BICR for confirmation of radiologic disease progression prior to discontinuing study treatment. PR and CR will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

7 Pharmacokinetic, Immunogenicity, Pharmacodynamic and Exploratory Assessments

7.1 Pharmacokinetic Assessments

For determination of mapatumumab concentration, serum samples will be collected as outlined in Table 6-1.

A manual will be provided regarding how to obtain blood samples, process samples, collect serum from the blood samples, and how to store and ship the serum samples. Bioanalysis will be carried out at Human Genome Sciences to determine mapatumumab concentration in each serum sample.

7.2 Immunogenicity

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

7.3 Pharmacodynamic Assessments

Subjects will be given the option to participate in an exploratory biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine and quantify biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The parameters evaluated may include, but may not be limited to, M30, TNFα, sTRAIL, soluble Fas ligand, interferon-α, interferon-γ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, interleukin-12, and FC gamma receptor and interleukin-6 gene polymorphisms. The biomarker sub-study is detailed in Appendix 6.

7.4 Exploratory Assessments (B and T Lymphocyte Subsets)

7.4.1 Rationale for B and T Lymphocyte Analysis

Over 400 subjects have received mapatumumab in doses ranging from 0.01 to 30 mg/kg across multiple Phase 1 and Phase 2 clinical trials in subjects with solid and hematologic malignancies. While there is no evidence to date that mapatumumab exacerbates adverse events associated with chemotherapy, the most commonly observed laboratory abnormality associated with mapatumumab has been lymphopenia. The lymphopenia has been intermittent and reversible and was not associated with infectious events. However, the lymphocyte subpopulation(s) affected have not been characterized.

The evaluation of lymphocytes will include complete blood count/differential and lymphocyte subpopulation analysis (numbers and percentages of T and B cells) by flow cytometry at a central laboratory. Blood samples will be examined by flow cytometry for levels of T helper (CD4+), T cytotoxic (CD8+) and mature B cells (CD19+).

7.4.2 Collection of Samples for B and T Lymphocyte Analysis

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2 as outlined in Table 6-1.

8 Adverse Event Reporting

8.1 Definitions

ADVERSE EVENT (EXPERIENCE) - any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. This includes worsening (eg, increase in frequency or severity) of pre-existing conditions.

SERIOUS ADVERSE EVENT – an adverse event resulting in any of the following outcomes:

- death
- is life threatening (ie, an immediate threat to life)
- inpatient hospitalization
- prolongation of an existing hospitalization
- persistent or significant disability / incapacity
- congenital anomaly / birth defect
- is Medically Important*

*Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

Note: Hospitalizations not associated with an adverse event, for example, for administration of chemotherapy or hydration for chemotherapy administration, are not considered serious adverse events.

UNEXPECTED ADVERSE EVENT - An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means that the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

8.2 Reporting Adverse Events to the Sponsor or Designee

All adverse events (AEs) that are identified from the start of any study agent administration through the specified study follow-up period (through 30 days following administration of the

final study agent dose) will be recorded on the paper/electronic Adverse Event Case Report Form (AE case report form). All data fields on the AE case report form will be completed.

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and sent to HGS within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All pages of the SAE Worksheet will be completed, but the SAE worksheet will not be held until all information is available. Additional information and corrections will be provided on subsequent SAE Worksheets as described in the Study Procedure Manual. SAE Worksheets will be sent by facsimile to the Drug Safety Department at HGS using the fax number listed below.

FAX #: PPD

8.3 Laboratory Abnormalities as Adverse Events

A laboratory abnormality will be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, additional assessments (excluding follow-up labs), or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition will be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased).

8.4 Other Events Requiring Rapid Reporting

Protocol Specified Events are additional events [toxicities] specifically identified in this protocol that must be reported to Human Genome Sciences or designee in an expedited manner. Protocol Specified Events may or may not be SAEs as defined in this protocol. They are SAEs if they meet one or more of the criteria for an SAE (see Section 8.1). Protocol Specified Events are recorded on SAE Worksheets and sent to Human Genome Sciences within 24 hours of site personnel becoming aware of the event.

The Protocol Specified Events for the study:

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- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transaminase, amylase and lipase abnormalities for which the following criteria apply:
  - Grade 4 elevations in transaminases.
  - Grade 4 elevations in lipase or amylase.
  - Grade 3 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, resulting in chronic damage to the pancreas.
- Any adverse event that results in discontinuation of treatment if that event is assessed as possibly, probably, or definitely related to mapatumumab or sorafenib.

8.5 Reporting a Pregnancy

Any pregnancy in a female participant or a female partner of a male participant must be reported to Human Genome Sciences Drug Safety as soon as the site becomes aware of the pregnancy. All pregnancies are reported up to 30 days following the last study agent treatment. Human Genome Sciences Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. Additional Pregnancy Assessment Forms will be sent to the site every 3 months for reporting of follow-up information. Pregnancy assessment forms must be completed by the investigator until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 8.2.

8.6 Investigator Evaluation of Adverse Events

The Investigator will evaluate all adverse events with respect to seriousness (criteria listed in Section 8.1 above), severity (intensity or grade) and causality (relationship to study agent) according to the following guidelines listed below.

SEVERITY

Severity will be graded using the NCI-CTCAE, Version 4.0. The NCI-CTCAE may be downloaded from the Cancer Treatment Evaluation Program website (http://ctep.info.nih.gov/reporting/ctc.html). In the event that an AE does not have an NCI-CTCAE code, the following severity classifications will be used:

Mild	causing no limitation of usual activities
Moderate	causing some limitation of usual activities
Severe	causing inability to carry out usual activities
Life Threatening*	potentially life threatening or disabling

***Note** – a severity assessment of life threatening is not necessarily the same as life threatening as a "Serious" criterion. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.

CAUSALITY

Definitely Related	reasonable temporal relationship to study agent administration follows a known response pattern (eg, drug is known to cause this AE) there is no alternative etiology
Probably Related	reasonable temporal relationship follows a suspected response pattern (eg, based on similar drugs) no evidence for a more likely alternative etiology
Possibly Related	reasonable temporal relationship little evidence for a more likely alternative etiology
Probably Not Related	does not have a reasonable temporal relationship, OR good evidence for a more likely alternative etiology
Not Related	does not have a temporal relationship, OR definitely due to alternative etiology

ICH guidelines (March, 1995) clarify "reasonable causal relationship" to mean "that there are facts [evidence] or arguments to suggest a causal relationship".

The causality assessment must be made by the investigator based on information available at the time that the SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

***Note -** If there is evidence that mapatumumab/placebo contributed to or exacerbated an event related to sorafenib; the event will be recorded as possibly, probably or definitely related to both sorafenib and mapatumumab.

8.7 Follow-up of Adverse Events

Adverse events that occur during the course of the study are followed until final outcome is known or until the end of the safety follow-up period (30 days following the final dose of any study agent). Adverse events that have not resolved by the end of the safety follow-up period are recorded as ongoing.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for a SAE (eg, the subject is lost to follow up), the reason a final outcome could not be obtained will be documented by the investigator.

8.8 Serious Adverse Events Assessed During Long-Term Follow-up

SAEs that occur after the safety follow-up period (30 days following the final dose of study agent) that are assessed by the investigator as possibly, probably, or definitely related to study agent must be reported to Human Genome Sciences on an SAE worksheet, as described in Section 8.2. Post-study SAEs will not be documented on the AE case report form.

8.9 Reporting Serious Adverse Events to the Institutional Review Board/Ethics Committee

All SAEs that are considered unexpected and related to the study agent will be reported by Human Genome Sciences or its designee as expedited (ie, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators. Each investigator must notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) responsible for reviewing the study at their site of all expedited reports. In addition, Human Genome Sciences or its designee will follow all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

9 Endpoints and Statistical Analysis

9.1 General Statistical Considerations

Analyses will be applied to a modified intention-to-treat population unless stated otherwise. This population is defined as the set of all randomized subjects who receive at least 1 dose of study treatment (mapatumumab/placebo and/or sorafenib) with subjects analyzed according to the groups they are randomized to, regardless of the treatment they subsequently receive. Additional analyses may be performed on the as-treated population, defined as the set of subjects receiving at least 1 dose of study medication analyzed according to the treatment that they actually receive.

Analyses will be performed using the SAS System™, WinNonlin Enterprise Edition™, StatXact™, and the R statistical package.

9.2 Sample Size Rationale

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

9.3 Efficacy

9.3.1 Primary Efficacy Endpoint

The primary endpoint is time to progression (TTP) defined as the time from randomization to radiologic disease progression based on blinded independent review of imaging scans.

9.3.2 Primary Efficacy Analysis

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with testing the hazard

ratio for time to progression at a 1-sided significance level of 0.10 with a Cox proportional hazards model controlling for the factors stratifying the randomization as covariates. AM01 21Dec10

9.3.3 Secondary Efficacy Endpoints

Secondary endpoints include progression-free survival, overall response, disease control, overall survival, time to response, and duration of response (for responders) as defined below:

- OS: time from randomization to death from any cause.
- PFS: time from randomization to disease progression or death from any cause.
- Objective response (CR+PR according to mRECIST for HCC).
- Disease control (CR+PR+SD according to mRECIST for HCC).
- Time to response: time from randomization to 1st PR or CR in responders only.
- Duration of response: time from 1st PR or CR to disease progression; in responders only.

All secondary endpoints will be based on blinded independent review of imaging scans.

9.3.4 Secondary Efficacy Analyses

Secondary analyses include estimates, using Kaplan Meier methods, of median PFS and median OS along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test).

9.4 Safety

9.4.1 Definition of Safety Variables

The safety parameters assessed are given by the following:

- Frequency, and severity of adverse events (AEs):
  - All AEs will be classified by System Organ Class and Preferred Term under the Medical Dictionary for Regulatory Activities (MedDRA) system of classification with a severity assigned according to the NCI-CTCAE (Version 4.0, 29 May 2009), or the rules specified in Section 8.6.
  - Laboratory parameters as presented in Appendix 7.
  - Laboratory toxicities will be graded based on the NCI-CTCAE (Version 4.0, 29 May 2009).
- Anti-mapatumumab antibody response.
- Vital signs.
- For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

9.4.2 Human Genome Sciences Safety Review Committee

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

9.4.3 Analysis of Safety Variables

The safety analysis will consist of a presentation of rates of AEs observed. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality observed will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall, as well as categorized by the MedDRA system of classification. AEs will be presented overall, by severity, by relation to mapatumumab/placebo, and by relation to sorafenib.

9.5 Pharmacokinetics

9.5.1 Definition of Pharmacokinetic Evaluation

Serum mapatumumab concentration data obtained from this study will be pooled with data obtained from other studies for use in a population PK analysis, which will be reported separately.

9.5.2 Analysis of Pharmacokinetics

The serum mapatumumab concentration will be determined by enzyme-linked immunosorbent assay. Serum mapatumumab concentration results for this study will be presented using appropriate graphic and tabular summaries.

9.6 Pharmacodynamics

Expression of biomarkers in tumor tissue and peripheral blood will be correlated with clinical outcomes and may be reported separately from the clinical study report.

10 Study Administration

10.1 Informed Consent

A copy of the proposed informed consent document(s) must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with ICH Good Clinical Practices, will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 Data Collection and Management

Data collected for each study subject are recorded electronically on case report forms provided or approved by the sponsor.

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documents related to the study, including any films, tracings, computer discs, or tapes. The investigator must promptly review the completed case report forms for each subject. As the person ultimately responsible for the accuracy of all data, the investigator must sign the Investigator's Statement in each subject's case report form.

The anonymity of participating subjects must be maintained. Subjects are identified by an assigned subject number on case report forms and other documents submitted to the sponsor. Documents that identify the subject beyond subject number are not submitted to the sponsor (ie, the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Sites enter subject data directly into the electronic data capture (EDC) system and the EDC system automatically generates queries resulting from computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. At study end, each site is provided with a compact disk containing the electronic case report forms for each of their subjects.

Upon completion of the study, or after reaching a pre-specified point in the study, Data Management locks the database and generates the SAS datasets necessary for data analysis and reporting.

10.6 Study Monitoring

The study sponsor, Human Genome Sciences, Inc., or designee, will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review the paper subject diaries and electronic case report forms and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make paper subject diaries and electronic case report forms and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators will promptly notify Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7 Drug Accountability

Upon receipt, the designated unblinded pharmacy personnel at the study site are responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this

inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by an unblinded Clinical Research Associate, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by Human Genome Sciences or its designee.

10.8 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated, or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9 Financial Disclosure

The investigator will provide Human Genome Sciences sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10 Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be pooled and analyzed. The investigator acknowledges that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and sponsor's representatives. Neither institution nor principal investigator shall independently publish or present the results of the study prior to the publication of the multi-center study publication. The investigator agrees that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until the entire sponsor's comments on the proposed publication or presentation have been considered and any information determined by sponsor to be confidential information has been removed.

If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11 Study or Study Site Termination

If Human Genome Sciences, the investigator, IRB/IEC, or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between Human Genome Sciences and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of Human Genome Sciences to suspend or discontinue testing, evaluation, or development of the product.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to Human Genome Sciences, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

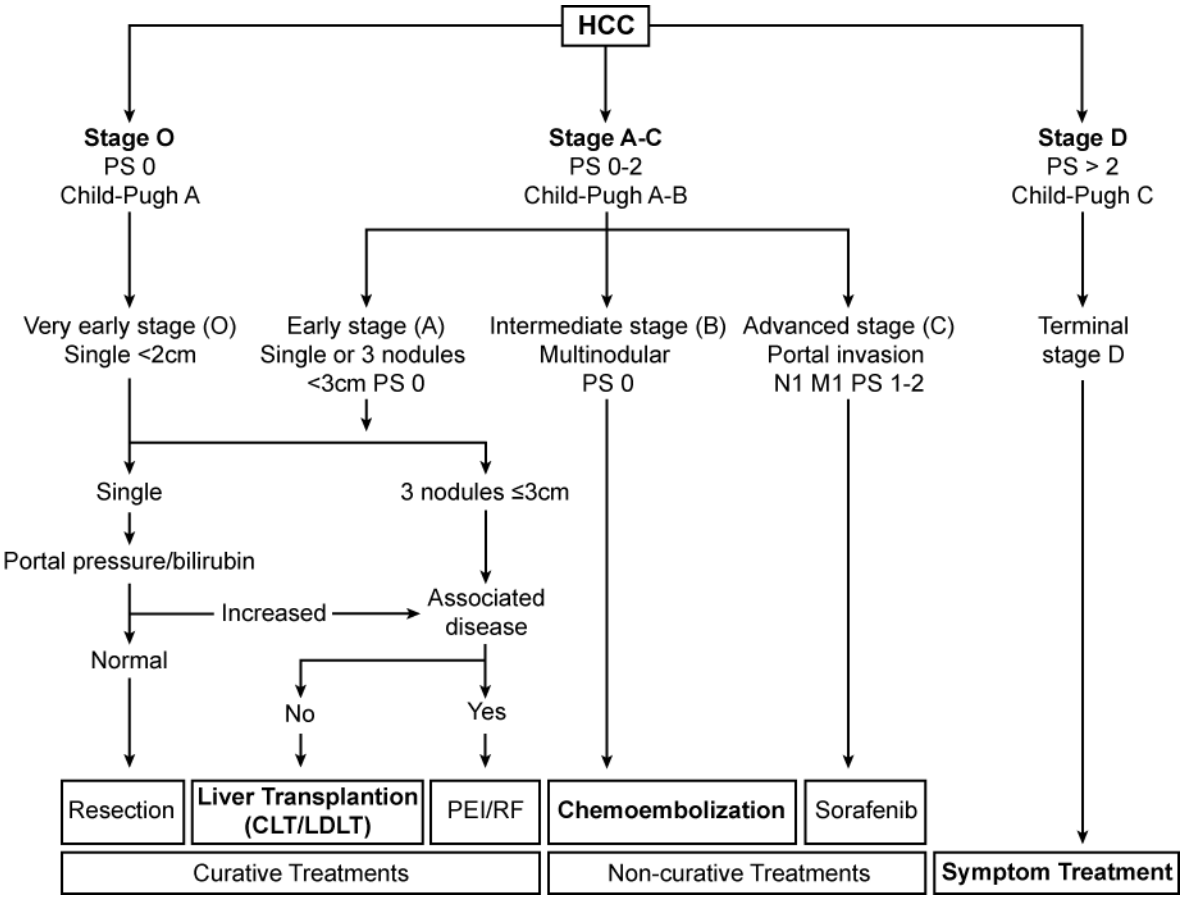
Appendix 1 Child-Pugh Classification

(Zimmerman H and Reichen J, 2000)

	No. of Points		
Factor	**1**	**2**	**3**
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (increased seconds)	1–3	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Minimal	Advanced

Grade	Score
A	5 – 6
B	7 – 9
C	10 – 15

Appendix 2 BCLC Staging and Treatment Strategy



Forner et al, 2010

Appendix 3 Eastern Cooperative Oncology Group (ECOG) Performance Status

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Appendix 4 New York Heart Association Classification for Congestive Heart Failure

(The Criteria Committee of the New York Heart Association; Little, Brown & Co. 1994)

Class	New York Heart Association Classification for Congestive Heart Failure
1	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
2	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
3	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
4	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 5 Modified Response Evaluation Criteria in Hepatocellular Carcinoma (mRECIST for HCC)

AM01
21Dec10

(Adapted from Lencioni and Llovet, 2010 for use in this study)

Measurable disease: The presence of at least 1 target lesion, by contrast enhanced computerized tomography (CT) with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI).

Target lesion: Meets all the following criteria:

- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well-delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

A maximum of 5 target lesions may be selected.

Nontarget lesion: Other lesions, including small lesions (≤ 2 cm in the axial plane). Note that malignant portal vein thrombosis should be considered a nonmeasurable, and therefore nontarget, lesion. Lymph nodes at the portal hepatic can be considered as malignant if the lymph node short axis is at least 2 cm. Selection of effusion, including ascities, as a nontarget lesion is prohibited. Similarly, bone lesions or any other lesion outside the CT or MRI of the abdomen or obtained by other modality, may not be selected as nontarget lesions.

Measurement of lesions: Imaging studies will be by contrast enhanced CT, with use of multislice scanners, or contrast enhanced MRI. The same method must be used at baseline and during follow up. Note that the longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured. The measurement of the viable tumor diameter should not include any major intervening areas of necrosis. (Please see the HGS1012-C1103 Radiographic Data Collection Manual).

Evaluation of target lesions:

Complete Response (CR): Disappearance of 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.

Stable Disease (SD): Any cases that do not qualify for CR, PR or PD.

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.

Evaluation of nontarget lesions:

Complete Response (CR): Disappearance of intratumoral arterial enhancement.

Incomplete Response/Stable Disease (IR/SD): Persistence of intratumoral arterial enhancement in 1 or more nontarget lesions.

Progressive Disease (PD): Unequivocal progression of existing nontarget lesions.

Evaluation of new lesions: A newly detected hepatic nodule will be classified as evidence of progression when its longest diameter is ≥ 1 cm and the nodule shows the hypervascularization in the arterial phase with washout in the portal venous or late venous phase.

Liver lesions ≥ 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least a 1 cm-interval growth in subsequent scans.

An individual radiologic event will be adjudicated in retrospect as progression at the time it was 1st detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

Images by another modality may be obtained, as clinically indicated post-baseline. Sites may conclude that post-baseline images based on another modality that indicate disease are evidence of radiologic progression if: (1) there was no imaging done at baseline; (2) if there was imaging done at baseline showing no disease present at that time; or (3) if there was imagine done at baseline indicating that the on-treatment assessment represents unequivocal worsening. In these cases the disease will be reported as ‘new lesions’.

All images obtained on study will be provided the BICR for the independent efficacy read, or for confirmation of progression if required or requested.

Evaluation of Overall Response: The overall response is determined at each assessment and is a result of the combined assessment of target lesions, nontarget lesions and new lesions.

Overall Response Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response*
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*AFP is not included in assessment of overall response.

Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression. To be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

Appendix 6 Exploratory Biomarker Sub-study

1. Background

Mapatumumab is a targeted therapy. Presently, the relationship between expression of the target, TRAIL-R1, and the anti-tumor activity of the antibody is incompletely understood. Studies conducted with cell lines derived from human tumors have suggested that the relationship between receptor expression and mapatumumab-induced tumor cell death may be complex. However, studies of human tumor cells in vitro and transplanted into animals may not accurately reflect the relationship between receptor expression and response to mapatumumab that may be observed in patients with cancer. One feature of this biomarker study is to compare TRAIL-R1 expression from available biopsy material. This could allow for a greater understanding of patterns of TRAIL-R1 expression in advanced hepatocellular carcinoma.

It is also likely that other factors involved in TRAIL-R1 signaling could critically affect response to mapatumumab treatment. A 2nd goal of this biomarker study is to evaluate biomarkers that may be potential indicators or modifiers of response to mapatumumab. To identify factors that may indicate that a patient is responding to treatment, serum-based markers will be compared before and after treatment. To explore factors that are associated with the outcome of therapy and could be used prior to treatment to predict which patients will respond, somatic (inherited) differences that modify a patient's drug response will be examined.

The information generated from this sub-study will be used solely for research purposes to improve future treatment with mapatumumab. It will not be used to change diagnoses or alter therapy. Participation in this sub-study is optional.

2. Study Objectives and Design

2.1. Indicators of Response

2.1.1. Serum-Based Markers of Response

Induction of cell death in tumor cells can elicit the release of certain biomarkers into the serum. These markers can be quantified to evaluate treatment effect. To assess release of biomarkers associated with cell death, serum-based assays will be conducted, including, but not limited to, assessments of M30, a fragment of cytokeratin 18 that is generated by induction of programmed cell death in epithelial tissues. Other examples of markers of tumor cell death that will be examined include the cytokines TRAIL, TNFα, soluble Fas ligand, interferonα, interferonγ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, and interleukin-12. The levels of these factors will be examined before and after treatment to see if they correlate with response to treatment.

Serum will be isolated and the level of cytokines and other markers like M30 will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2. Modifiers of Response

2.2.1. Neoplastic Modifiers of Response

Historically collected tumor biopsy material, if available, will be collected from subjects during Cycle 1. Samples will also be obtained from subjects who undergo a biopsy during the treatment period. Samples of resected tumor tissue that has been formalin-fixed and embedded in paraffin is acceptable; either tissue blocks or slides may be provided. Frozen samples of tumor tissue may also be provided. Biopsy material collected from fine needle aspirates may be provided; either cell pellets or cytological slides are acceptable.

Levels of TRAIL receptors will be assessed in biopsy material using immunohistochemical techniques if samples are available as formalin-fixed/paraffin-embedded tissue blocks or slides. Historically obtained biopsy material or biopsy material obtained during the treatment period that is in the form of fresh frozen tissue or cell pellet samples will be utilized to isolate RNA for analysis of TRAIL receptor gene expression.

Similar techniques will be used to evaluate other potential biomarkers and factors that may influence mapatumumab response. These may include but are not limited to caspase 8, AKT and Mcl-1.

See the laboratory manual for collection, processing and handling of these samples.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2.2. Somatic Modifiers of Response

Inherited differences in the genes that code for drug targets or components of signaling pathways related to the target can dramatically influence the effect of pharmacotherapy. Variations in genes that could potentially impact mapatumumab's activity, including polymorphic changes in the Fc gamma receptor and interleukin-6 promoter and K-Ras gene mutations, will be examined to see if they correlate with response to treatment.

DNA will be isolated from the blood and polymorphisms and mutations in specific response-related genes will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

3. Statistical Analysis

Associations will be assessed between candidate biomarkers and treatment outcomes captured in the clinical database. Statistical tests to be performed may include Pearson chi-square testing, Fisher's exact test, ANOVA and ANCOVA. Results of the biomarker sub-study may be reported independent of the results of HGS1012-C1103.

4. Subject Selection and Withdrawal

Subjects enrolled in the HGS1012-C1103 research study are given the option to participate in the Biomarkers Sub-study. A subject may withdraw from the sub-study at any time by contacting their Study Investigator, who will contact the sponsor. The sponsor will destroy any remaining sample materials and will send a letter back to the Investigator confirming sample destruction. Any data or analysis generated from the sample prior to the request for destruction will not be destroyed. However, no new information will be generated from the sample and no new analysis will be performed.

5. Confidentiality

Information about sub-study subjects will be kept confidential and managed according to the requirements of local privacy regulations. Information obtained from samples will not be returned to subjects and will not be placed in the subject's medical record.

6. Ethical Considerations

All subjects enrolled in the HGS1012-C1103 research study who agree to participate in the Biomarker Sub-study will be asked to sign a separate Biomarker Informed Consent. Choosing to not participate in this sub-study will not affect the subject's ability to participate in the main clinical trial. The Biomarker Informed Consent will be submitted along with the main research study informed consent for review by the Institutional Review Board/Ethical Committee.

7. Publication of Biomarker Results

Any significant findings, based upon the analysis of aggregate data collected from this sub-study may be published by Human Genome Sciences. Personal identifiers will not be used in any publication resulting from this sub-study.

Appendix 7 Laboratory Tests

CBC with Differential	Chemistry
Total white blood cell (WBC) count differential:	Electrolytes:
Neutrophils	Sodium
Bands	Potassium
Lymphocytes	Magnesium
Monocytes	Chloride
Eosinophils	Carbon dioxide/bicarbonate*
Basophils	Calcium
Hemoglobin	Enzymes:
Hematocrit	SGOT (AST)
Red blood cell count	SGPT (ALT)
Platelet count	Alkaline phosphatase
Absolute Neutrophil Count	Amylase
Total white blood cell count	Lipase
	Gamma glutamyl transferase (GGT)
Prothrombin time (PT)	
Partial thromboplastin time (PTT)	Other:
International normalized ratio (INR)	Creatinine
	Blood Urea Nitrogen
Other:	Total bilirubin
Serum and Urine pregnancy	Total protein
Hepatitis B surface antigen	Albumin
Hepatitis C antibody	
B and T lymphocytes	
HCV RNA	
HBV DNA	
HBsAb	

*To be collected if included in routine automated serum chemistry panel.

Refer to Section 6 (Study Procedures) for laboratory test collection schedule.

Appendix 8 Treatment of Allergic/Hypersensitivity Reactions

In the event of allergic/hypersensitivity reactions to mapatumumab/placebo, investigators will institute treatment measures according to best medical and nursing practice. The grading is based upon the NCI-CTCAE Version 4.0.0.

The following treatment guidelines will be employed:

- If chills and fever occur, the infusion will be interrupted. Subjects may be treated symptomatically and the infusion will be restarted at 50% of the original rate.

Grade 1 allergic/hypersensitivity reaction (transient flushing or rash, drug fever < 38°C):

- Decrease infusion rate by 50% and monitor for worsening condition. If the reaction worsens, stop the infusion.

Grade 2 allergic/hypersensitivity reaction (rash, flushing, urticaria, dyspnea, drug fever < 38°C):

- Stop the infusion.
- Administer bronchodilators, oxygen, acetaminophen, etc as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop the infusion.

Re-treatment following Grade 1 or Grade 2 allergic/hypersensitivity reactions:

- Once the infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions.
- If the subject has a 2nd reaction at the lower infusion rate, the infusion will be stopped and the subject will receive no further treatment with mapatumumab/placebo.
- If the subject experiences a Grade 3 or Grade 4 allergic/hypersensitivity reaction at any time, the subject will receive no further treatment with mapatumumab/placebo.
- If there are questions concerning whether an observed reaction is an allergic/hypersensitivity of Grades 1-4, the medical monitor will be contacted immediately to assist with grading the reaction.

Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- A Grade 3 hypersensitivity reaction consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or asymptomatic hypotension not requiring treatment.
- A Grade 4 hypersensitivity reaction (ie, anaphylaxis) is a life-threatening event characterized by the same symptoms as in a Grade 3 reaction but also complicated by symptomatic hypotension or oxygen saturation of 90% or less.

Treatment of Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- Stop the infusion immediately and disconnect infusion tubing from the subject.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Contact Human Genome Sciences to report an SAE and fax SAE worksheet.

HGS Approval Page

PPD

PPD PhD
Senior Vice President, Regulatory Affairs

21 Dec 10
Date

PPD

PPD PPD MD
Executive Vice President, Research and Development

22 DEC 10
Date

CLINICAL PROTOCOL HGS1012-C1103
Protocol Amendment: 00
Date: 14 September 2010

TITLE OF STUDY:

A RANDOMIZED, MULTI-CENTER, BLINDED, PLACEBO-CONTROLLED STUDY OF MAPATUMUMAB ([HGS1012], A FULLY-HUMAN MONOCLONAL ANTIBODY TO TRAIL-R1) IN COMBINATION WITH SORAFENIB AS A FIRST-LINE THERAPY IN SUBJECTS WITH ADVANCED HEPATOCELLULAR CARCINOMA

STUDY SPONSOR: Human Genome Sciences, Inc.
14200 Shady Grove Road
Rockville, Maryland 20850

EudraCT Number: 2010-020798-17

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with Good Clinical Practice standards as defined by the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice, all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator:

Signature *Date*

Name (please type or print)

Institution

Address

Study Synopsis

Study Number: HGS1012-C1103

Title of the Study: A Randomized, Multi-Center, Blinded, Placebo-Controlled Study of Mapatumumab ([HGS1012], a Fully-Human Monoclonal Antibody to TRAIL-R1) in Combination with Sorafenib as a First-Line Therapy in Subjects with Advanced Hepatocellular Carcinoma

Clinical Development Phase: 2

Objectives:

Primary:

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

Secondary:

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

Diagnosis & Inclusion Criteria:

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
   - Located in the liver.
   - Can be accurately measured in at least 1 dimension.
   - Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
   - Suitable for repeat measurement.
   - Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be confirmed by the blinded, independent, central read (BICR) prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count $\geq 1.5 \times 10^9$ /L or ≥ 1500 /mm^3.
   - Platelet count $\geq 50 \times 10^9$ /L or $\geq 50{,}000$ /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal.
   - Serum albumin ≥ 2.5 g/dL or ≥ 25 g/L.
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

Exclusion Criteria:

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. Previously received mapatumumab and/or sorafenib.
4. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.
5. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
6. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
7. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
8. Hepatic encephalopathy, per the investigator's evaluation.

9. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
10. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
11. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
12. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
13. Known human immunodeficiency virus infection.
14. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
15. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
16. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
17. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
18. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
19. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
20. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
21. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
22. Hepatitis B virus DNA levels > 2,000 IU/mL.

Study Design and Schedule:

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma. In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio to receive 30 mg/kg mapatumumab or placebo.

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Approximately 100 advanced HCC subjects will be randomized/enrolled.

Study Treatment:

Mapatumumab will be supplied in open label vials and third party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent but independent of all other study activities. All other study personnel, the subject, the Sponsor will remain blinded to the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle.

Arm B: Sorafenib 400 mg orally twice daily continuously + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle.

Subjects will continue to receive study treatment(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiographic progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiographic progression. All subjects will have an end of treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks, starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented) and then every 3 months thereafter for survival until at least 90% of the subjects have met the survival endpoint.

Disease Assessments:

Radiologic disease assessments along with assessment of alpha fetoprotein will be performed at the end of every two 21-day cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The disease assessment will be performed and documented no earlier than 5 days before the start of the next cycle. Clinical responses will be evaluated according to mRECIST for HCC (see Section 6.7 and Appendix 5). The same assessment method will be used throughout the study for each subject. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent, central reader (BICR) for confirmation of disease progression. Partial response (PR) and complete response (CR) will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR). All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

Safety Assessments:

The safety of sorafenib and mapatumumab will be assessed by evaluation of the type, frequency, and severity of adverse events (ie, according to the NCI-CTCAE Version 4.0 grading) and changes in clinical laboratory tests (hematology and clinical chemistry) and immunogenicity over time. In the event that an adverse event does not have an NCI-CTCAE Version 4.0 grading, the severity grades in Section 8.6 will be used. Adverse events (including serious adverse events) will be captured from the start of study agent administration (sorafenib and/or mapatumumab/placebo) through at least 30 days following the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. Laboratory assessments will be performed at screening, and during each study visit outlined in the study calendar found in Section 6.3.

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

Immunogenicity:

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

Dose Modification/Delay:

Dose modifications will not be allowed for mapatumumab/placebo. Dose modifications of sorafenib for toxicity will be made according to the guidelines provided in the treatment section (Section 5.2.3) of the protocol.

Details regarding pre-treatment and management of hypersensitivity reactions related to mapatumumab are provided in Section 5.1.5 and Appendix 8.

Pharmacokinetics:

Multiple blood specimens will be obtained from subjects for serum mapatumumab concentration determinations as outlined in Table 6-1.

Pharmacodynamics:

Subjects will be given the option to participate in a biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and several blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The biomarker sub-study is detailed in Appendix 6.

Exploratory Assessments:

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

Study Endpoints:

The following will be evaluated (these endpoints and the respective analyses are defined in Section 9):

Primary:

- Time to progression (TTP).

Secondary:

- Overall survival.
- Progression-free survival.
- Objective response (complete response [CR] + partial response [PR]).
- Disease control (CR + PR + stable disease [SD]).
- Response duration and time to response in responders.
- Frequency and severity of treatment-emergent adverse events.
- Laboratory parameters.
- Serum mapatumumab concentrations for use in a population pharmacokinetic analysis.

Statistical Methods:

Sample Size:

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

Statistical Analysis:

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with logrank testing for a difference between treatment groups controlling for factors stratifying the

randomization. Secondary analyses include estimates, using Kaplan Meier methods, of median progression-free survival (PFS) and median overall survival (OS) along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test). For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

Study Calendar:

The study calendar is located in Section 6.3 of the protocol.

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List of Abbreviations

AE	adverse event
AFP	α - fetoprotein
ALT	alanine transaminase
AST	aspartate transaminase
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central read
CR	complete response
CT	computerized tomography
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
Fc	heavy chain constant region or fragment of antibody
GGT	gamma-glutamyl transpeptidase
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HGS	Human Genome Sciences
HGSRC	Human Genome Sciences Review Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IR	incomplete response
IRB	Institutional Review Board
kg	kilogram
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mRECIST	modified RECIST assessment for HCC
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
ng	nanogram
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease
PK	pharmacokinetics
PPT	partial thromboplastin time
PR	partial response
PS	performance status
PT	prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors

RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TRAIL	tumor necrosis factor-related apoptosis-inducing ligand
TRAIL-R1	TRAIL receptor 1
TRAIL-R2	TRAIL receptor 2
TTP	time to progression

1 Background

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma is the 5th most common cancer worldwide accounting for 2% of all malignancies. It is the 3rd leading cause of cancer-related death globally with 1 million new cases a year (WHO, 2007; IACR, 2002; Ferlay et al, 2004; Lopez et al, 2006).

Hepatocellular carcinoma is more prevalent in males with a male:female ratio as high as 8:1. Depending on the endemic risk factors, hepatocellular carcinoma is diagnosed during the 4th through 6th decades of life. The reported incidence of hepatocellular carcinoma is increasing because of a better ability to diagnose the disease and because of the long-term consequences of hepatitis C virus (HCV) and hepatitis B virus (HBV) infection (Reis et al, 2006). Worldwide the most common cause of hepatocellular carcinoma is chronic HBV infection (El-Serag et al, 2003). Endemic areas thus include China, South Asia and South Africa where the incidence of hepatocellular carcinoma can be as high as 120 cases per 100,000. In the United States, where HCV and alcohol are the main risk factors, the age-adjusted incidence rates have increased from 1.4 cases per 100,000 in 1980 to a current incidence of 4 cases per 100,000. This equates to about 8500-11,000 new cases diagnosed each year (IACR, 2002; Ferlay et al, 2004; Pawlik et al, 2004; Edwards, et al, 2005; Jemal et al, 2007; Bosch et al, 2004).

1.2 Treatment Options for Patients with Hepatocellular Carcinoma

Surgery, including transplantation, is the only curative modality for hepatocellular carcinoma (Venook, 1994; Cha et al, 2003). The 5-year survival rate for patients with unresectable hepatocellular carcinoma is 11% in the US (ACS, 2007), < 8% in Europe (Capocaccia et al, 2007), and < 10% in Asia (Teo and Fock, 2001). Symptomatic hepatocellular carcinoma has a very poor prognosis with a median survival of 1–8 months (Former et al, 2006; Llovet et al, 1999a, b).

Sorafenib, a multikinase inhibitor, is the 1st systemic therapy to significantly impact survival in patients with advanced hepatocellular carcinoma, as demonstrated in an international, multicenter Phase 3, placebo-controlled trial (Llovet et al, 2007). Sorafenib was approved in the United States and European Union for the 1st-line treatment of advanced hepatocellular carcinoma in late 2007 and the 2008 National Comprehensive Cancer Network guidelines have been updated with the addition of sorafenib as a treatment option for hepatocellular carcinoma patients. The updated Barcelona Clinic Liver Cancer (BCLC) guidelines recommend sorafenib for hepatocellular carcinoma patients with BCLC Advanced Stage (C) (Forner et al, 2010).

1.3 The Role of the TRAIL Pathway in HCC

1.3.1 TRAIL and TRAIL Receptors

TRAIL is a member of the tumor necrosis factor (TNF) ligand superfamily, with homology to Fas/Apo1 ligand (Pitti et al, 1996; Wiley et al, 1995). TRAIL induces programmed cell death primarily in tumor cells through activation of TRAIL death receptors, TRAIL-R1 (death receptor 4) or TRAIL-R2 (death receptor 5) (Ashkenazi et al, 1999; Evdokiou et al,

2002; Kothny-Wilkes et al, 1998; Lawrence et al, 2001; Pitti et al, 1996; Walczak et al, 1999; Wiley et al, 1995).

TRAIL-R1, the target of mapatumumab, is detectable on tumor cells derived from colon, lung, liver, gastric, pancreas, uterus and esophagus and in tissue sections from various tumors of the colon, lung, pancreas, liver and stomach without significant expression in parallel normal tissues (Halpern et al, 2004; Roach et al, 2004).

1.3.2 TRAIL and HBV/HCV Infection

Acutely infected tissues, including the liver, utilize the TRAIL pathway to eliminate virally and bacterially infected cells (Herr et al, 2007). In viral hepatitis, TRAIL and 1 of its receptors, TRAIL-R2, are upregulated and contribute to the elimination of infected hepatocytes associated with viral hepatitis (Bantel and Schulze-Osthoff, 2003; Lin et al, 2002; Matsuda et al, 2005). In addition to HBV and HCV infection, steatosis, exposure to bile acids and chronic alcohol exposure induce increased expression of TRAIL and TRAIL-R2, but not TRAIL-R1, in human hepatocytes (Dunn et al, 2007; Mundt et al, 2005). Cell surface expression of TRAIL-R2, but not TRAIL-R1, was altered and responsible for sensitization to TRAIL in hepatocytes exposed to bile acids (Higuchi et al, 2001; Malhi et al, 2007). These findings have been reproduced in preclinical models. Non-virally infected hepatocytes are refractory to TRAIL and TRAIL-R agonists but exposure of HCV-infected hepatocytes to TRAIL leads to a significant level of apoptosis (Volkmann et al, 2007). Inhibition of the TRAIL pathway may protect infected cells from apoptosis and allow for chronic infection (Mundt et al, 2003). Recent non-clinical observations demonstrated that natural killer cells expressing the ligand TRAIL, are enriched in the livers of patients with chronic HBV infection, and TRAIL is overexpressed in the livers of patients with HCV-associated steatosis (Mundt et al, 2005).

In summary, preclinical data suggest that mapatumumab may promote apoptosis of cancer cells, including hepatocellular carcinoma cells. Whether viral infection, including HBV or HCV infection, will attenuate or modulate the effects of mapatumumab on hepatocytes is not yet known, but experience to date in a Phase 1b trial of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody indicates that the safety experience is consistent with underlying disease and known sorafenib toxicities (see Section 1.2).

1.4 Mapatumumab

1.4.1 Mapatumumab Pharmacology

Mapatumumab is a fully human, agonist monoclonal antibody that activates the cell death pathway in tumor cells by specifically binding to TRAIL-R1 with high affinity. Mapatumumab efficiently induces apoptosis in human cancer cell lines expressing the TRAIL-R1 protein on the cell surface. Nonclinical studies have demonstrated that mapatumumab can induce cytotoxicity in multiple tumor cell lines representing both solid and hematological malignancies, including cancers of the biliary tract, colon, lung, breast, pancreas, esophagus, ovary, kidney, uterus, as well as lymphoma and various leukemias. Mapatumumab has also demonstrated anti-tumor activity as a single agent, preventing

tumor growth and in some cases causing regression of tumors in xenograft tumor models of multiple human malignancies, including lung, colon, kidney, and uterus (Camidge, 2007; Georgakis et al, 2005; Jin et al, 2007; Humphreys, 2004; Marini et al, 2006; Menoret et al, 2006; Pukac et al, 2005).

The relationship between receptor expression and response to therapy with mapatumumab remains unclear. In vitro studies of cell lines have shown that TRAIL-R1 expression level is not a consistent predictor of response to mapatumumab. Although both TRAIL-R1 expression and apoptosis in response to mapatumumab are increased in many tumor cell lines as compared with normal diploid cells, there are examples of mapatumumab cytotoxicity on cell lines with very low levels of detectable receptor, and conversely, mapatumumab resistant cell lines that have relatively high levels of TRAIL-R1 cell surface expression.

Tumor cell cytotoxic activity can be enhanced when mapatumumab is administered in combination with chemotherapeutics or other anti-neoplastic agents. Enhanced apoptotic signaling, in vitro cell killing and in vivo anti-tumor activity have been observed when mapatumumab has been combined with various types of therapeutic agents and treatments including microtubule poisons, anti metabolites, topoisomerase inhibitors, proteosome inhibitors, platinum agents and radiation. Both the level and spectrum of activity of mapatumumab is enhanced in in vitro cytotoxicity and in vivo xenograft studies in combination with various chemotherapeutic and anti-neoplastic agents, including a xenograft model of hepatocellular carcinoma in combination with cisplatin and gemcitabine (Camidge, 2007; Pukac et al, 2005; Georgakis et al, 2005; Humphreys, 2004; Jin et al, 2007; Human Genome Sciences data on file).

Please refer to the mapatumumab Investigator's Brochure for detailed information regarding the nonclinical pharmacology, toxicology, and PK of mapatumumab.

1.4.2 Non-Clinical Mapatumumab Safety Studies

To assess the nonclinical safety of mapatumumab, a 6-month toxicity study, with a 4-month recovery period, was conducted in chimpanzees. Mapatumumab was administered intravenously at up to 40 mg/kg every 10 days. No mapatumumab-specific toxicity was identified and no anti-mapatumumab antibodies were detected.

To assess its off-target effects, mapatumumab was administered intravenously weekly to cynomolgus monkeys, whose TRAIL R1 homolog does not bind mapatumumab. Mapatumumab was well tolerated at doses of up to 50 mg/kg and was not highly immunogenic: of the 40 monkeys treated, 1 developed anti-mapatumumab antibodies. The positive response was observed in an animal in the high dose (50 mg/kg) group.

In vitro, mapatumumab was found to decrease viability of normal human hepatocytes, although the observed effect was less than that observed with TRAIL. This effect was variable across donors and did not amplify with increasing concentrations of mapatumumab. It should be noted that in clinical studies, plasma mapatumumab concentrations have been achieved that are > 1100–fold greater than the minimum exposure resulting in reduced in vitro hepatocyte viability. Despite this, the clinical results do not reveal evidence of hepatotoxicity in those

studies. Hence it appears that the in vitro hepatocyte viability assay is not predictive of mapatumumab effects in vivo.

1.4.3 Clinical Experience with Mapatumumab

Over 400 subjects have received mapatumumab in clinical trials to date. Preliminary clinical data are available from 218 subjects who received mapatumumab as a single agent at doses ranging from 0.01 to 20 mg/kg across 6 clinical trials.

Based on available data, mapatumumab appears to be well tolerated and no significant safety issues have been observed. Adverse events have generally been mild to moderate in severity, manageable, and do not appear related to dose. The most frequently reported treatment-related adverse events occurring in > 10% of subjects were fatigue, hypotension, nausea and pyrexia. Severe events have been uncommon and generally judged not related to mapatumumab. Severe events judged at least possibly related to mapatumumab have been observed and a complete list can be found in the mapatumumab Investigator's Brochure. Grade 3 or Grade 4 hematologic, renal, or hepatic laboratory abnormalities also have been relatively uncommon with no significant trend or dose-response evident. Lymphopenia was the most commonly observed laboratory abnormality, but tended to be intermittent and reversible and was not associated with infectious events.

In subjects with solid tumors, stable disease has been the best response observed with mapatumumab as a single-agent. However, 2 complete responses (CRs) and 1 partial response (PR) were observed in subjects with follicular lymphoma.

In addition, preliminary clinical data are available from 234 subjects who received mapatumumab at doses ranging from 1 to 30 mg/kg every 21 days in combination with chemotherapy in 5 clinical trials (carboplatin/paclitaxel [N = 100], gemcitabine/cisplatin [N = 49], bortezomib [n = 69], or sorafenib [n = 16]. Mapatumumab has been generally well tolerated; adverse events and laboratory abnormalities have been consistent with those expected with underlying disease or chemotherapy. A listing of severe events considered at least possibly related to mapatumumab can be found in the mapatumumab Investigator's Brochure. The most commonly occurring laboratory abnormalities have been hematologic (ie, anemia, neutropenia, thrombocytopenia, and leukopenia), as expected with chemotherapy. Grade 3/4 laboratory abnormalities have been relatively uncommon. Higher frequencies of Grade 3/4 neutropenia, leukopenia, lymphopenia, and thrombocytopenia have been observed. Data from randomized Phase 2 studies in combination with chemotherapy suggest that mapatumumab may increase rates of lymphopenia.

One subject receiving mapatumumab in combination with carboplatin/paclitaxel has achieved a CR. Twenty-two subjects receiving mapatumumab in combination with paclitaxel/carboplatin and 12 subjects receiving mapatumumab in combination with gemcitabine/cisplatin have achieved PRs. Three subjects receiving mapatumumab in combination with bortezomib achieved CRs; 25 subjects receiving mapatumumab in combination with bortezomib achieved a PR.

1.5 Rationale for the Evaluation of Mapatumumab in Combination with Sorafenib in Hepatocellular Carcinoma

Sorafenib is the standard of care for treatment of patients with advanced hepatocellular carcinoma. Sorafenib is a multikinase inhibitor that targets the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase signaling pathway, blocks tumor angiogenesis and induces apoptosis (Panka et al, 2006; Rahmani et al, 205; Yu et al, 2005; Wilhelm et al, 2004). Sorafenib was approved by the European Medicines Agency and the Food and Drug Administration in 2007 for treatment of patients with hepatocellular carcinoma based on the demonstration of improved overall survival in the 602 patient randomized, placebo-controlled, Phase 3 "Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol" (SHARP) trial. Approximately half the 602 patients had either hepatitis C virus or hepatitis B virus as underlying etiology and 26% had alcohol-related cirrhosis. The median overall survival was 10.7 months for patients in the sorafenib arm compared with 7.0 months for patients in the placebo arm (hazard ratio in the sorafenib group, 0.69 95% confidence interval, 0.55 to 0.87; $p < 0.001$). The median time to radiologic progression was 5.5 months in the sorafenib arm, compared with 2.8 months in the placebo arm ($p < 0.0001$) (Llovet et al, 2008). Seven patients in the sorafenib group (2%) and 2 patients in the placebo group (1%) had a PR; no patients had a CR.

A 2nd randomized, placebo-controlled Phase 3 trial was conducted in the Asia-Pacific region (Cheng et al, 2009). The 226 patients randomly assigned to sorafenib or placebo in this trial appeared to have more advanced disease than those in the SHARP trial, with a higher frequency of extrahepatic spread, poorer ECOG PS, and higher levels of AFP, but still showed a benefit from treatment with sorafenib. The majority (73%) had hepatitis B virus as an underlying etiology. The median overall survival was 6.5 months for patients in the sorafenib arm, compared with 4.2 months in the placebo group (hazard ratio, 0.68, 95% confidence interval, 0.50-0.93; $p = 0.014$). The median time to progression was 2.8 months in the sorafenib group, compared with 1.4 months in the placebo group (hazard ratio, 0.57, 95% confidence interval 0.42-0.79; $p = 0.0005$).

The mechanisms of sorafenib and mapatumumab action suggest that these agents could interact synergistically. Sorafenib sensitizes human cancer cell lines, including cell lines derived from hepatocellular carcinoma, to apoptotic stimuli by reducing expression of apoptotic regulatory proteins; Mcl-1, Bcl-xL, and FLIP (Kim et al,2008; Koehler et al, 2009; Rosato et al, 2007; Liu et al, 2006; Rahmani et al, 2005; Yu et al, 2005). Mcl-1, Bcl-xL and FLIP have also been shown to mediate sensitivity of a wide range of tumor cell lines to TRAIL receptor agonists (Meng et al, 2007; Rosato et al, 2007; Llobet et al 2010; Blechacz et al, 2009; Katz et al, 2009; Huang and Sincrope, 2010; and Menoret et al, 2006). Recent studies demonstrated the combination of sorafenib with TRAIL or TRAIL receptor antibodies has significant activity in hepatocellular carcinoma cell lines (Koehler et al, 2009) and colon tumor xenografts (Ricci et al, 2007) that were resistant to TRAIL and an antibody against TRAIL-R2.

Mapatumumab activity has been evaluated preclinically in hepatocellular carcinoma cell lines by in vitro cytotoxicity assays both as a single agent and in combination with doxorubicin, cisplatin, gemcitabine or sorafenib. Single agent mapatumumab activity was observed in 4 of

10 hepatocellular carcinoma cell lines. Increased in vitro cytotoxicity, including examples of synergy, were observed in 8 of 10 cell lines when mapatumumab was combined with doxorubicin or cisplatin or the combination of cisplatin and gemcitabine (Humphreys et al, 2008). Two of these hepatocellular carcinoma cell lines were evaluated for in vitro cytotoxicity of mapatumumab in combination with sorafenib. One displayed an increase in cytotoxicity from 30% to 60% when treated with a combination of sorafenib and mapatumumab. Importantly, treatment of a primary human hepatocyte cell line did not induce any apoptosis at doses of mapatumumab that were cytotoxic to hepatocellular carcinoma cell lines (PPD and PPD [personal communication], 2008; Abdulghani et al, 2008). Therefore, collectively, the expression of TRAIL-R1 in hepatocellular carcinoma and preclinical activity observed with combinations of mapatumumab with chemotherapy or sorafenib supports the rationale that this combination may be able to effectively target hepatocellular carcinoma.

1.6 Rationale for Dose Selection

As of June 2010, mapatumumab has been administered with chemotherapy (ie, carboplatin/paclitaxel, gemcitabine/cisplatin, bortezomib, or sorafenib) to 234 subjects, including 61 subjects who received 20 mg/kg and 50 subjects who received 30 mg/kg mapatumumab. Based on available data, mapatumumab in combination with chemotherapy is generally well tolerated at dose levels up to and including 30 mg/kg, and no significant safety issues have been observed in the course of the clinical trials even at the higher doses.

Preliminary PK data are available for subjects who received 1, 10, 20 or 30 mg/kg mapatumumab in combination with gemcitabine and cisplatin (n = 49), 10 or 30 mg/kg mapatumumab in combination with paclitaxel and carboplatin (n = 73), and 3, 10, or 30 mg/kg mapatumumab in combination with sorafenib (n = 17). Serum or plasma mapatumumab concentrations are consistently within the range of expected concentrations predicted from Phase 1 study results in solid tumor patients administered mapatumumab as monotherapy. Mapatumumab PK is linear and not affected by the addition of therapeutic agents. As expected, the observed peak and trough levels of mapatumumab at 30 mg/kg are 2 to 3 times higher than those observed at 10 mg/kg. Exposure appears to increase in proportion to dose and exposures for a given dose are similar across studies.

A Phase 1b dose escalation study of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma who are positive for hepatitis B surface antigen or hepatitis C antibody is being conducted. Safety observations have been consistent with the underlying disease and known sorafenib toxicities. As of June 2010, 6 subjects have received 3 mg/kg, 9 subjects have received 10 mg/kg, and 1 subject has received 30 mg/kg mapatumumab. The number of cycles completed ranges from 1 to 20; 4/16 (25.0%) of subjects have completed 11 or more cycles. Adverse events have generally been consistent with published reports of the toxicities associated with sorafenib and previous experience with mapatumumab, as well as underlying disease. The most frequently occurring treatment-emergent adverse events, regardless of severity or attribution of causality, include diarrhea (10/16, 62.5%), fatigue (9/16, 56.3%), nausea (9/16, 56.3%), and vomiting (7/16, 43.8%). Serious adverse events, regardless of attribution of causality, include hypertension, upper respiratory tract infection, atrial fibrillation, hyperbilirubinemia,

hypoglycemia, and hepatic pain. Severe adverse events considered at least possibly related to mapatumumab or its interaction with sorafenib include elevated lipase (3/16, 18.8%), hepatic pain (1/16, 6.3%), and thrombocytopenia (1/16, 6.3%). Laboratory abnormalities have generally been mild or moderate in severity, manageable, and/or consistent with those expected with chemotherapy or the underlying disease. The most frequent Grade 3 or Grade 4 laboratory abnormalities include elevated total bilirubin (Grade 3, 4/16, 25.0%; Grade 4, 1/16, 6.3%) and lymphopenia (Grade 3, 3/16, 18.8%; Grade 4, 2/16, 12.5%). Additional information on the safety experience can be found in the mapatumumab Investigators' Brochure.

Based on the information currently available, the safety profile continues to be favorable, supporting continued evaluation of mapatumumab in combination with chemotherapy, including sorafenib. The maximum tolerated dose has not been reached in any of the Phase 1 or Phase 2 trials conducted to date. Thus, further evaluation of the 30 mg/kg dose is warranted.

The dose of sorafenib for this study, 400 mg twice daily, is the approved dose for the treatment of unresectable hepatocellular carcinoma.

2 Study Objectives

2.1 Primary Objective

- To evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

2.2 Secondary Objective

- To evaluate the safety of the mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.
- To determine serum mapatumumab concentrations.

3 Study Design

3.1 Basic Design Characteristics

This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

In addition to receiving sorafenib, subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio: 30 mg/kg mapatumumab or placebo.

Mapatumumab will be supplied in open label vials and third party unblinding will be employed. The study agent will be reconstituted by the unblinded site pharmacist or unblinded designee. The unblinded site pharmacist or unblinded designee will also be the person responsible for receiving and dispensing study agent, but independent of all other study activities. All other study site personnel, the subject, and the Sponsor will remain blinded to

the study agent received. Separate monitors will be responsible for the clinical (blinded monitor) and study agent (unblinded monitor) aspects of the study.

Number of Subjects:

Approximately 100 subjects with advanced HCC will be randomized/enrolled.

Treatment Groups:

Subjects will receive treatment every 21 days (ie, a cycle) as outlined below:

Arm A: Sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle

Arm B: Sorafenib 400 mg orally twice daily continuously in each cycle + mapatumumab (30 mg/kg) intravenously on Day 1 of each cycle

Randomization

Randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2).

Estimated Study Duration:

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib with or without mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Estimated median length of subject treatment is 6-8 months. All subjects will have an End of Treatment visit at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, whichever is later. After discontinuation of treatment, subjects will continue to be followed for radiologic disease assessments every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on treatment, until documented radiologic disease progression (if not previously documented). Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

4 Inclusion and Exclusion Criteria

4.1 Inclusion Criteria

Subjects enrolled in the study must meet the following inclusion criteria:

1. Child-Pugh Class A (see Appendix 1).
2. Barcelona Clinic Liver Cancer (BCLC) advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate (see Appendix 2).
3. Measurable disease demonstrating intratumoral arterial enhancement by contrast enhanced computerized tomography (CT), with use of multislice scanners, or contrast enhanced

dynamic magnetic resonance imaging (MRI), with at least 1 tumor lesion that meets the following criteria:
- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is > 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

4. Radiologic eligibility (measurable disease) must be must be confirmed by the BICR prior to randomization.
5. Adequate bone marrow, renal and liver function:
   - Absolute neutrophil count ≥ 1.5 x 10^9 /L or ≥ 1500 /mm^3.
   - Platelet count ≥ 50 x 10^9 /L or ≥ 50,000 /mm^3.
   - Hemoglobin ≥ 9 g/dL (≥ 5.6 mmol/L) without growth factor support or transfusional support.
   - Serum creatinine level ≤ 2.0 mg/dL or ≤ 176.8 µmol/L.
   - Total bilirubin < 3.0 mg/dL or < 51.3 µmol/L.
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 5.0 x upper limit of normal.
   - Amylase and lipase ≤ 1.5 x upper limit of normal.
   - Serum albumin ≥ 2.5 g/dL or ≥ 25 g/L.
   - International normalized ratio ≤ 1.5.
6. Performance status of 0, 1 or 2 on the Eastern Cooperative Oncology Group (ECOG) Scale (see Appendix 3).
7. Age 18 years or older.
8. Have the ability to understand the requirements of the study, provide written informed consent (including consent for the use and disclosure of research-related health information), and comply with the study and follow-up procedures.

4.2 Exclusion Criteria

Subjects will be excluded from participating in the study if they meet any of the following exclusion criteria:

1. Any co-morbid condition that in the judgment of the investigator renders the subject at high risk of treatment complications or reduces the possibility of assessing clinical effect.
2. Received prior investigational or non-investigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including but not limited to monoclonal antibodies, small molecules or other immunotherapy) to treat hepatocellular carcinoma.
3. Previously received mapatumumab or sorafenib.
4. Underwent resection, radiofrequency ablation, radiation or chemoembolization within 4 weeks before enrollment or not recovered from such treatments.

5. Need for concomitant anticancer therapy (surgery, radiation therapy, chemotherapy, immunotherapy, radiofrequency ablation) or other investigational agents during the study treatment period.
6. Major surgery (ie, the opening of a major body cavity, requiring the use of general anesthesia) within 4 weeks before enrollment; minor surgery (except for insertion of vascular access device) within 2 weeks before enrollment; or not yet recovered from the effects of the surgery.
7. Systemic steroids within 1 week before enrollment except steroids used as part of an antiemetic regimen or maintenance-dose steroids for non-cancerous disease.
8. Hepatic encephalopathy, per the investigator's evaluation.
9. History of clinically significant gastrointestinal bleeding requiring procedural intervention (eg, variceal banding, transjugular intrahepatic portosystemic shunt procedure, arterial embolization, topical coagulation therapy) within 4 weeks before enrollment.
10. Gastrointestinal disease resulting in an inability to take oral medication or a requirement for intravenous hyperalimentation.
11. History of any infection requiring hospitalization or intravenous antibiotics within 2 weeks before enrollment.
12. Known brain or spinal cord metastases unless adequately treated (surgery or radiotherapy) with no evidence of progression and neurologically stable off anticonvulsants and steroids.
13. Known human immunodeficiency virus infection.
14. Unstable angina, myocardial infarction, cerebrovascular accident, ≥ Class II congestive heart failure according to the New York Heart Association Classification for Congestive Heart Failure (see Appendix 4) within 6 months before enrollment.
15. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin.
16. Uncontrolled hypertension (systolic blood pressure > 150 mmHg or diastolic pressure > 90 mmHg despite optimal medical management).
17. Using and unable to discontinue use of concomitant strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital).
18. Pregnant female or nursing mother. All females with an intact uterus (unless amenorrheic for the 24 months before enrollment) must have a negative serum pregnancy test at screening. All non-sterile or non-postmenopausal females must practice a medically accepted method of contraception over the course of the study and for 60 days after the last dose of study agent.
19. Males who do not agree to use effective contraception during the study and for a period of 60 days following the final dose of study agent.
20. Subject is currently enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s) or subject is receiving other investigational agents.
21. Acute or chronic severe renal insufficiency (glomoerular filtration rate < 30 mL/min/1.73 m^2) or acute renal insufficiency of any severity due to the hepato-renal syndrome.
22. Hepatitis B virus DNA levels > 2,000 IU/mL.

5 Study Treatment Regimen

Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, the sorafenib should be taken at the same time as any other calendar day.

5.1 Mapatumumab and Placebo

5.1.1 Formulation

Mapatumumab will be supplied as a lyophilized formulation in sterile, single-use 10 mL vials containing 100 mg mapatumumab. Upon reconstitution with 5.0 mL of sterile water for injection, each vial will contain 20 mg/mL mapatumumab in 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 19 mg/mL glycine, 5 mg/mL sucrose, 0.2 mg/mL polysorbate 80, pH 6.5.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

5.1.2 Packaging, Labeling, Preparation, and Storage

The Pharmacy Manual will provide instructions for preparation and storage of study agent. The product will be securely stored at 2-8ºC.

The study agent label will contain, at a minimum, the following information:

- Product name
- Concentration
- Lot number
- Storage instructions
- Investigational drug statement
- Manufacturer's name and address

Study agent inventory/accountability forms will be examined and reconciled by the unblinded study monitor or designee. At the end of the study, all used and unused investigational study agent will be accounted for on a study agent accountability form provided to the investigator by the Sponsor or designee. Please refer to the HGS1012-C1103 Pharmacy Manual for more details regarding storage, handling and drug accountability.

5.1.3 Mapatumumab/Placebo Dose, Route of Administration and Schedule

The dose of mapatumumab is 30 mg/kg. Mapatumumab dose calculations will be based upon the subject's weight measured on Day 1 or within 3 days before Day 1 of each cycle. The planned duration of each treatment cycle will be 21 days. Mapatumumab/placebo will be administered on Day 1 of each cycle.

After reconstitution with sterile water for injection, the calculated mapatumumab dose to be administered to the subject will be further diluted in normal saline to a total volume of 250 mL for intravenous infusion. After adding the reconstituted product, the bag will be gently inverted to mix the solution. Following reconstitution and/or dilution in normal saline, mapatumumab will be stored at 2-8ºC. The product will be administered to the subject within 8 hours of reconstitution. Refer to the HGS1012-C1103 Pharmacy Manual for instructions on admixing and administering study agent.

Two hundred-fifty mL normal saline solution for intravenous infusion will be administered as placebo for mapatumumab.

Mapatumumab/placebo will be infused at a constant rate over 1 hour.

Infusion and hypersensitivity reactions may occur. A suggested pre-medication regimen for mapatumumab/placebo consists of diphenhydramine and acetaminophen administered within 1 hour prior to the start of the mapatumumab/placebo dose. Use of a pre-medication regimen and alternatives to this regimen are at the investigator's discretion.

Subjects will be monitored closely during and after infusion for any sign of acute adverse reaction. If an allergic reaction occurs, see Section 5.1.5 and Appendix 8 for suggested medical management.

5.1.4 Mapatumumab/Placebo Dose Toxicity/Delay

Mapatumumab/placebo may be delayed up to 2 weeks for toxicities considered related to mapatumumab as described below or if the investigator believes that a delay in dosing is warranted in the interest of subject safety.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.0) will be used to grade AEs.

- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transient transaminase, amylase and lipase abnormalities for which the following criteria will apply:
  - Grade 3 or Grade 4 elevations in transaminases that do not resolve to baseline or Grade 1 before the next cycle.
  - Grade 4 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, or resulting in chronic damage to the pancreas.
  - Any Grade 4 elevations in lipase or amylase for > 4 consecutive days.

If mapatumumab/placebo is delayed for toxicity and the toxicity does not resolve (≤ Grade 1) or return to baseline within 2 weeks after the delayed dose was originally scheduled (based on a 21-day treatment cycle), the subject will be withdrawn from further treatment with mapatumumab/placebo. If mapatumumab/placebo is delayed because the investigator believes a delay is warranted in the interest of subject safety and dosing of mapatumumab/placebo is not resumed within 2 weeks after the delayed dose was originally scheduled (based on a

21-day treatment cycle), the subject will be withdrawn from future treatment with mapatumumab/placebo. Sorafenib dosing will continue while mapatumumab/placebo dosing is held. The subject will continue receiving sorafenib until radiologic progressive disease or an unacceptable toxicity occurs, at the discretion of the Investigator.

Doses of mapatumumab may not be altered.

5.1.5 Management of Allergic/Hypersensitivity Reactions to Mapatumumab/Placebo

The administration of any recombinant protein has the potential to induce local or system immunologic reactions; subjects could experience, for example, acute allergic reactions. To date, 2 such SAEs have been reported which were considered related to mapatumumab (hypersensitivity and angioedema/facial edema). In the event of allergic/hypersensitivity reactions, investigators will institute treatment measures according to best medical and nursing practice. Guidelines for treatment are provided in Appendix 8.

For a NCI-CTCAE Version 4.0 Grade 3 or Grade 4 hypersensitivity reaction, treatment with mapatumumab/placebo will be discontinued.

If mapatumumab/placebo is discontinued for Grade 3 or Grade 4 hypersensitivity reactions, the subject will continue to receive sorafenib, until radiologic progression or unacceptable toxicity.

5.2 Sorafenib

5.2.1 Packaging, Labeling, Preparation, and Storage

Sorafenib is supplied as tablets, each containing 274 mg sorafenib tosylate, equivalent to 200 mg of sorafenib.

The recommended daily dose of sorafenib is 400 mg (2 x 200 mg tablets) taken orally twice daily without food (at least 1 hour before or 2 hours after a meal).

Sorafenib will be stored at room temperature (15-30°C, 59-86°F) in a dry place.

For country-specific formulation and packaging information, please refer to the instructions provided in the sorafenib product labeling.

Supplier: Commercially available.

5.2.2 Anticipated Toxicities with Sorafenib

Toxicities anticipated with the use of sorafenib include the following:

- Cardiac: Cardiac ischemia and/or infarction, hypertension.
- Dermatologic: Hand-foot skin reaction, rash/desquamation.
- Hemorrhagic: Increased risk of bleeding.
- Gastrointestinal: Gastrointestinal perforation.

- Other: Wound-healing complications, fatigue, weight-loss, alopecia, pruritis, dry skin, diarrhea, anorexia, nausea, vomiting, constipation, liver dysfunction and abdominal pain.

Laboratory abnormalities observed in hepatocellular carcinoma patients treated with sorafenib include hypophosphatemia, lipase elevations, amylase elevations, hypoalbuminemia, international normalized ratio elevations, lymphopenia and thrombocytopenia.

Refer to the product labeling accompanying the product for information approved in your country.

5.2.3 Alteration of Sorafenib Dose/Schedule Due to Toxicity

Sorafenib may be reduced or delayed for toxicities considered related to sorafenib as described below, or if the investigator believes that a reduction in dose is warranted in the interest of subject safety. When a dose reduction is necessary, sorafenib dose may be reduced to 400 mg once daily. If an additional dose reduction is required, sorafenib may be reduced to a single 400 mg dose every other day (see Table 5-1). A maximum of 2 dose reductions of sorafenib will be allowed per subject. Additional dose reductions not mentioned in Table 5-1 will need to be discussed with the medical monitor.

Table 5-1 Sorafenib dose levels

Dose Levels	Sorafenib
0	400 mg twice daily
-1	400 mg once daily
-2	400 mg once every other day

Skin toxicity and hypertension are associated with sorafenib. Guidelines for the management of these events are provided in Table 5-2 and Table 5-3, respectively.

Skin Toxicity

Hand-foot skin reaction and rash are common in subjects treated with sorafenib. Management may include topical therapies for symptomatic relief, temporary treatment interruption and/or dose modification, or in severe or persistent cases, permanent discontinuation. Skin toxicities will be managed according to Table 5-2.

Table 5-2 Dose modifications of sorafenib for skin toxicity

Skin Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, parethesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the subject'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 subject'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 1 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 subject 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 1 dose level (400 mg daily or 400 mg every other day).
	3rd occurrence	Discontinue sorafenib treatment.

Hypertension

Hypertension is a known and potentially serious adverse event associated with sorafenib treatment. Subjects will have their blood pressure monitored and recorded. If the subject's blood pressure is elevated at any time (> 150/100 mmHg), even outside clinic visits, they will contact their study investigator. Guidelines for the management of hypertension are provided in Table 5-3.

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 1	None	Routine	No change
Grade 2 (asymptomatic)	Initiate monotherapy (suggest dihydropyridine calcium channel blocker)	Increase frequency and monitor by a health professional every 2 days until stabilized.	No change
Grade 2 (symptomatic/ persistent) **OR** diastolic BP > 110 mm Hg **OR** Grade 3	Add agent(s): calcium channel blocker (if not already used), K+ channel opener (angiotensin blockers), beta-blocker, thiazide diuretic	Increase frequency and monitor by health professional every 2 days until stabilized; continue monitoring every 2 days to stabilization after dosing restarted.	Hold* sorafenib until symptoms resolve <u>and</u> diastolic BP < 100 mm/Hg Resume treatment at 1 dose level lower**

Table 5-3 Dose modifications of sorafenib for hypertension

Grade (CTCAE v3.0)	Antihypertensive Therapy	Blood Pressure Monitoring	Sorafenib Dose
Grade 4	Discontinue sorafenib	Discontinue sorafenib	Discontinue sorafenib

*Subjects requiring a delay of > 21 days will discontinue sorafenib, in the study investigator's opinion, the subject may benefit from continued treatment.

**Subjects requiring > 2 dose reductions will discontinue sorafenib.

BP = Blood pressure.

Refer to NCI-CTCAE v4.0 for grade definitions.

(concluded)

Guidelines for the management of other non-hematologic and hematologic sorafenib-associated toxicities are provided in Table 5-4. Those toxicities that are at least possibly related to an interaction with mapatumumab/placebo will have the mapatumumab toxicity guidelines in Section 5.1.4 applied.

Table 5-4 Dose modifications of sorafenib for sorafenib-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3*	Grade 4*
Non-hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 1, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 1, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.
Hematologic	Continue at the same dose level	Continue at the same dose level	Withhold dose until toxicity is Grade ≤ 2, then resume treatment at the same dose level. If subject experiences a 2nd Grade 3 toxicity, withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg orally daily and resume treatment.	Withhold dose until toxicity is Grade ≤ 2, then reduce dose to 400 mg daily and resume treatment, or discontinue at the discretion of the principal investigator after discussion with study sponsor.

See Table 5-2 and Table 5-3 for dose modifications due to skin toxicity and hypertension respectively.

*Subjects who develop Grade 3 fever/chills, Grade 3 elevation of hepatic transaminases with ALT and AST < 10X upper limit of normal, Grade 3 hyperlipasemia or hyperamylasemia without clinical or other evidence of pancreatitis, Grade 3 leukopenia, or Grade 3/Grade 4 lymphopenia may continue sorafenib treatment without interruption at the discretion of the investigator.

Sorafenib Discontinuation

Temporary or permanent discontinuation of sorafenib will be considered in subjects who develop cardiac ischemia and/or infarction or severe or persistent hypertension despite institution of antihypertensive therapy. If a subject experiences a bleeding event that necessitates medical intervention or a gastrointestinal perforation, sorafenib will be

permanently discontinued. Subjects, who undergo a surgical procedure or intervention to decrease portal hypertension, including transjugular intrahepatic portosystemic shunt, will discontinue sorafenib.

If the subject is withdrawn from further treatment with sorafenib, the subject may continue to receive mapatumumab/placebo alone every 21 days until radiologic progression or unacceptable toxicity.

5.3 Concurrent Medications and Therapies

5.3.1 Allowable Regimens

Subjects may continue their baseline medication(s). The daily dose of each medication will be maintained throughout the study if possible. If for any reason deemed necessary by the investigator, a subject requires additional medication(s) or change of dose, the medication(s), dosage change, route of administration, and the indication for which it was given must be recorded in the source documents. All concomitant medications will be recorded on the appropriate case report form.

Systemic, inhaled and topical steroids used as part of an antiemetic regimen or maintenance-dose for non-cancerous disease are permitted.

5.3.2 Prohibited Medications

Subjects who require the use of strong CYP3A4 inducers (eg, including but not limited to St. John's Wort, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) are not eligible for this study and use of these agents is prohibited as long as the subject is receiving sorafenib in this study.

Subjects will not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies) or immunotherapy to treat hepatocellular carcinoma during the treatment period. Alternative anticancer therapies may be administered after radiologic disease progression has been documented, but will be avoided if possible during the 30 day safety follow up period after the last dose of study agent (mapatumumab/placebo and/or sorafenib) whichever is last. These medications are allowed in the long-term follow-up period after the 30 day safety follow-up period and documentation of radiologic disease progression.

5.3.3 Prohibited Therapies

Subjects will not undergo major or elective surgery during the treatment period of the study; if surgery is required, the subject will be withdrawn from study treatment.

6 Study Procedures

6.1 Screening Procedures

The nature of this study and the potential risks and benefits associated with participation in the study will be explained to all potential study subjects. Written informed consent (including

consent for the use and disclosure of research-related health information) must be obtained before any screening procedures are performed that are not considered standard of care.

All of the following assessments must be performed within 28 days prior to enrollment:

- Obtain written informed consent for participation in the study.
- Obtain informed consent for participation in the optional biomarker sub-study.
  - If consented, obtain tissue block/slides or cell pellet from diagnostic histologic/ cytologic sample.
- Record demographics.
- Obtain medical history, to include history of all treatments used to treat the current cancer and all prior cancer treatments.
- Perform baseline complete physical examination including body weight and height.
- Assess vital signs (blood pressure, heart rate, respiratory rate and temperature).
- Evaluate performance status (ECOG scale; see Appendix 3).
- Draw blood for laboratory tests (see Appendix 7): complete blood count with differential, chemistry**,** hepatitis B surface antigen, Hepatitis B virus DNA, hepatitis C antibody and testing for serum pregnancy (all females with an intact uterus [unless amenorrheic for the previous 24 months] regardless of age).
- Obtain radiologic disease and AFP assessments. The method of disease assessment, as per mRECIST for HCC (see Appendix 5), will be consistent throughout the study.
- Obtain electrocardiogram.
- Record medications used within 28 days before enrollment.
- Confirm that subject meets all inclusion/exclusion criteria.

6.2 Study Enrollment/Randomization Procedures

Subjects that meet the eligibility criteria will be randomly assigned treatment by a central interactive voice response system in a 1:1 ratio to 1 of 2 treatment arms. The randomization will be stratified according to BCLC advanced stage C vs BCLC intermediate stage B and ECOG performance status (0 vs 1, 2). The 1st planned dose of sorafenib and mapatumumab/placebo will be administered no more than 3 days following randomization and not prior to randomization. All study site personnel (with the exception of the unblinded site pharmacist or unblinded designee), the subject, and the Sponsor will remain blinded to the study agent received.

6.3 On-treatment Study Procedures

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Informed consent		X															
Laboratory																	
CBC with differential; Coagulation parameters	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy	2	X	X														
Hepatitis	1	X															
B and T lymphocyte subsets	3		X				X	X			X						
Immunogenicity	4		X					X				X				X	
Pharmacokinetics	5		X			X		X				X				X	
Biomarkers	6		X	X	X	X	X	X	X	X	X						
Study Agent Admin																	
Sorafenib	7		Twice daily														
Mapatumumab/ Placebo	7		X					X				X					
Physical/Clinical																	
Med Hx / Phys.Exam	-	X															
Vital signs	8	X	X			X	X	X		X	X	X					
Body weight	9	X	X					X				X					
Performance Status	10	X	X					X				X				X	

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	
Record AEs/ Conmeds	11	X	<----------Throughout the study---------->														
Disease Assessments	12	X	Performed at the end of every 2 cycles (ie, Cycles 2, 4, 6) and every 2 cycles thereafter until radiologic PD is documented.														X
α – Fetoprotein (AFP)	12	X	Performed at the end of every 2 cycles (ie Cycles 2, 4, 6) and every 2 cycles thereafter until radiographic PD is documented.														X
ECG	-	X	Repeat as clinically indicated														
Survival	13																X

AE = adverse event; CBC = complete blood count; CT = computerized tomography; ECG -= electrocardiogram; PD = progressive disease.

[1] Safety Labs: Day 1 (complete blood count with differential, coagulation parameters [INR, PT, PTT] and chemistry) must be performed within 3 days prior to dosing on Day 1 of each cycle. See Appendix 7 for a detailed list of required laboratory assessments.

[2] Pregnancy: Serum test at screening, urine test pre-dose Cycle 1 Day 1; must be negative to receive treatment.

[3] B and T lymphocyte subsets: Blood samples for quantification of B and T lymphocytes will be obtained in Cycles 1 and 2 only. Samples will be obtained on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2.

[4] Immunogenicity: Obtain prior to dosing on Day 1 of Cycles 1, 2, 4, 6, every 2 cycles thereafter and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

[5] Pharmacokinetics: Blood specimens will be collected for determination of serum mapatumumab concentrations from subjects as follows: Cycle 1 (on Day 1 prior to the administration mapatumumab/placebo and at the completion of the mapatumumab/placebo infusion, and on Day 8), Cycles 2, 4 and 6 and thereafter on each even cycle (prior to dosing on Day 1), on the day of each disease assessment, and at the end of treatment visit (at least 30 days after the last dose). On days when immunogenicity and pharmacokinetic samples are collected they will be collected together.

[6] Biomarkers: For subjects participating in the optional biomarker sub-study, historical biopsy samples will be collected, if available, and samples will be collected if obtained during the treatment period in Cycle 1 Days 1 (pre-dose mapatumumab), 2, 3, 8 and 15 and Cycle 2 Days 1 (pre-dose mapatumumab), 3, 8 and 15. In addition, blood samples will be obtained as follows: blood for isolation of DNA will be collected once, preferably in Cycle 1. Blood for isolation of serum will be collected in Cycles 1 and 2 (pre-dose on the day of mapatumumab/placebo dosing). Further details on the biomarker sub-study are outlined in Appendix 6.

[7] Study Agent Administration: Sorafenib will be administered at a dose of 400 mg twice daily without food (at least 1 hour before or 2 hours after a meal). On days when both sorafenib and mapatumumab/placebo are administered together, sorafenib should be taken at the same time as any other calendar day.

[8] Vital Signs: Blood pressure will be monitored weekly for the first 6 weeks. Vital signs will be obtained within 30 minutes prior to administration of mapatumumab/placebo and at the end of infusion on Day 1 of each cycle.

[9] Body Weight: To be obtained on the day of or within 3 days before dosing on Day 1 of each cycle.

Table 6-1 Study calendar

			Cycle 1					Cycle 2				Additional Cycles[14]			Safety Follow-up Phase		Long-Term Follow-up
Procedure	Footnotes	Screen Phase	Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15	Day 22 of last cycle on treatment	≥ 30 days following last dose	

[10] Performance Status: Obtained prior to dosing on Day 1 of each cycle.

[11] Adverse Events: AE collection begins with the start of 1st study agent administration. Concurrent medications will be recorded within 28 days prior to Cycle 1 Day 1.

[12] Disease and α – Fetoprotein (AFP) Assessments: Radiologic and AFP assessments will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6, etc). For subjects discontinuing treatment prior to documentation of radiologic disease progression, disease assessments will be performed every 6 weeks (± 3 days), starting 6 weeks after the previous disease assessment while on study, until radiologic disease progression is documented. If disease progression is based only on new lesions or is equivocal, images will be provided to the blinded, independent reader for confirmation of disease progression. All imaging scans used for disease assessments will be made available for independent radiology review by the Sponsor or designee.

[13] Survival**:** Contact will be made with the subject every 3 months to document survival until at least 90% of subjects have met the survival endpoint.

[14] Subjects who discontinue mapatumumab/placebo will complete the current cycle assessments per the study calendar. Subsequently, subjects receiving sorafenib alone will return at least every 21 days and on additional days as clinically indicated for safety labs (CBC with differential, chemistry and coagulation parameters) for the duration of treatment. Disease assessments must be performed every 6 weeks until radiologic disease progression. Adverse events and concomitant medications will be recorded throughout the study.

(concluded)

6.4 Follow-up Procedures

6.4.1 Safety Follow-up

After discontinuation of study treatment, all subjects will return 1 day after cycle completion (approximately Day 22) and at least 30 days after the last dose of sorafenib and/or mapatumumab/placebo, for scheduled safety follow-up assessments as outlined in Table 6-1.

6.4.2 Long-term Follow-up

For subjects discontinuing treatment prior to documentation of radiologic disease progression, and for subjects who experience stable disease or a response (PR, CR) but are no longer receiving treatment, radiologic disease assessments will be performed at 6 week intervals (± 3 days), starting 6 weeks after the previous radiologic disease assessment while on treatment, until radiologic disease progression is documented. Thereafter, subjects will be followed every 3 months for survival until at least 90% of subjects have met the survival endpoint.

6.5 Withdrawal of Subjects from Treatment

Subjects will be free to withdraw from treatment at any time, for any reason, or they may be withdrawn/removed, if necessary, to protect their health (see reasons for withdrawal below). It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawal of subjects will be avoided.

Subjects may be withdrawn from treatment for any of the following reasons:

- Radiologic disease progression.
- Continued unacceptable toxicities despite optimal treatment or dose reduction.
- Intercurrent illness, at the investigator's discretion.
- Withdrawal of consent.
- Non-compliance/Lost to follow-up.
- Pregnancy.
- Termination of the study by the sponsor.

Subjects who withdraw are to be followed for radiologic progression as outlined in Section 6.4.2. In addition, every effort will be made to collect safety information on each subject through 30 days following the last dose of study treatment, unless the subject withdraws consent and refuses to comply with the protocol stipulated safety follow-up and radiologic disease progression assessments, or share information obtained after the date of withdrawal of consent.

6.6 Withdrawal of Subjects from Study

Subjects may be withdrawn from the study for any of the following reasons:

- Withdrawal of consent.

- Non-compliance/Lost to follow-up.
- Termination of the study by the sponsor.

Every effort will be made to collect follow-up information on subjects in the long-term follow-up period of the study, unless the subject withdraws consent and refuses to share information obtained during the long-term follow-up period obtained after the date of withdrawal of consent.

6.7 Disease Response Assessments

Imaging endpoints will be determined using the modified RECIST criteria for HCC proposed by Lencioni and Llovet (2010; mRECIST). mRECIST for HCC is a joint guideline of the American Association for the Study of Liver Diseases and the Journal of the National Cancer Institute.

Lesions which manifest typical imaging characteristics for HCC demonstrate intratumoral arterial contrast on CT and MRI images. mRECIST accounts for newer therapies which may impact tumor vascularity and may not yield a typical cytotoxic decrease in tumor size by incorporating changes in vascularity into the criteria for target lesion response. Diligence in obtaining images during the hepatic arterial contrast enhancement phase is a requirement at baseline and all subsequent scans. The same imaging method must be used at baseline and during follow up.

As in conventional RECIST, overall response is the result of the combined assessment of target, nontarget, and new lesions. There are also specifications for incorporating portal vein thrombosis, portal hepatic lymph nodes, and pleural effusions/ascites into the response assessment. As with conventional RECIST, the appearance of any new lesion overrides any existing lesion response, resulting in classification as progressive disease (PD). Key aspects of mRECIST as adapted for this study are summarized in Appendix 4.

Baseline images will be provided to the BICR for confirmation of radiologic eligibility (measurable disease). Confirmation of radiologic eligibility for the study will be provided to the site by the BICR within 72 hours of receipt of images and will be required for randomization.

Disease assessments and an assessment of α -fetoprotein will be performed at the end of every 2 cycles (ie, Cycles 2, 4, 6 and every 2 cycles thereafter). The response assessment will be performed and documented no more than 5 days before the start of the next cycle. All images will be provided to the BICR following each disease assessment.

If disease progression is based only on new lesions or is equivocal, images will be provided to the BICR for confirmation of radiologic disease progression prior to discontinuing study treatment. PR and CR will be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

7 Pharmacokinetic, Immunogenicity, Pharmacodynamic and Exploratory Assessments

7.1 Pharmacokinetic Assessments

For determination of mapatumumab concentration, serum samples will be collected as outlined in Table 6-1.

A manual will be provided regarding how to obtain blood samples, process samples, collect serum from the blood samples, and how to store and ship the serum samples. Bioanalysis will be carried out at Human Genome Sciences to determine mapatumumab concentration in each serum sample.

7.2 Immunogenicity

Blood samples for serum antibodies to mapatumumab will be obtained as outlined in Table 6-1.

7.3 Pharmacodynamic Assessments

Subjects will be given the option to participate in an exploratory biomarker research sub-study. Consenting subjects will be asked to provide a historically obtained biopsy sample, if available, and blood samples. In addition, samples will be requested from subjects who undergo a biopsy during the treatment period.

To examine and quantify biomarkers present peripherally, blood will be drawn during Cycles 1 and 2, from which DNA and serum proteins will be isolated. The parameters evaluated may include, but may not be limited to, M30, TNFα, sTRAIL, soluble Fas ligand, interferon-α, interferon-γ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, interleukin-12, and FC gamma receptor and interleukin-6 gene polymorphisms. The biomarker sub-study is detailed in Appendix 6.

7.4 Exploratory Assessments (B and T Lymphocyte Subsets)

7.4.1 Rationale for B and T Lymphocyte Analysis

Over 400 subjects have received mapatumumab in doses ranging from 0.01 to 30 mg/kg across multiple Phase 1 and Phase 2 clinical trials in subjects with solid and hematologic malignancies. While there is no evidence to date that mapatumumab exacerbates adverse events associated with chemotherapy, the most commonly observed laboratory abnormality associated with mapatumumab has been lymphopenia. The lymphopenia has been intermittent and reversible and was not associated with infectious events. However, the lymphocyte subpopulation(s) affected have not been characterized.

The evaluation of lymphocytes will include complete blood count/differential and lymphocyte subpopulation analysis (numbers and percentages of T and B cells) by flow cytometry at a central laboratory. Blood samples will be examined by flow cytometry for levels of T helper (CD4+), T cytotoxic (CD8+) and mature B cells (CD19+).

7.4.2 Collection of Samples for B and T Lymphocyte Analysis

Blood samples will be collected for quantification of B and T lymphocyte subsets on Day 1 (prior to dosing) and Day 15 of Cycles 1 and 2 as outlined in Table 6-1.

8 Adverse Event Reporting

8.1 Definitions

ADVERSE EVENT (EXPERIENCE) - any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. This includes worsening (eg, increase in frequency or severity) of pre-existing conditions.

SERIOUS ADVERSE EVENT – an adverse event resulting in any of the following outcomes:

- death
- is life threatening (ie, an immediate threat to life)
- inpatient hospitalization
- prolongation of an existing hospitalization
- persistent or significant disability / incapacity
- congenital anomaly / birth defect
- is Medically Important*

*Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

Note: Hospitalizations not associated with an adverse event, for example, for administration of chemotherapy or hydration for chemotherapy administration, are not considered serious adverse events.

UNEXPECTED ADVERSE EVENT - An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Expected means that the event has previously been observed with the study agent and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

8.2 Reporting Adverse Events to the Sponsor or Designee

All adverse events (AEs) that are identified from the start of any study agent administration through the specified study follow-up period (through 30 days following administration of the

final study agent dose) will be recorded on the paper/electronic Adverse Event Case Report Form (AE case report form). All data fields on the AE case report form will be completed.

Serious Adverse Events (SAEs) must ALSO be recorded on the SAE Worksheet and sent to HGS within 24 hours of site personnel becoming aware of a SAE, regardless of expectedness. All pages of the SAE Worksheet will be completed, but the SAE worksheet will not be held until all information is available. Additional information and corrections will be provided on subsequent SAE Worksheets as described in the Study Procedure Manual. SAE Worksheets will be sent by facsimile to the Drug Safety Department at HGS using the fax number listed below.

FAX #: PPD

8.3 Laboratory Abnormalities as Adverse Events

A laboratory abnormality will be reported as an adverse event if it is associated with an intervention. Intervention includes, but is not limited to, discontinuation of treatment, dose reduction/delay, additional assessments (excluding follow-up labs), or concomitant therapy. In addition, any medically important laboratory abnormality may be reported as an adverse event at the discretion of the investigator. This includes laboratory abnormalities for which there is no intervention but the abnormal value(s) suggests a disease or organ toxicity. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition will be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cells increased).

8.4 Other Events Requiring Rapid Reporting

Protocol Specified Events are additional events [toxicities] specifically identified in this protocol that must be reported to Human Genome Sciences or designee in an expedited manner. Protocol Specified Events may or may not be SAEs as defined in this protocol. They are SAEs if they meet one or more of the criteria for an SAE (see Section 8.1). Protocol Specified Events are recorded on SAE Worksheets and sent to Human Genome Sciences within 24 hours of site personnel becoming aware of the event.

The Protocol Specified Events for the study:

- Grade 4 neutropenia for > 7 consecutive days or febrile neutropenia.
- Grade 4 thrombocytopenia.
- Grade 3 or greater non-hematologic AEs except transient transaminase, amylase and lipase abnormalities for which the following criteria apply:
- Grade 3 or Grade 4 elevations in transaminases that do not resolve to baseline or Grade 1 before the next cycle
- Grade 4 elevations in lipase or amylase associated with clinical/imaging findings of pancreatitis, or resulting in chronic damage to the pancreas.
- Any Grade 4 elevations in lipase or amylase for > 4 consecutive days.
- Grade 3/4 elevations in liver function tests regardless of causality.

- Any adverse event that results in discontinuation of treatment if that event is assessed as possibly, probably, or definitely related to mapatumumab or sorafenib.

8.5 Reporting a Pregnancy

Any pregnancy in a female participant or a female partner of a male participant must be reported to Human Genome Sciences Drug Safety as soon as the site becomes aware of the pregnancy. All pregnancies are reported up to 30 days following the last study agent treatment. Human Genome Sciences Drug Safety sends an acknowledgement memorandum to the principal investigator along with a Pregnancy Assessment Form. Additional Pregnancy Assessment Forms will be sent to the site every 3 months for reporting of follow-up information. Pregnancy assessment forms must be completed by the investigator until live birth, elective termination of the pregnancy, or miscarriage. The site is responsible for following the subject's pregnancy to final outcome.

Pregnancies are not considered adverse events. Complications or medical problems associated with a pregnancy are considered AEs and may be SAEs. Complications or medical problems are reported as AEs/SAEs according to the procedure described in Section 8.2.

8.6 Investigator Evaluation of Adverse Events

The Investigator will evaluate all adverse events with respect to seriousness (criteria listed in Section 8.1 above), severity (intensity or grade) and causality (relationship to study agent) according to the following guidelines listed below.

SEVERITY

Severity will be graded using the NCI-CTCAE, Version 4.0. The NCI-CTCAE may be downloaded from the Cancer Treatment Evaluation Program website (http://ctep.info.nih.gov/reporting/ctc.html). In the event that an AE does not have an NCI-CTCAE code, the following severity classifications will be used:

Mild	causing no limitation of usual activities
Moderate	causing some limitation of usual activities
Severe	causing inability to carry out usual activities
Life Threatening*	potentially life threatening or disabling

***Note** – a severity assessment of life threatening is not necessarily the same as life threatening as a "Serious" criterion. The latter means that the event is an immediate threat to life as opposed to a potential threat to life.

CAUSALITY

Definitely Related	reasonable temporal relationship to study agent administration follows a known response pattern (eg, drug is known to cause this AE) there is no alternative etiology
Probably Related	reasonable temporal relationship follows a suspected response pattern (eg, based on similar drugs) no evidence for a more likely alternative etiology
Possibly Related	reasonable temporal relationship little evidence for a more likely alternative etiology
Probably Not Related	does not have a reasonable temporal relationship, OR good evidence for a more likely alternative etiology
Not Related	does not have a temporal relationship, OR definitely due to alternative etiology

ICH guidelines (March, 1995) clarify "reasonable causal relationship" to mean "that there are facts [evidence] or arguments to suggest a causal relationship".

The causality assessment must be made by the investigator based on information available at the time that the SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

***Note -** If there is evidence that mapatumumab/placebo contributed to or exacerbated an event related to sorafenib; the event will be recorded as possibly, probably or definitely related to both sorafenib and mapatumumab.

8.7 Follow-up of Adverse Events

Adverse events that occur during the course of the study are followed until final outcome is known or until the end of the safety follow-up period (30 days following the final dose of any study agent). Adverse events that have not resolved by the end of the safety follow-up period are recorded as ongoing.

SAEs that have not resolved by the end of the follow-up period are followed until final outcome of recovered or recovered with sequelae is achieved. If it is not possible to obtain a final outcome for a SAE (eg, the subject is lost to follow up), the reason a final outcome could not be obtained will be documented by the investigator.

8.8 Serious Adverse Events Assessed During Long-Term Follow-up

SAEs that occur after the safety follow-up period (30 days following the final dose of study agent) that are assessed by the investigator as possibly, probably, or definitely related to study agent must be reported to Human Genome Sciences on an SAE worksheet, as described in Section 8.2. Post-study SAEs will not be documented on the AE case report form.

8.9 Reporting Serious Adverse Events to the Institutional Review Board/Ethics Committee

All SAEs that are considered unexpected and related to the study agent will be reported by Human Genome Sciences or its designee as expedited (ie, 15-Day) reports to the appropriate regulatory authorities AND to all participating investigators. Each investigator must notify the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) responsible for reviewing the study at their site of all expedited reports. In addition, Human Genome Sciences or its designee will follow all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

9 Endpoints and Statistical Analysis

9.1 General Statistical Considerations

Analyses will be applied to a modified intention-to-treat population unless stated otherwise. This population is defined as the set of all randomized subjects who receive at least 1 dose of study treatment (mapatumumab/placebo and/or sorafenib) with subjects analyzed according to the groups they are randomized to, regardless of the treatment they subsequently receive. Additional analyses may be performed on the as-treated population, defined as the set of subjects receiving at least 1 dose of study medication analyzed according to the treatment that they actually receive.

Analyses will be performed using the SAS System™, WinNonlin Enterprise Edition™, StatXact™, and the R statistical package.

9.2 Sample Size Rationale

A total of approximately 100 subjects will be randomly assigned to 1 of 2 arms and treated with either sorafenib + placebo or the 2-agent combination of sorafenib and mapatumumab at 30 mg/kg in a 1:1 ratio. A sample size of 50 subjects randomized and treated in each group is sufficient to estimate the median time to progression with a precision of approximately -1.9 M to +2.6 M relative to the observed median. In addition, a sample size of 50 patients per arm will provide 80% power to detect an improvement in TTP from 5.5 to 8.9 M with at a one-sided significance level of 0.10.

9.3 Efficacy

9.3.1 Primary Efficacy Endpoint

The primary endpoint is time to progression (TTP) defined as the time from randomization to radiologic disease progression based on blinded independent review of imaging scans.

9.3.2 Primary Efficacy Analysis

The primary analysis will be an estimate of median time to progression in each arm using Kaplan Meier methods, reported with 95% confidence intervals, along with logrank testing at

a 1-sided significance level of 0.10 for a difference between treatment groups controlling for factors stratifying the randomization.

9.3.3 Secondary Efficacy Endpoints

Secondary endpoints include progression-free survival, overall response, disease control, overall survival, time to response, and duration of response (for responders) as defined below:

- OS: time from randomization to death from any cause.
- PFS: time from randomization to disease progression or death from any cause.
- Objective response (CR+PR according to mRECIST for HCC).
- Disease control (CR+PR+SD according to mRECIST for HCC).
- Time to response: time from randomization to 1st PR or CR in responders only.
- Duration of response: time from 1st PR or CR to disease progression; in responders only.

All secondary endpoints will be based on blinded independent review of imaging scans.

9.3.4 Secondary Efficacy Analyses

Secondary analyses include estimates, using Kaplan Meier methods, of median PFS and median OS along with associated logrank testing. In addition, estimates of overall response rate (CR+PR) and disease control rate (CR+PR+SD) will be reported with 95% confidence intervals and an estimate of the difference in response rates and disease control rates between groups will be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test).

9.4 Safety

9.4.1 Definition of Safety Variables

The safety parameters assessed are given by the following:

- Frequency, and severity of adverse events (AEs):
  - All AEs will be classified by System Organ Class and Preferred Term under the Medical Dictionary for Regulatory Activities (MedDRA) system of classification with a severity assigned according to the NCI-CTCAE (Version 4.0, 29 May 2009), or the rules specified in Section 8.6.
  - Laboratory parameters as presented in Appendix 7.
  - Laboratory toxicities will be graded based on the NCI-CTCAE (Version 4.0, 29 May 2009).
- Anti-mapatumumab antibody response.
- Vital signs.
- For frequency and severity of adverse events and laboratory toxicity grading, counts and rates will be presented.

9.4.2 Human Genome Sciences Safety Review Committee

The Human Genome Sciences Review Committeee (HGSRC) is comprised of the Department Heads of Biostatistics, Regulatory Affairs and Drug Development. The HGSRC will review safety data after: (1) 10 subjects have completed 1 cycle; and (2) 30 subjects have completed 1 cycle. HGSRC reviews of safety data will be conducted approximately every 4 months thereafter, until 90% of subjects have reached radiologic progression. The HGSRC may conduct additional reviews at their own request and/or at the request of the Medical Monitor. The HGSRC may request the unblinding of treatment assignment for a subject and/or treatment groups. If treatment assignments are unblinded, the rationale for the unblinding will be documented.

9.4.3 Analysis of Safety Variables

The safety analysis will consist of a presentation of rates of AEs observed. Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality observed will be reported. If any associations of interest between AEs and baseline characteristics are observed, additional stratified results may be presented. All treatment-emergent AEs will be summarized overall, as well as categorized by the MedDRA system of classification. AEs will be presented overall, by severity, by relation to mapatumumab/placebo, and by relation to sorafenib.

9.5 Pharmacokinetics

9.5.1 Definition of Pharmacokinetic Evaluation

Serum mapatumumab concentration data obtained from this study will be pooled with data obtained from other studies for use in a population PK analysis, which will be reported separately.

9.5.2 Analysis of Pharmacokinetics

The serum mapatumumab concentration will be determined by enzyme-linked immunosorbent assay. Serum mapatumumab concentration results for this study will be presented using appropriate graphic and tabular summaries.

9.6 Pharmacodynamics

Expression of biomarkers in tumor tissue and peripheral blood will be correlated with clinical outcomes and may be reported separately from the clinical study report.

10 Study Administration

10.1 Informed Consent

A copy of the proposed informed consent document(s) must be submitted to the sponsor or designee for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local, and institutional regulations or requirements.

It is the responsibility of the investigator to provide each subject with full and adequate verbal and written information using the IRB/IEC approved informed consent document(s), including the objective and procedures of the study and the possible risks involved before inclusion in the study. Each subject must voluntarily provide written informed consent (including consent for the use and disclosure of research-related health information). The consent must be obtained prior to performing any study-related procedures that are not part of normal patient care, including screening and changes in medications including any washout of medications. A copy of the signed informed consent must be given to the study subject.

10.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

The investigator or sponsor (as appropriate per national regulations) shall assure that an IRB/IEC, constituted in accordance with ICH Good Clinical Practices, will provide initial and continuing review of the study.

Prior to shipment of the study agent and enrollment of study subjects, documented IRB/IEC approval of the protocol, informed consent form, and any advertisement for subject recruitment must be obtained and provided to the sponsor or designee.

The IRB/IEC must also be informed of all protocol amendments prior to implementation. The investigator must provide reports of any change in research activity (ie, the completion, termination, or discontinuation of a study) to the IRB/IEC.

10.3 Protocol Compliance

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as described. Any such change must be reported immediately to the sponsor and to the IRB/IEC.

10.4 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are affected by the amendment.

10.5 Data Collection and Management

Data collected for each study subject are recorded electronically on case report forms provided or approved by the sponsor.

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each subject. The investigator is also responsible for maintaining any source documents related to the study, including any films, tracings, computer discs, or tapes. The investigator must promptly review the completed case report forms for each subject. As the person ultimately responsible for the accuracy of all data, the investigator must sign the Investigator's Statement in each subject's case report form.

The anonymity of participating subjects must be maintained. Subjects are identified by an assigned subject number on case report forms and other documents submitted to the sponsor. Documents that identify the subject beyond subject number are not submitted to the sponsor (ie, the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Sites enter subject data directly into the electronic data capture (EDC) system and the EDC system automatically generates queries resulting from computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. At study end, each site is provided with a compact disk containing the electronic case report forms for each of their subjects.

Upon completion of the study, or after reaching a pre-specified point in the study, Data Management locks the database and generates the SAS datasets necessary for data analysis and reporting.

10.6 Study Monitoring

The study sponsor, Human Genome Sciences, Inc., or designee, will monitor the study. Study monitors representing the sponsor will visit study sites routinely throughout the trial. The sponsor will review the paper subject diaries and electronic case report forms and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Auditors representing the sponsor may also similarly evaluate the study and its monitors. For these purposes, the investigator will make paper subject diaries and electronic case report forms and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators will promptly notify Human Genome Sciences of any audits they have scheduled with any regulatory authority.

10.7 Drug Accountability

Upon receipt, the designated unblinded pharmacy personnel at the study site are responsible for taking an inventory of the study agent, including any buffers or diluents. A record of this

inventory must be kept and usage must be documented on study agent inventory forms provided by the sponsor.

Study agent inventory forms will be examined and reconciled by an unblinded Clinical Research Associate, or designee. At the end of the study, all used and unused study agent must be accounted for on a study agent accountability form provided to the investigator by Human Genome Sciences or its designee.

10.8 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated, or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

10.9 Financial Disclosure

The investigator will provide Human Genome Sciences sufficient and accurate information on financial interests (proprietary or equity interests, payments exclusive of clinical trial costs) to allow complete disclosure to regulatory authorities. The investigator shall promptly update this information if any relevant changes occur during the course of the investigation and for a period of 1 year following study completion.

10.10 Publication Policy

This study is being conducted as part of a multi-center clinical study. Data from all sites participating in the multi-center clinical study will be pooled and analyzed. The investigator acknowledges that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and sponsor's representatives. Neither institution nor principal investigator shall independently publish or present the results of the study prior to the publication of the multi-center study publication. The investigator agrees that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center trials, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center trial results are published or 12 months after the end or termination of the multi-center trial at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until the entire sponsor's comments on the proposed publication or presentation have been considered and any information determined by sponsor to be confidential information has been removed.

If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

10.11 Study or Study Site Termination

If Human Genome Sciences, the investigator, IRB/IEC, or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between Human Genome Sciences and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of Human Genome Sciences to suspend or discontinue testing, evaluation, or development of the product.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to Human Genome Sciences, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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List of Appendices

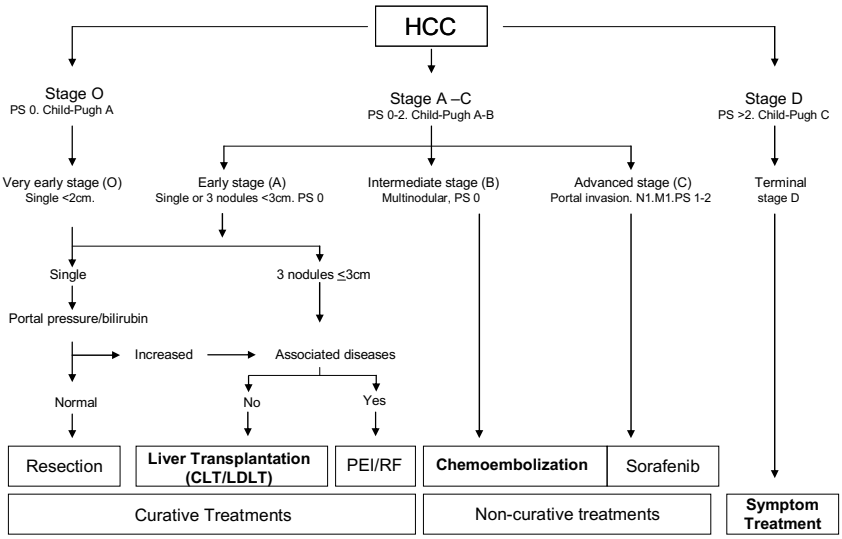
Appendix 1 Child-Pugh Classification

(Zimmerman H and Reichen J, 2000)

	No. of Points		
Factor	**1**	**2**	**3**
Bilirubin (mg/dL)	< 2	2–3	> 3
Albumin (g/dL)	> 3.5	2.8–3.5	< 2.8
Prothrombin time (increased seconds)	1–3	4–6	> 6
Ascites	None	Slight	Moderate
Encephalopathy	None	Minimal	Advanced

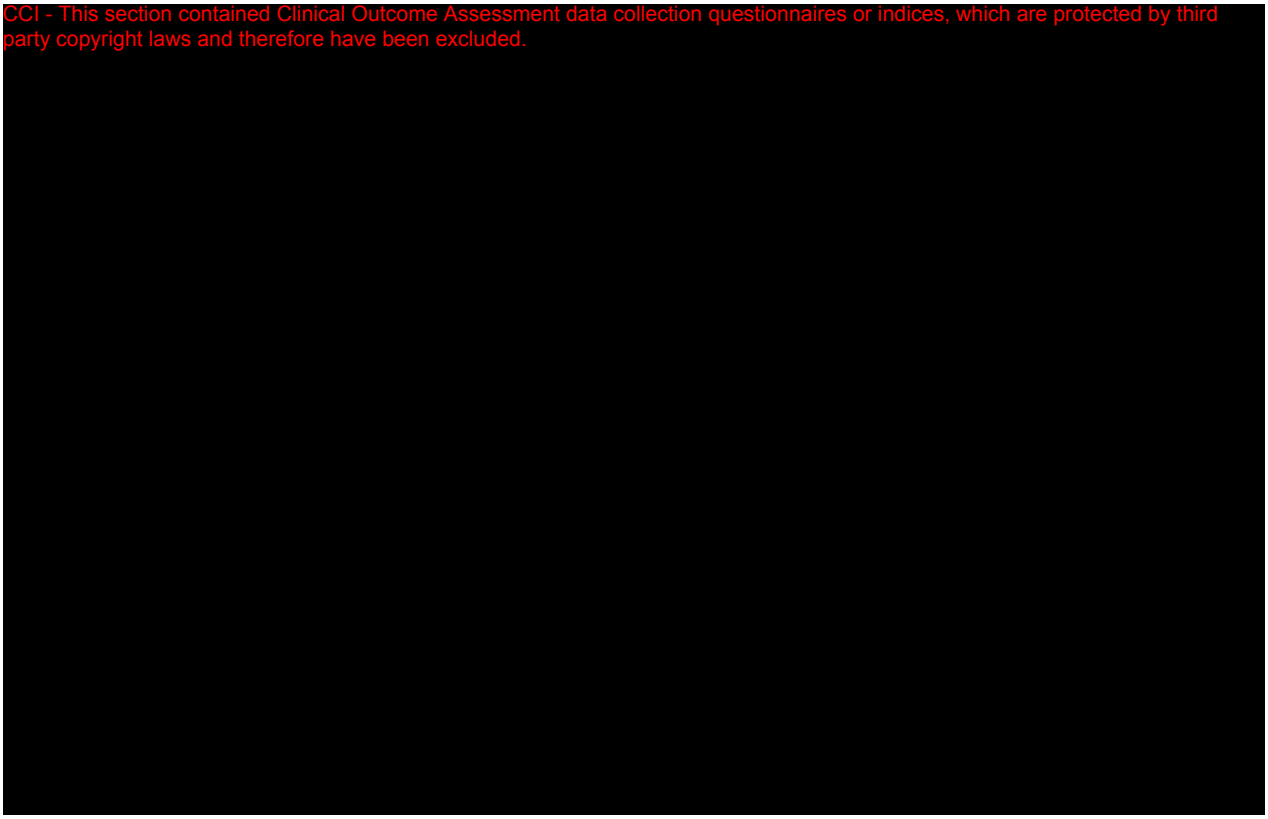
Grade	Score
A	5 – 6
B	7 – 9
C	10 – 15

Appendix 2 BCLC Staging and Treatment Strategy



Forner et al, 2010

Appendix 3 Eastern Cooperative Oncology Group (ECOG) Performance Status



Appendix 4 New York Heart Association Classification for Congestive Heart Failure

(The Criteria Committee of the New York Heart Association; Little, Brown & Co. 1994)

Class	New York Heart Association Classification for Congestive Heart Failure
1	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
2	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
3	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
4	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 5 Response Evaluation Criteria in Solid Tumors (mRECIST for HCC)

(Adapted from Lencioni and Llovet, 2010 for use in this study)

Measurable disease: The presence of at least 1 target lesion, by contrast enhanced computerized tomography (CT) with use of multislice scanners, or contrast enhanced dynamic magnetic resonance imaging (MRI).

Target lesion: Meets all the following criteria:

- Located in the liver.
- Can be accurately measured in at least 1 dimension.
- Well-delineated area of viable, hypervascular (contrast enhancement in the arterial phase) tumor that is ≥ 2 cm in the axial plane.
- Suitable for repeat measurement.
- Not previously treated with locoregional or systemic treatment unless the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is ≥ 2 cm in the axial plane. (If the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion).

A maximum of 5 target lesions may be selected.

Nontarget lesion: Other lesions, including small lesions (< 2 cm in the axial plane). Note thatmalignant portal vein thrombosis should be considered a nonmeasurable, and therefore nontarget, lesion. Lymph nodes at the portal hepatic can be considered as malignant if the lymph node short axis is at least 2 cm. Inclusion of effusion, notably ascities, as a nontarget lesion is discouraged. If effusion is selected as a nontarget lesion, it must be confirmed by cytopathologic confirmation. In addition, cytopathologic confirmation of any effusion that appears or worsens is required when the target lesion(s) have met criteria for response or stable disease.

Measurement of lesions: Imaging studies will be by contrast enhanced CT, with use of multislice scanners, or contrast enhanced MRI. The same method must be used at baseline and during follow up. Note that the longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured. The measurement of the viable tumor diameter should not include any major intervening areas of necrosis. (Please see the HGS1012-C1103 Radiographic Data Collection Manual).

Evaluation of target lesions:

Complete Response (CR): Disappearance of 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.

Stable Disease (SD): Any cases that do not qualify for CR, PR or SD.

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.

Evaluation of nontarget lesions:

Complete Response (CR): Disappearance of intratumoral arterial enhancement.

Incomplete Response/Stable Disease (IR/SD): Persistence of intratumoral arterial enhancement in 1 or more nontarget lesions.

Progressive Disease (PD): Unequivocal progression of existing nontarget lesions.

Evaluation of new lesions: A newly detected hepatic nodule will be classified as evidence of progression when its longest diameter is ≥ 1 cm and the nodule shows the hypervascularization in the arterial phase with washout in the portal venous or late venous phase.

Liver lesions ≥ 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least a 1 cm-interval growth in subsequent scans.

An individual radiologic event will be adjudicated in retrospect as progression at the time it was 1st detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

Evaluation of Overall Response: The overall response is determined at each assessment and is a result of the combined assessment of target lesions, nontarget lesions and new lesions.

Overall Response Assessment

Target Lesions	Nontarget Lesions	New Lesions	Overall Response*
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

*AFP is not included in assessment of overall response.

Best Overall Response:

The best overall response is the best response recorded from the start of treatment until disease progression. To be assigned a best overall response of CR or PR, changes in tumor measurements must be confirmed at the next scheduled disease assessment (no fewer than 4 weeks after the initial documentation of PR or CR).

Appendix 6 Exploratory Biomarker Sub-study

1. Background

Mapatumumab is a targeted therapy. Presently, the relationship between expression of the target, TRAIL-R1, and the anti-tumor activity of the antibody is incompletely understood. Studies conducted with cell lines derived from human tumors have suggested that the relationship between receptor expression and mapatumumab-induced tumor cell death may be complex. However, studies of human tumor cells in vitro and transplanted into animals may not accurately reflect the relationship between receptor expression and response to mapatumumab that may be observed in patients with cancer. One feature of this biomarker study is to compare TRAIL-R1 expression from available biopsy material. This could allow for a greater understanding of patterns of TRAIL-R1 expression in advanced hepatocellular carcinoma.

It is also likely that other factors involved in TRAIL-R1 signaling could critically affect response to mapatumumab treatment. A 2nd goal of this biomarker study is to evaluate biomarkers that may be potential indicators or modifiers of response to mapatumumab. To identify factors that may indicate that a patient is responding to treatment, serum-based markers will be compared before and after treatment. To explore factors that are associated with the outcome of therapy and could be used prior to treatment to predict which patients will respond, somatic (inherited) differences that modify a patient's drug response will be examined.

The information generated from this sub-study will be used solely for research purposes to improve future treatment with mapatumumab. It will not be used to change diagnoses or alter therapy. Participation in this sub-study is optional.

2. Study Objectives and Design

2.1. Indicators of Response

2.1.1. Serum-Based Markers of Response

Induction of cell death in tumor cells can elicit the release of certain biomarkers into the serum. These markers can be quantified to evaluate treatment effect. To assess release of biomarkers associated with cell death, serum-based assays will be conducted, including, but not limited to, assessments of M30, a fragment of cytokeratin 18 that is generated by induction of programmed cell death in epithelial tissues. Other examples of markers of tumor cell death that will be examined include the cytokines TRAIL, TNFα, soluble Fas ligand, interferonα, interferonγ, interleukin-2, interleukin-6, interleukin-8, interleukin-10, and interleukin-12. The levels of these factors will be examined before and after treatment to see if they correlate with response to treatment.

Serum will be isolated and the level of cytokines and other markers like M30 will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2. Modifiers of Response

2.2.1. Neoplastic Modifiers of Response

Historically collected tumor biopsy material, if available, will be collected from subjects during Cycle 1. Samples will also be obtained from subjects who undergo a biopsy during the treatment period. Samples of resected tumor tissue that has been formalin-fixed and embedded in paraffin is acceptable; either tissue blocks or slides may be provided. Frozen samples of tumor tissue may also be provided. Biopsy material collected from fine needle aspirates may be provided; either cell pellets or cytological slides are acceptable.

Levels of TRAIL receptors will be assessed in biopsy material using immunohistochemical techniques if samples are available as formalin-fixed/paraffin-embedded tissue blocks or slides. Historically obtained biopsy material or biopsy material obtained during the treatment period that is in the form of fresh frozen tissue or cell pellet samples will be utilized to isolate RNA for analysis of TRAIL receptor gene expression.

Similar techniques will be used to evaluate other potential biomarkers and factors that may influence mapatumumab response. These may include but are not limited to caspase 8, AKT and Mcl-1.

See the laboratory manual for collection, processing and handling of these samples.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

2.2.2. Somatic Modifiers of Response

Inherited differences in the genes that code for drug targets or components of signaling pathways related to the target can dramatically influence the effect of pharmacotherapy. Variations in genes that could potentially impact mapatumumab's activity, including polymorphic changes in the Fc gamma receptor and interleukin-6 promoter and K-Ras gene mutations, will be examined to see if they correlate with response to treatment.

DNA will be isolated from the blood and polymorphisms and mutations in specific response-related genes will be characterized. Collection, processing and handling of these samples are described in the laboratory manual.

Samples collected in this study will be stored for up to 15 years and may be analyzed with samples collected in other studies, but will only be used for mapatumumab-related research.

3. Statistical Analysis

Associations will be assessed between candidate biomarkers and treatment outcomes captured in the clinical database. Statistical tests to be performed may include Pearson chi-square testing, Fisher's exact test, ANOVA and ANCOVA. Results of the biomarker sub-study may be reported independent of the results of HGS1012-C1103.

4. Subject Selection and Withdrawal

Subjects enrolled in the HGS1012-C1103 research study are given the option to participate in the Biomarkers Sub-study. A subject may withdraw from the sub-study at any time by contacting their Study Investigator, who will contact the sponsor. The sponsor will destroy any remaining sample materials and will send a letter back to the Investigator confirming sample destruction. Any data or analysis generated from the sample prior to the request for destruction will not be destroyed. However, no new information will be generated from the sample and no new analysis will be performed.

5. Confidentiality

Information about sub-study subjects will be kept confidential and managed according to the requirements of local privacy regulations. Information obtained from samples will not be returned to subjects and will not be placed in the subject's medical record.

6. Ethical Considerations

All subjects enrolled in the HGS1012-C1103 research study who agree to participate in the Biomarker Sub-study will be asked to sign a separate Biomarker Informed Consent. Choosing to not participate in this sub-study will not affect the subject's ability to participate in the main clinical trial. The Biomarker Informed Consent will be submitted along with the main research study informed consent for review by the Institutional Review Board/Ethical Committee.

7. Publication of Biomarker Results

Any significant findings, based upon the analysis of aggregate data collected from this sub-study may be published by Human Genome Sciences. Personal identifiers will not be used in any publication resulting from this sub-study.

Appendix 7 Laboratory Tests

CBC with Differential	Chemistry
Total white blood cell (WBC) count differential:	Electrolytes:
Neutrophils	Sodium
Bands	Potassium
Lymphocytes	Magnesium
Monocytes	Chloride
Eosinophils	Carbon dioxide/bicarbonate*
Basophils	Calcium
Hemoglobin	Enzymes:
Hematocrit	SGOT (AST)
Red blood cell count	SGPT (ALT)
Platelet count	Alkaline phosphatase
Absolute Neutrophil Count	Amylase
Total white blood cell count	Lipase
	Gamma glutamyl transferase (GGT)
Prothrombin time (PT)	
Partial thromboplastin time (PTT)	Other:
International normalized ratio (INR)	Creatinine
	Blood Urea Nitrogen
Other:	Total bilirubin
Serum and Urine pregnancy	Total protein
Hepatitis B surface antigen	Albumin
Hepatitis C antibody	
B and T lymphocytes	
HCV RNA	
HBV DNA	
HBsAb	

*To be collected if included in routine automated serum chemistry panel.

Refer to Section 6 (Study Procedures) for laboratory test collection schedule.

Appendix 8 Treatment of Allergic/Hypersensitivity Reactions

In the event of allergic/hypersensitivity reactions to mapatumumab/placebo, investigators will institute treatment measures according to best medical and nursing practice. The grading is based upon the NCI-CTCAE Version 4.0.0.

The following treatment guidelines will be employed:

- If chills and fever occur, the infusion will be interrupted. Subjects may be treated symptomatically and the infusion will be restarted at 50% of the original rate.

Grade 1 allergic/hypersensitivity reaction (transient flushing or rash, drug fever < 38°C):

- Decrease infusion rate by 50% and monitor for worsening condition. If the reaction worsens, stop the infusion.

Grade 2 allergic/hypersensitivity reaction (rash, flushing, urticaria, dyspnea, drug fever < 38°C):

- Stop the infusion.
- Administer bronchodilators, oxygen, acetaminophen, etc as medically indicated.
- Resume infusion at 50% of previous rate once reaction has decreased to ≤ Grade 1 in severity. Monitor closely for any worsening. If the reaction recurs, stop the infusion.

Re-treatment following Grade 1 or Grade 2 allergic/hypersensitivity reactions:

- Once the infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions.
- If the subject has a 2nd reaction at the lower infusion rate, the infusion will be stopped and the subject will receive no further treatment with mapatumumab/placebo.
- If the subject experiences a Grade 3 or Grade 4 allergic/hypersensitivity reaction at any time, the subject will receive no further treatment with mapatumumab/placebo.
- If there are questions concerning whether an observed reaction is an allergic/hypersensitivity of Grades 1-4, the medical monitor will be contacted immediately to assist with grading the reaction.

Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- A Grade 3 hypersensitivity reaction consists of symptomatic bronchospasm requiring parenteral medications with or without urticaria, allergy-related edema/angioedema, or asymptomatic hypotension not requiring treatment.
- A Grade 4 hypersensitivity reaction (ie, anaphylaxis) is a life-threatening event characterized by the same symptoms as in a Grade 3 reaction but also complicated by symptomatic hypotension or oxygen saturation of 90% or less.

Treatment of Grade 3 or Grade 4 allergic/hypersensitivity reaction:

- Stop the infusion immediately and disconnect infusion tubing from the subject.
- Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc, as medically indicated.

Contact Human Genome Sciences to report an SAE and fax SAE worksheet.

HGS Administrative Letter

From: PPD CPM

To: HGS1012-C1103 Clinical Sites and Master File

Date: 11 October 2010

Re: Administrative Letter for Protocol HGS1012-C1103, Amendment 00

This letter serves as documentation and clarification of a typographical error in Amendment 00 of Protocol HGS1012-C1103 (dated 14 September 2010) as described below.

Appendix 5 defines the Response Evaluation Criteria in Solid Tumors (mRECIST for HCC). On page 64, stable disease (SD) is defined as follows:

> Any cases that do not qualify for CR, PR or **SD**.

Instead the protocol should define SD as:

> Any cases that do no qualify for CR, PR or PD.

The errors in the Appendix 5 have been corrected and a revised version is attached for reference.

Please file this memo in the Sponsor Correspondence section of your study binder.

Signatures:

PPD

Regulatory

PPD

PPD

11 Oct 2010
Date

11 Oct 2010
Date

11 OCT 2010
Date

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- Suitable for repeat measurement.
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Overall Response Assessment

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Any	PD	Yes or no	PD
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Best Overall Response:

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