HUMAN GENOME SCIENCES

Human Genome Sciences, Inc.

Analytical Plan for Protocol HGS1012-C1103 (200149)

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

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List of Abbreviations

AE	adverse event
AFP	α-fetoprotein
ATC	Anatomical Therapeutic Chemical
BCLC	Barcelona Clinic Liver Cancer
BICR	blinded independent central review
CR	complete response
DNA	deoxyribonucleic acid
eCRF	electronic case report form
ECOG	Eastern Cooperative Oncology Group
HCC	hepatocellular carcinoma
HGS	Human Genome Sciences
IWRS	interactive web response system
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MITT	modified intention-to-treat
mRECIST	modified Response Evaluation Criteria in Solid Tumors assessment
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OS	overall survival
PD	progressive disease
PFS	progression free survival
PR	partial response
PT	preferred term
RFA	radiofrequency ablation
SAE	serious adverse event
SD	stable disease
SLD	sum of longest diameters
SOC	system organ class
TRAIL-R1	tumor necrosis factor-related apoptosis inducing ligand receptor 1
TTP	time to progression
WHO	World Health Organization

1   Introduction

HGS1012-C1103 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.

2   Study Objectives

2.1   Primary Study Objectives

The primary objective of this study is to evaluate the efficacy of mapatumumab in combination with sorafenib in subjects with advanced hepatocellular carcinoma.

2.2   Secondary Study Objectives

The secondary objectives of this study are:

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

- To determine serum mapatumumab concentrations.

3   Study Administrative Structure

Human Genome Sciences (HGS) is the sponsor of this study. Data collected for this study will be recorded electronically on case report forms (eCRFs) provided or approved by the sponsor.

Sites will enter subject data directly into the eCRF system which will automatically generate 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 electronic data capture system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the electronic data capture system audit trail.

HGS will have discretion to lock the database when 90% of all randomized and treated subjects have been followed to radiologic disease progression, or when all subjects have been followed for at least 12 months at which point blinded review of the remaining data will facilitate a decision on whether to lock the database or wait for remaining events.

4   Study Design

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. Approximately 100 subjects with advanced hepatocellular carcinoma will be randomized. Randomization will be stratified according to Barcelona Clinic Liver Cancer (BCLC) advanced stage C vs. BCLC intermediate stage B and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs. 1, 2).

Radiologic eligibility must be confirmed by a blinded independent central review (BICR) prior to randomization. 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

The study is estimated to occur over approximately 24 months. Subjects will continue to receive sorafenib and/or mapatumumab/placebo until radiologic disease progression or unacceptable toxicity. Subjects may discontinue either sorafenib or mapatumumab/placebo separately and remain on treatment. 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.

If disease progression is based only on a new lesion(s) or is equivocal, images will be provided to the BICR for confirmation of radiologic disease progression prior to discontinuing study treatment. Decisions regarding subject treatment will remain the responsibility of the investigator. Additionally, all images obtained on study will be provided to the BICR for the independent efficacy read.

4.1   Choice of Control Group

The control group in this study is Arm A: sorafenib 400 mg orally twice daily continuously in each cycle + placebo intravenously on Day 1 of each cycle. The control group will be used for comparison purposes for both primary and secondary efficacy and safety analyses. It will also be used to provide a measure of internal validity to the interpretation of results from the sorafenib + mapatumumab 30 mg/kg study arm, commensurate with consistency of observed outcomes in the sorafenib + placebo study arm to historical outcomes in this patient population.

4.2   Study Population

The study population consists of subjects 18 years of age or older with advanced hepatocellular carcinoma who meet a Child-Pugh Classification of A and either BCLC advanced stage (C) hepatocellular carcinoma, or BCLC intermediate stage (B) hepatocellular carcinoma if treatment with transarterial chemoembolization is not considered appropriate. Subjects must also have a performance status of 0, 1 or 2 on the ECOG scale and meet the radiologic and laboratory eligibility criteria as defined in Section 4 of the protocol.

4.3   Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are stated in Section 4 of the protocol.

4.4   Treatment Assignment

Subjects that meet the eligibility criteria will be randomly assigned treatment by a central interactive web response system (IWRS) in a 1:1 ratio to 1 of 2 treatment arms (Arm A: sorafenib + placebo or Arm B: sorafenib + mapatumumab 30 mg/kg). The randomization will be stratified according to BCLC advanced stage C vs. BCLC intermediate stage B and ECOG performance status (0 vs. 1, 2) as defined in Appendices 2 and 3 of the protocol, respectively.

4.5   Data Monitoring

To assure appropriate study conduct and adherence to Good Clinical Practice, this study incorporates ongoing and continuous monitoring as specified in Section 10.6 of the protocol.

4.6   Interim Analysis

This study has no interim analysis planned.

5   General Statistical Considerations

Statistical analyses performed on the efficacy data will be applied to a modified intention-to-treat (MITT) population unless stated otherwise. This population is defined as the set of all randomized subjects who receive at least part of 1 dose of study agent (mapatumumab/placebo and/or sorafenib) with subjects analyzed according to the groups to which they are randomized, 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 part of 1 dose of study agent analyzed according to the treatment that they actually receive. All analyses performed on safety, subject disposition, exposure and completion status will be applied to the as-treated population. Analyses performed on demographics and concomitant medications data will be applied to the MITT population.

Assessments will be referred to by day of cycle beginning with Cycle 1/Day 1. This will allow data from subjects with small fluctuations in cycle length, or dosing delays to be reported in a consistent fashion. Cycle 1/Day 1 (predose) will typically be the baseline assessment unless data are missing, in which case screening data closest to the Cycle 1/Day 1 assessment will be used. In the instance a subject discontinues all treatment, or discontinues mapatumumab/placebo, but remains on sorafenib treatment, an off-treatment distinction will be made when referencing disease assessments.

Categorical data analyses using the Pearson chi-square test will substitute Fisher's exact test if > 20% of expected contingency table cell counts are < 5.

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

5.1   Determination of 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 + mapatumumab 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 (TTP) with a precision of approximately -1.9 months to +2.6 months 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 months with at a one-sided significance level of 0.10.

6   Study Subjects

6.1   Subject Disposition

Subject eligibility, compliance, and study completion will be summarized. Reasons for failing screening, failing enrollment (randomized but never received treatment) or not completing the study (as defined in Section 6.3 below) will be identified.

6.2   Extent of Exposure

The extent of exposure to mapatumumab/placebo and to sorafenib will be assessed by examining duration of exposure in both months and cycles (cycles only relevant while subject is administered mapatumumab/placebo), dose intensity, relative dose intensity, dose reductions, dose omissions and dose delays by treatment group.

Duration of exposure for mapatumumab/placebo will be calculated as the date of dosing for the last cycle plus 21 days minus the date of 1st treatment. For subjects who die prior to Day 21 of the last cycle, duration of exposure will be calculated as the date of death

minus the date of 1st treatment plus 1 day. Duration of exposure for sorafenib will be calculated as the date of last dose minus the date of 1st treatment plus 1 day.

Cumulative dose received for mapatumumab will be calculated as

$$\text{Cumulative dose received} = \sum_{k=1}^{K} \text{Dose received at each cycle (mg/kg)}$$

where K = total number of treatment cycles received by the subject. In the case that body weight is unknown at a visit, the last non-missing measurement prior to the visit will be used.

Cumulative dose received for sorafenib will be calculated as

$$\text{Cumulative dose received} = \sum_{m=1}^{M} \text{Dose received each day (mg)}$$

where M = total number of days the subject received sorafenib.

Dose intensity will be expressed as the cumulative dose for mapatumumab (mg/kg) and sorafenib (mg) received, respectively, divided by duration of treatment (weeks) for each treatment, respectively.

$$\text{Dose intensity} = \frac{\text{Cumulative dose received (mg/kg or mg)}}{\text{Duration of treatment (weeks)}}$$

such that the definition of duration of treatment is dependent on the order of treatment discontinuation. If both mapatumumab and sorafenib are discontinued on the same date the duration of treatment for mapatumumab is defined as the date of dosing of mapatumumab in the last cycle plus 21 days minus the date of 1st treatment and the duration of treatment for sorafenib is defined as the date of last dose of sorafenib minus the date of 1st treatment plus 1 day. If mapatumumab is discontinued prior to sorafenib the duration of treatment for mapatumumab is defined as either the date of dosing of mapatumumab for the last cycle plus 21 days minus the date of 1st treatment, or the date of last dose of sorafenib minus the date of 1st treatment plus 1 day, whichever is greater. Duration of treatment for sorafenib will not differ from when both mapatumumab and sorafenib are discontinued on the same date. If sorafenib is discontinued prior to mapatumumab the duration of treatment for sorafenib is defined as the date of dosing of mapatumumab in the last cycle minus the date of 1st treatment plus 1 day. Duration of

treatment for mapatumumab will not differ from when both mapatumumab and sorafenib are discontinued on the same date.

Relative dose intensity will be expressed as the ratio of dose intensity and planned dose intensity

$$\text{Relative dose intensity} = \frac{\text{Dose intensity (mg/kg/weeks or mg/weeks)}}{\text{Planned dose intensity (mg/kg/weeks or mg/weeks)}}$$

such that planned dose intensity for mapatumumab is equal to the planned dose (mg/kg) divided by the number of weeks within a cycle and planned dose intensity for sorafenib is 800 mg times the duration of exposure to sorafenib in days divided by the number of weeks on treatment.

Mapatumumab/placebo doses that are administered 2 or more days from the target date of dosing will be considered delayed. The target date of dosing for each cycle is the previous date of dosing plus 21 days. The length of delay for a delayed dose is calculated as the actual date of dosing minus the target date of dosing. Descriptive statistics will be provided by treatment group.

Dose reductions are not permitted for mapatumumab/placebo. However, any mapatumumab/placebo dosing interruptions that take place resulting in a reduction from the intended dose will be considered dose reductions. Sorafenib dose reductions will be summarized. A dose reduction will be defined as a physician decision to reduce the prescribed dose to a lower level relative to the previous prescribed dose while on treatment (including reductions to 0 mg which would constitute dose omission, also analyzed separately, see below). The number of subjects requiring at least 1 dose reduction will be summarized along with the maximum dose level reduction attained for each subject. In addition, rates of subjects requiring dose reductions due to adverse events (AEs) or laboratory abnormalities will be provided. Statistical analysis of dose reduction rates will include Pearson chi-square testing (or Fisher's exact testing, as appropriate) for differences between groups. Dosing errors for either mapatumumab/placebo or sorafenib will not be identified as dose reductions in the analysis.

In addition, all sorafenib dose reductions observed (possibly multiple events per subject) will be summarized by treatment group and reason. The percent of dose reductions that resulted in an eventual return to the original dose level from which the subject was reduced will be calculated.

The number of subjects requiring sorafenib dose omissions will be summarized by treatment group. A subject will be determined to have a dose omission if the prescribed dose for a given time interval (while on sorafenib treatment) is 0 tablets per day. Statistical analysis of the rate of subjects requiring dose omission (overall, due to AEs,

and due to laboratory abnormalities) will include Pearson chi-square testing (or Fisher's exact testing, as appropriate). In addition, all dose omissions (possibly multiple events per subject) will be summarized by treatment group and reason.

6.3   Completion Status

Subjects will continue to receive study agent(s) until radiologic disease progression or unacceptable toxicity. Subjects unable to tolerate sorafenib may continue to receive mapatumumab/placebo every 21 days until radiologic disease progression. Subjects unable to tolerate mapatumumab/placebo may continue to receive sorafenib until radiologic disease 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. 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.

Completion will be summarized with respect to completion of the planned course of treatment, completion of required short-term follow-up and completion of required long-term follow-up. Completion of the planned course of treatment will be satisfied by subjects who are treated until radiologic disease progression. Completion of short-term follow-up will be satisfied by subjects who are followed through at least 30 days after the final dose (of any study agent) for scheduled safety assessments (or a pending disease assessment visit to confirm disease response if required), regardless of the reason for treatment discontinuation. Completion of long-term follow-up will be satisfied by those subjects who are followed for overall survival (OS). Completion of the study is defined as completing study treatment, completing short-term follow-up and completing long-term follow-up. Subjects still being followed at the time of any analysis will be counted as "ongoing".

6.4   Demographics and other Baseline Characteristics

Summary information related to medical history, sex, age, race, baseline disease state, and previous therapies will be presented. In general, counts and percentages will be presented for categorical data and mean, median, standard deviation, minimum, and maximum will be presented for continuous data.

6.5   Concomitant Medications

Concomitant medications will be coded according to drug name as defined in the World Health Organization (WHO) Drug Dictionary, classified according to the Anatomical Therapeutic Chemical (ATC) classification system and presented in tables and listings.

7   Efficacy Analyses

Efficacy analyses will be based on the BICR assessment. Evaluation of efficacy endpoints based on investigator data will be provided by applying modified Response Evaluation Criteria in Solid Tumors for hepatocellular carcinoma (mRECIST for HCC) (Lencioni, 2010 and Llovet, 2008) to investigator assessed tumor measurements. In addition, investigator reported objective response and disease control rates will be summarized with the caveat that these may differ from the application of mRECIST for HCC to the investigator assessed tumor measurements. Investigator reported disease progression dates will be presented in listings but not analyzed using time to event analysis techniques. Instead these analyses will be performed on time to progression (TTP) and progression free survival (PFS) dates resulting from application of mRECIST for HCC to investigator assessed tumor measurements along with the censoring guidelines and missing data rules described in this Analytical Plan.

7.1   Primary Efficacy Endpoint Analyses

7.1.1 Primary Efficacy Endpoint(s)

The primary endpoint is TTP defined as the time from randomization to radiologic disease progression based on BICR assessments of imaging scans using mRECIST for HCC (Llovet, et al, 2008 and Thomas, et al, 2010).

7.1.2 Primary Efficacy Analyses

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

7.1.3 Additional Analyses of Time to Progression

While the primary analysis of TTP is based on the BICR determination of radiologic disease progression, additional analysis will be performed.

- An analysis of TTP as determined by the BICR censoring subjects at the date of the last complete disease assessment performed prior to any protocol prohibited medications/therapy as specified in Section 5.3 of the protocol (eg, cytotoxic chemotherapy, hormonal therapy, biological therapy, immunotherapy or locoregional therapy).

- An analysis of TTP based on application of mRECIST for HCC to investigator assessed tumor measurements. In this analysis all subjects will be censored for TTP at the date of the last complete disease assessment performed prior to any protocol prohibited locoregional therapy.

- An analysis of TTP based on application of mRECIST for HCC to investigator assessed tumor measurements censoring subjects at the date of the last complete disease assessment performed prior to any protocol prohibited medications/therapy (eg, cytotoxic chemotherapy, hormonal therapy, biological therapy, immunotherapy or locoregional therapy).

7.1.4 Adjustment for Covariates

Adjustment for covariates including the stratification factors BCLC advanced stage C vs. BCLC intermediate stage B and ECOG performance status (0 vs. 1, 2) is planned for the primary analysis as well as the analyses described in Section 7.1.3.

7.1.5 Subgroup Analyses

Subgroup analyses may be performed on the stratification factors BCLC advanced stage C vs. BCLC intermediate stage B and ECOG performance status (0 vs. 1, 2). Subgroup analyses may also be performed on laboratory parameters testing for the hepatitis B surface antigen and the hepatitis C surface antibody (positive for the hepatitis B surface antigen vs. not, positive for the hepatitis C surface antibody vs. not).

7.2 Major Secondary Efficacy Endpoint Analyses

7.2.1 Major Secondary Efficacy Endpoints

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

- Overall survival (OS): time from randomization to death from any cause.

- Progression free survival (PFS): time from randomization to radiologic 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 radiologic disease progression; in responders only.

such that CR is complete response, PR is partial response and SD is stable disease.

All secondary endpoints will be based on BICR assessments of imaging scans. Additional analyses based on application of mRECIST for HCC to investigator assessed tumor measurements, or investigator determination of disease response will be performed. For

the purposes of establishing SD based on BICR or application of mRECIST for HCC to investigator assessed tumor measurements, at least 6 weeks from the baseline measurement must elapse without progressive disease (PD) in order to assign a best overall response of SD. Confirmation of PR and CR will occur no fewer than 4 weeks after initial documentation of PR or CR. If PR or CR that is pending confirmation is designated at an assessment followed by 1 or more non-evaluable assessments or assessments of SD, response may be confirmed thereafter.

7.2.2 Major Secondary Efficacy Analyses

Secondary analyses include estimates, using Kaplan Meier methods, of median PFS and median OS along with associated logrank testing. The hazard ratio will also be estimated for PFS and OS using Cox proportional hazard modeling adjusting for factors stratifying the randomization as covariates. 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, as appropriate). The analysis of PFS as determined by the BICR described in this section will be repeated, but with PFS based on application of mRECIST for HCC to investigator assessed tumor measurements. Analyses of TTP as described in Section 7.1.3 will be repeated for PFS. In addition, the analyses of objective response, disease control, time to response and duration of response will be repeated with 2 analyses: 1) with endpoints based on application of mRECIST for HCC to investigator assessed tumor measurements and 2) with endpoints as provided directly by the investigator.

7.2.3 Adjustment for Covariates

Adjustment for covariates including the stratification factors BCLC advanced stage C vs. BCLC intermediate stage B and ECOG performance status (0 vs. 1, 2) is planned for secondary endpoints PFS and OS in Cox proportional hazard modeling and logrank testing.

7.2.4 Subgroup Analyses

Subgroup analyses may be performed on the stratification factors BCLC advanced stage C vs. BCLC intermediate stage B and ECOG performance status (0 vs. 1, 2). Subgroup analyses may also be performed on laboratory parameters testing for the hepatitis B surface antigen and the hepatitis C surface antibody (positive for the hepatitis B surface antigen vs. not, positive for the hepatitis C surface antibody vs. not).

7.3 Handling of Dropouts and Missing Data

These rules will apply uniformly to all efficacy analyses based on the BICR assessment as well as efficacy analyses resulting from application of mRECIST for HCC to investigator assessed tumor measurements. For investigator reported outcomes, analyses

will present outcomes reported by the investigator without consideration of missing data or censoring rules. In general, subjects not classifiable under the mRECIST for HCC response categories due to insufficient data or early death will be classified as non-evaluable for objective response, but will be counted in the denominator of all response rate calculations.

7.3.1 Handling of Missing Data

7.3.1.1   Missing Data at Baseline

If a subject has missing target lesion measurements at baseline, the subject will be assigned PD if criteria for PD is exhibited at the first disease assessment. Otherwise, the subject will be classified as non-evaluable for objective response and censored at date of randomization for TTP. For PFS the subject will be censored at date of randomization unless the subject dies within the first 6W post-baseline in which case this date will qualify as a PFS event.

7.3.1.2   Missing Data at a Disease Assessment

If a subject has missing tumor measurements at some assessment for 1 or more target lesions, the sum of the longest diameters (SLD) will be reported for the remaining target lesions. These data will be used to indicate radiologic disease progression if the SLD for the observed lesions increases at least 20% from the nadir SLD of all lesions, in spite of the missing data (or if other criteria for PD are met). If a subject has missing tumor assessments at some assessment for 1 or more non-target lesions, radiologic disease progression will be determined if at least 1 of the remaining non-target lesions exhibits unequivocal progression (or if other criteria for PD are met). If a subject has missing tumor measurements at some assessment(s) for 1 or more target or missing recorded response at some assessment(s) for 1 or more non-target lesions and criteria for PD are not met, an overall response of non-evaluable will be assigned for the assessment(s).

7.3.1.3   Missing Disease Assessment(s)

If a subject has a completely missed assessment(s) followed by an assessment showing radiologic disease progression, then PD will be assigned at the target date of the first missed assessment following an assessment showing no progression. This target date is defined as 42 days after the previous disease assessment showing no progression. If a subject has a missed assessment(s) followed by an assessment showing no radiologic disease progression, then the assumption will be that the subject remained stable during the missed assessment(s).

7.3.2 Other Censoring Rules

Subjects who reach the survival endpoint due to any reason prior to experiencing a radiologic disease progression will be censored for TTP at the date of their last complete disease assessment. Subjects remaining on study without radiologic disease progression or death at the time of analysis will be censored for TTP and PFS at the date of their last

complete disease assessment. Subjects lost to follow-up prior to experiencing a radiologic disease progression or death will be censored for TTP and PFS at the date of their last complete disease assessment.

7.4   Protocol Prohibited Therapies and Medications

As specified in Section 5.3 of the protocol, subjects should not receive any investigational or noninvestigational cytotoxic chemotherapy, hormonal therapy, biological therapy (including monoclonal antibodies), immunotherapy or any locoregional therapy (such as embolization, radiofrequency ablation (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.

7.4.1 Protocol Prohibited Locoregional Therapy

These censoring rules apply to the primary analysis of TTP as well as PFS and disease response endpoints as determined by the BICR. Any locoregional therapy received while on study including embolization, RFA or percutaneous ethanol injection and the date performed will be reported to the BICR. If the BICR reviewer believes that one of the target lesions selected at baseline has been affected by such therapy, and that subsequent response or SD is attributable to locoregional therapy, the BICR reviewer will call that subject non-evaluable at all future disease assessments that occur on or after the date of locoregional therapy. Otherwise, the BICR reviewer will assess the subject ignoring the locoregional therapy.

7.4.2 Protocol Prohibited Medications

The primary analysis of TTP as well as PFS and disease response endpoints as determined by the BICR will not be impacted by protocol prohibited medications. Instead, additional analyses as described in Section 7.1.3 will be performed.

7.5   Assignment of Dates of Disease Progression or Disease Response

For all analyses of endpoints as assessed by BICR or by application of mRECIST for HCC to investigator assessed tumor measurements, there may be cases in which disease assessments span a series of dates. For establishing the start date of a subsequently confirmed response in which the disease assessment spans multiple days, the response date assigned will be the latest date of evaluations corresponding to the disease assessment. The date of latest assessment will also be assigned for a mid-study assessment showing SD as the date assigned to that SD for the purposes of censoring duration of SD.

The date of PD will be the 1st date at which any objective diagnostic test provides data indicating PD. Specifically, the date of PD will be the earliest of the following 3 dates:

- Date of PD as indicated by target lesions: if PD is triggered by a change in SLD of target lesions, and all evaluations occurred on the same day, assign that date. If the dates of evaluation of the target lesions vary for the same assessment, assign the first evaluation date among target lesions.

- Date of PD as indicated by non-target lesions: the 1st date for which any non-target lesion exhibits a response of PD.

- Date of PD as indicated by new lesions: the 1st date for which any new lesion is detected.

7.6   Other Efficacy Analyses

7.6.1 Exploratory Alpha Fetoprotein Analysis

Alpha fetoprotein (AFP) assessments will be performed in conjunction with radiologic disease assessments.

A positive AFP outcome will be defined for this exploratory analysis as at least a 20% decrease in AFP serum levels from baseline. Additional definitions of positive AFP outcomes may be explored further. Estimates of positive AFP outcome rate may be reported with 95% confidence intervals and an estimate of the difference in positive AFP outcome rates between groups may be reported and tested for significance with a Pearson chi-square test (or Fisher's exact test, as appropriate). Subjects included in this analysis are those with AFP levels elevated to ≥ 400 µg/L at baseline. Additional criteria may be explored further.

AFP serum levels may be summarized by study visit and may include descriptive statistics such as mean, median, standard deviation, minimum, and maximum, and the changes from baseline. Additional analyses may be performed.

7.6.2 Time to Disease Assessments Analysis

Estimates of median time to disease assessments in each arm using Kaplan Meier methods, reported with 95% confidence intervals will be provided for the first four disease assessments on study along with associated logrank testing. Subjects lost to follow-up or that reach the survival endpoint will be censored at the date of their last disease assessment. For disease assessments that span multiple days, the disease assessment date assigned will be the date when the first imaging scan from the disease assessment was performed.

8   Safety Analysis

8.1   Definition of Safety Variables

The safety parameters assessed are given by the following:

- Frequency, and severity of AEs:
  - All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) under the Medical Dictionary for Regulatory Activities (MedDRA) system of classification with a severity assigned according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.0), or the rules specified in Section 8.6 of the protocol.
  - Laboratory parameters as presented in Appendix 7 of the protocol.
  - Laboratory toxicities will be graded based on the NCI-CTCAE (Version 4.0).
- Vital signs.
- Anti-mapatumumab antibody response.

All analyses performed on safety will be performed on the as-treated population.

8.2   Analysis of Adverse Events

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.

8.3   Serious Adverse Events

Serious adverse events (SAEs) will be summarized by relation to mapatumumab/placebo and by relation to sorafenib.

8.4   Deaths and Discontinuations due to Adverse Events

A summary of all subjects who die due to any cause or who discontinue study agent (mapatumumab/placebo and/or sorafenib) due to AEs will be provided.

8.5   Clinical Laboratory Evaluation

Laboratory parameters will be assessed at baseline and throughout the study. Frequencies of worst observed grade 0 to 4 toxicity as defined by the NCI-CTCAE (Version 4.0) will be presented for each laboratory parameter.

Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts from baseline. Specific laboratory tests are listed in Appendix 7 of the protocol. Some laboratory tests can be graded for toxicity for either an increase or a decrease (sodium, potassium, magnesium, calcium, and glucose). Because of this, they will be listed twice in each presentation, once to detect an increase and once to detect a decrease (eg, hypoglycemia and hyperglycemia). For presentation of shifts from baseline in these cases, a 0 at baseline will indicate an absence of toxicity in the direction being detected (eg, for shift tables for hyperglycemia, a 0 at baseline will indicate an absence of hyperglycemia). For laboratory tests not graded by the NCI-CTCAE, tables summarizing shifts outside of the normal range will be presented.

8.5.1 Exploratory Assessments (B & T Lymphocyte Subsets) Analysis

As part of an exploratory analysis, blood samples will also be collected for quantification of B and T lymphocyte subsets to assess the effect of treatment on lymphocyte subpopulations. The results of these assessments will be presented in tabular form, and the outcome of the exploratory analyses of these results may be reported separately.

8.6   Vital Signs

Vital signs will be assessed at baseline and throughout the study. Vital signs will be summarized by study visit and will include descriptive statistics such as mean, median, standard deviation, minimum, and maximum for the value of the parameters and the changes from baseline.

8.7   Immunogenicity

Serum samples for antibodies to mapatumumab will be obtained at baseline (prior to dosing on Cycle 1/Day 1), 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). Rates of antibody response (persistent positive, transient positive, and negative) will be tabulated, and all data will be summarized in listings. A persistent positive immune response is defined as a subject who has 2 or more positive samples or for whom the last sample is positive. A transient positive response is defined as a subject who has only 1 positive response (if it is not the last sample). In these definitions, all data are counted, including baseline.

8.8   Subgroup Analyses

Subgroup analyses for safety data will be performed on laboratory parameters testing for the hepatitis B surface antigen and the hepatitis C surface antibody (positive for the hepatitis B surface antigen, positive for the hepatitis C surface antibody vs. others). There are no additional preplanned subgroup analyses for this study for the safety analysis.

9   Pharmacokinetic and Pharmacodynamic Analyses

Serum mapatumumab concentration data obtained from this study will be pooled with data obtained from other studies for use in a population pharmacokinetic analysis, which will be reported separately. For this study report, serum mapatumumab concentration results, determined by enzyme-linked immunosorbent assay, will be presented using appropriate graphic and tabular summaries.

An optional exploratory biomarker sub-study is being conducted in conjunction with this study. As described in Section 7.3 and Appendix 6 of the protocol, serum proteins and DNA will be isolated from consenting subjects for an exploratory analysis of response-related proteins and genes. In addition, samples of historical and post-treatment biopsy samples will be collected, if available, to assess the expression of factors associated with tumor response. Analysis of biological markers of apoptosis and potential indicators of biological response will consist of descriptive statistical summaries. 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 (as appropriate), ANOVA and ANCOVA. In addition, analysis may be stratified based on disease response in order to evaluate potential association between fluctuations in these markers and clinical outcome. Results from these analyses may be reported separately.

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10   Other Analytical Considerations

There are no other analytical considerations.

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11   References

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