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Clinical Protocol CA209459

A Randomized, Multi-center Phase III Study of Nivolumab versus Sorafenib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma

(CheckMate 459: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 459)

Revised Protocol Number: 04
Incorporates: Amendment 18 and Administrative Letter 04

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 04	15-Jan-2019	Incorporates Amendment 18 and Administrative Letter 04.
Amendment 18	15-Jan-2019	The primary reason for this amendment is to update several protocol sections to reflect the most recent guidance for treating study participants with nivolumab. In addition, an exploratory objective evaluating the correlation of tumor inflammation with efficacy based on recent preliminary data has been added. Several minor inconsistencies in study objectives and endpoints and minor administrative changes are also addressed.
Administrative Letter 04	28-Aug-2017	Update summary of change for Amendment 16 to reflect implementation as soon as possible, and to update the overall alpha in Section 8.4.2.1
Revised Protocol 03	15-Aug-2017	Incorporates Amendment 16 and Administrative Letters 02 and 03
Amendment 16	15-Aug-2017	The purpose of this amendment is to change Overall Response Rate (ORR) from a co-primary objective to a secondary objective of the study. Overall Survival (OS) will be the sole Primary Endpoint of the study. [redacted] his amendment applies to all subjects enrolled.
Administrative Letter 03	15-Mar-2017	Clarify that local Hepatitis D testing is an option in the event the Central Laboratory is unable to perform Hepatitis D testing in certain circumstances.
Administrative Letter 02	02-Mar-2017	Update to Study Director's office location
Revised Protocol 02	24-Aug-2016	Incorporates Amendment 11
Amendment 11	24-Aug-2016	• Updated Study Director/Medical Monitor information • Co-primary endpoint and objective changed from time to progression (TTP) to objective response rate (ORR) – Added requirement for confirmatory scan to be performed for CR/PR assessment of best overall response (BOR) • Management algorithms updated per revised nivolumab IB
Revised Protocol 01	01-Oct-2015	Incorporates Amendment 02
Amendment 02	01-Oct-2015	Addition of collection of peripheral blood mononuclear cells (PBMCs) and myeloid derived suppressor cells (MDSCs) collected from subjects at baseline from selected sites, reduction of frequency of HCV RNA testing for HCV infected subjects, clarification of locoregional therapy inclusion criteria, as

SYNOPSIS

Clinical Protocol CA209459

(CheckMate 459: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 459)

Protocol Title: A Randomized, Multi-center Phase III Study of Nivolumab versus Sorafenib as First-Line Treatment in Patients with Advanced Hepatocellular Carcinoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

Nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity;

Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity

Study Phase: Phase 3

Research Hypothesis: Nivolumab administration in subjects with advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy will improve OS compared with sorafenib.

Objectives:

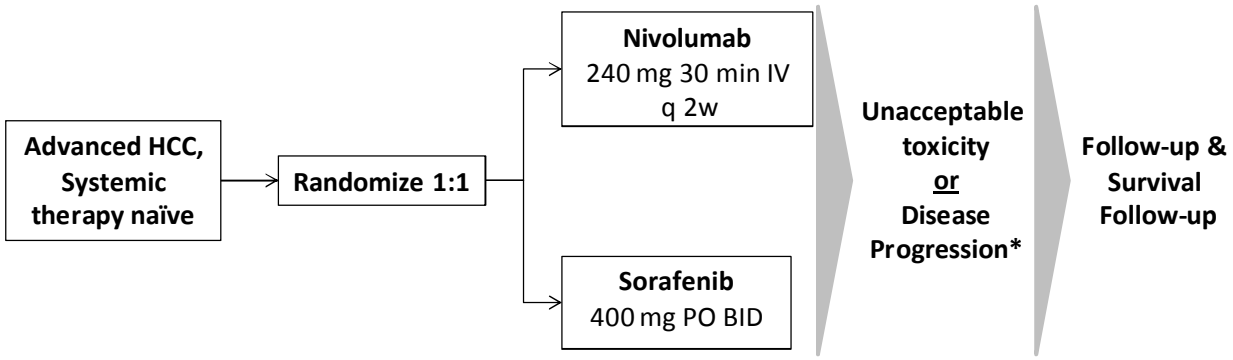
Primary Objectives

To compare the overall survival (OS) of nivolumab to sorafenib in subjects with advanced HCC who have not received prior systemic therapy.

Secondary Objectives

- To compare the objective response rate (ORR) of nivolumab to sorafenib. ORR will be determined from assessment by a blinded independent central review (BICR) based on RECIST 1.1.
- To compare progression free survival (PFS) of nivolumab and sorafenib. PFS will be determined from assessments by a blinded independent central review (BICR) based on RECIST 1.1
- To evaluate the relationship between tumor PD-L1 expression and efficacy

Study Design:



* Subjects may be treated beyond disease progression under protocol-defined conditions. See Section 3.1.6

Stratification factors:

- Etiology (HCV vs. non-HCV [ie, HBV- and HCC with no history of hepatitis virus infection])
- Vascular invasion &/or extrahepatic spread (present or absent),
- Geography (Asia vs Non-Asia).

Study Population: Adult (≥ 18 years) male and female subjects with advanced HCC. Subjects must not be amenable for management with surgery or loco-regional therapy or have progressed after surgery or loco-regional therapy. Surgical and/or locoregional therapy to reduce overall tumor burden prior to study entry is not allowed. Subjects must not have received prior systemic therapy for advanced HCC in keeping with the first-line setting of this study.

Eligibility criteria are defined in the protocol.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA209459		
Medication	**Potency**	**IP/Non-IP**
Nivolumab Solution for Injection	100 mg (10 mg/mL)	IP
Sorafenib Tablets	200 mg	IP

Study Assessments: On treatment visits will occur at Day 1 and every 2 weeks thereafter. Tumor imaging assessments will occur 8 weeks from the date of randomization (+/-1 wk), then every 8 weeks (+/- 1 wk) thereafter up to 48 weeks, then it will be every 12 weeks (+/- 1 week) until disease progression or treatment is discontinued (whichever occurs later). Subjects will be treated until unacceptable toxicity or disease progression. Following discontinuation of therapy, safety will be assessed through post-treatment Follow Up visit 2 (~ 100 days from last dose). Survival status will be assessed every 3 months after follow up visits are completed, and may be completed via telephone or in person visits.

Statistical Considerations:

Sample Size:

The sample size determination of this study is based on OS comparison between subjects randomized to receive nivolumab and sorafenib. With a total of 726 subjects randomized in a 1:1 ratio, approximately 91.5% power will be achieved with an overall type I error 0.05 for OS comparison. The number of events and power for the OS comparison are calculated based on simulation and assuming an exponential distribution for OS in each randomization arm. The study requires at least 520 OS events to ensure approximately 91.5% power to detect a hazard ratio of 0.74 with an overall type I error of 0.05 (two-sided) for OS. The HR of 0.74 corresponds to a 35% increase in the median OS for both non-HCV infected subjects and HCV infected subjects, assuming a median OS of 10 months for non-HCV infected subjects and a median OS of 14 months for HCV infected subjects in the sorafenib arm. One formal interim analysis will be conducted with 80% OS events observed. The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. Assuming a piecewise constant accrual rate, it will take approximately 33 months to obtain the required number of deaths for the final OS analysis (13 months for randomization and 20 months for follow-up) and approximately 25 months (13 months for randomization and 12 months for follow-up) for the OS interim analysis.

Endpoints:

Primary Endpoints

- Overall Survival (OS)

  OS is defined as the time from the date of randomization to the date of death due to any cause in all randomized subjects. Subjects who are alive will be censored at the last known alive dates.

Secondary Endpoints

- Objective Response Rate (ORR)

  ORR, as determined based on BICR-assessed tumor response according to RECIST 1.1, is defined as the proportion of all randomized subjects whose best overall response (BOR) is either a CR or PR. BOR is determined by the best response designation recorded between the date of randomization and the date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For a BOR of CR or PR, the initial response assessment must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

- Progression-Free Survival (PFS)

  PFS is defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by BICR according to RECIST 1.1 or death due to any cause. Subjects who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have baseline tumor assessment will be censored on the date they were randomized. Subjects who did not have any on-study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to subsequent anti-cancer therapy.

- PD-L1 expression

  The objective of evaluating the relationship between PD-L1 expression and efficacy will be measured by efficacy based on PD-L1 expression. Definition of PD-L1 expression will be described in the SAP.

Exploratory endpoints are described in detail in the protocol.

Analyses:

Additional analyses are described in detail in the protocol.

- Analysis of OS

  A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses (overall alpha=0.05). The distribution of OS will be compared in the two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by the stratification factors using allocated alpha based on Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary.. The hazard ratio (HR) and the corresponding 100x (1-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product limit method. Median OS and the corresponding two-sided 95% CIs will be computed using the log-log transformation. Survival rates at select milestones will be computed as well as the corresponding two-sided 95% CIs using the log-log transformation.

- Analysis of ORR

  ORR based on BICR assessment per RECIST 1.1 between the two randomized arms in all randomized subjects will be compared using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors. The associated odds ratio and CI will also be calculated. ORR along with its 95% exact CI using the Clopper-Pearson method will be provided for each randomization arm. Hierarchical testing of ORR will be performed upon demonstration of superiority in OS at OS interim or final analyses for all randomized subjects.

- Analysis of PFS

  Hierarchical testing of PFS will be performed upon demonstration of superiority in ORR at OS interim or final analysis for all randomized subjects. Details of timing for the analysis and alpha allocated will be described in the SAP.

  PFS will be compared using a two-sided stratified log-rank test. The HR and the corresponding two-sided confidence intervals (CIs) will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by the stratification factors. PFS curves will be estimated using the KM product-limit method. Median PFS and the corresponding two-sided 95% CIs will be computed using the log-log transformation. In

addition, PFS rate at select milestone will be computed as well as the corresponding two sided 95% CIs using the log-log transformation.

- Safety Analysis

  The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All on-treatment AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

1.1 Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related death. The incidence of HCC varies geographically largely due to variations in hepatitis B and C virus infection. The majority (> 80%) of cases occur in sub-Saharan Africa and eastern Asia. China alone accounts for 55% of cases worldwide. In almost all populations, males have higher rates of liver cancer than females with an overall sex ratio around 2.4[1].

HCC has the highest mortality-to-incidence rate ratio of 0.98 followed by lung (0.85) and esophageal (0.83) cancers[2]. The numbers of deaths is close to the number of new cases because most HCCs are detected at an advanced stage and occur in patients with underlying liver dysfunction, making HCC a highly lethal cancer. The prognosis is also poor because of the low effectiveness of available treatments. The 5-year HCC survival rate is approximately 5%-6% compared with 72% and 22% for breast cancer stages III and IV respectively[3,4,5].

Treatment of HCC is challenging because the disease is highly heterogeneous with different etiologies, varying approaches to diagnosis and treatment, and variations in responses to therapy[6]. In contrast to other high-incidence cancers, treatment decisions in HCC are hampered by the limits of high-quality evidence across all clinical scenarios. As with other tumors, treatment selection depends on disease stage, the tumor extent, and the patient's performance status. However, the patient's underlying liver function has an important influence on HCC treatment decisions. A total of 90% of HCC patients have an underlying cirrhosis requiring management of both the malignancy and the cirrhosis. Additionally, many patients require ongoing support for concomitant underlying disease such as hepatitis B virus (HBV) or hepatitis C virus (HCV) or non-viral related liver disease, eg, non-alcoholic steatohepatitis (NASH). Treatment strategies are therefore complex and best served by a multidisciplinary team[7].

Relatively few patients are eligible for curative treatment because of the late appearance of symptoms.[7] In the West, only around 30% of all patients are diagnosed early enough to be eligible for potentially curative treatment such as resection, transplantation and radiofrequency ablation. Approximately 20% are diagnosed in the intermediate stage and can gain survival benefits of up to 20 months from transarterial chemoembolization (TACE). The majority of patients, however, are diagnosed in the advanced stages of the disease when the disease is beyond resection and locoregional treatments are ineffective. The prognosis for these patients is poor[8].

The multi-tyrosine kinase inhibitor, sorafenib, is the only systemic agent proven to provide a survival benefit in patients who are not expected to benefit from surgery or locoregional therapies. However, the prognosis of patients with advanced HCC has not been radically improved.[9] The survival improvement with sorafenib over placebo is modest, at 2.8 months in the pivotal Western trial and 2.3 months in the related Asian trial.[10],[11] GIDEON, the largest real-life study conducted on the use of sorafenib, reported sorafenib-related adverse events (AEs) in 64% of patients, 23%

of which were Grade 3 or 4 AEs. In 28% of patients, AEs resulted in permanent discontinuation of sorafenib.[12] In the 2 pivotal sorafenib trials, dose reductions were common. Hand-foot-skin reactions (HFSR) (10%-11% of patients) and diarrhea (5%-7% of patients) were the most common significant AEs leading to dose reduction.[10,11] Asians experience more HFSR than other populations with a reported rate of 45% for any Grade in the sorafenib Asia-Pacific study compared with 21% in the West. The landmark sorafenib trials also failed to demonstrate symptomatic improvement or improvement in quality of life.[7] Post-marketing clinical studies showed that although sorafenib treatment has shown a significant increase in mean overall survival in different studies, only a portion of patients show real benefits, while the incidence of drug related significant adverse effects and the economic costs are relatively high.[13] Finally, predictive biomarkers for sorafenib benefit that could refine the risk-benefit ratio for therapy have not yet been validated.[7,8] All other drugs tested for HCC in recent years have failed in both the first and second line settings.[14,15] There therefore is a need for new treatment options for advanced HCC.

1.3 Research Hypothesis

Nivolumab administration in subjects with advanced hepatocellular carcinoma (HCC) who have not received prior systemic therapy will improve OS compared with sorafenib.

1.4 Objectives(s)

1.4.1 Primary Objectives

To compare the overall survival (OS) of nivolumab to sorafenib in subjects with advanced HCC who have not received prior systemic therapy.

1.4.2 Secondary Objectives

- To compare the objective response rate (ORR) of nivolumab to sorafenib. ORR will be determined from assessment by a blinded independent central review (BICR) based on RECIST 1.1.
- To compare progression free survival (PFS) of nivolumab and sorafenib. PFS will be determined from assessments by a blinded independent central review (BICR) based on RECIST 1.1
- To evaluate the relationship between tumor PD-L1 expression and efficacy

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) and Regulatory Authority (ies) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives (as per country guidelines) are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is an open-label, two-arm, randomized, Phase 3 study in adult (≥ 18 years) male and female subjects with advanced HCC. Subjects must not be amenable for management with surgery or loco-regional therapy or have progressed after surgery or loco-regional therapy. Subjects must not have received prior systemic therapy for advanced HCC in keeping with the first-line setting of this study.

After screening for eligibility and signing of informed consent, qualified subjects will be randomized in a 1:1 ratio to receive nivolumab or sorafenib. It is expected that approximately 908 subjects will be screened for the study with approximately 726 subjects entering the treatment phase. Approximately 363 subjects will be randomized to each study arm. Stratification will occur

by etiology (HCV vs. non-HCV [ie, HBV- and HCC with no history of hepatitis virus infection]), vascular invasion &/or extrahepatic spread (present or absent), geography (Asia vs Non-Asia).

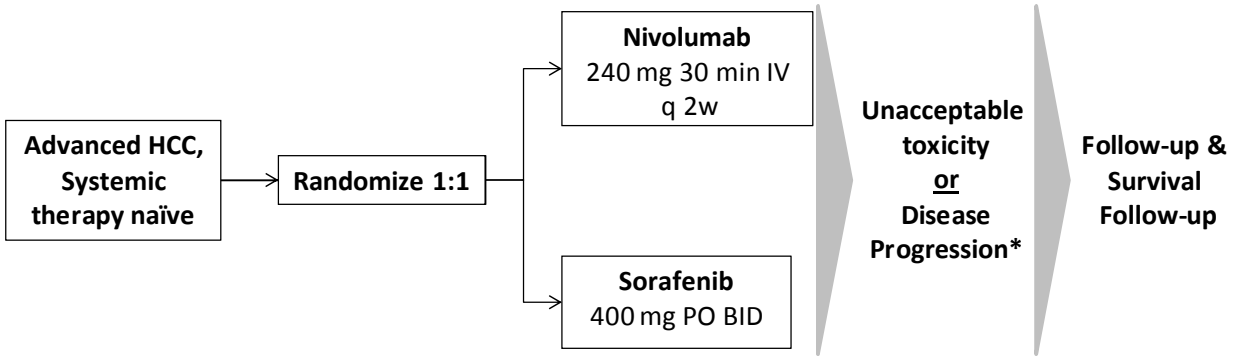
Subjects will receive open-label treatment with one of the following:

- Nivolumab 240 mg IV every 2 weeks until disease progression or unacceptable toxicity
- Sorafenib 400 mg PO BID until disease progression or unacceptable toxicity

On both arms, treatment beyond initial investigator-assessed RECIST 1.1 defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating study drug, as specified in Section 3.1.6. Specific requirements for subjects treated with nivolumab and sorafenib are described in Sections 4.5.1.6 and 4.5.3.4, respectively.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



* Subjects may be treated beyond disease progression under protocol-defined conditions. See Section 3.1.6

Stratification factors:
- Etiology (HCV vs. non-HCV [ie, HBV- and HCC with no history of hepatitis virus infection])
- Vascular invasion &/or extrahepatic spread (present or absent),
- Geography (Asia vs Non-Asia).

3.1.1 Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF)
- Subject is enrolled using the Interactive Voice Response System (IVRS)
- Subject is assessed for study eligibility with the required timeframe found in Table 5.1-1
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analysis. Central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to subject randomization (The tissue submitted will be assessed for quality with an H&E stain and only those subjects who have meet tissue quality thresholds can be randomized)
- The screening phase either ends with confirmation of full eligibility and treatment assignment of the subject or with the confirmation that the subject is a screen failure.

3.1.2 Treatment Phase

The treatment phase begins with the randomization call to the IVRS. The subject is randomly assigned to one of the two treatment arms. Study treatment must begin within 3 days of randomization.

Nivolumab 240 mg IV is administered as a 30-minute IV infusion every 2 weeks. Sorafenib 400 mg is administered twice a day. Both study drugs are continued until disease progression, unacceptable toxicity, withdrawal of consent or study closure. Study assessments are to be collected as outlined in Table 5.1-2 and Table 5.1-3.

Nivolumab or sorafenib treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator assessed clinical benefit and is tolerating study drug, as specified in Section 3.1.6. Specific requirements for subjects treated with nivolumab and sorafenib, including dose modifications, dose delays, and treatment discontinuation criteria are described in Sections 4.5.1 and 4.5.3, respectively.

The treatment phase ends when the subject is discontinued from study drug (see Section 3.5). Subjects will then enter the Study Follow-Up Phase.

3.1.3 Follow Up Phase

This phase begins when the decision to discontinue study drug is made. Two follow up visits are required, occurring 35 days ± 7 days from the last dose (X01) and 80 days ± 7 days from X01 (X02). Follow up visits include targeted physical examination, laboratory tests, tumor assessments, adverse event and concomitant medication assessments, and PRO instrument collection. Additional details and requirements are outlined in Table 5.1-4. After completion of the first two follow-up visits, subjects will be followed every 3 months for survival, as outlined in Table 5.1-4.

Subjects who discontinue study drug for reasons other than radiographic disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-2 and Table 5.1-3 until progression.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after the last dose of study drug.

3.1.4 Study Duration

The duration of the study from start of randomization to final analysis of OS will be approximately 33 months, when the requested number of death events are expected to occur. The study may be stopped earlier for superiority at OS interim analysis. Additional survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up collection has concluded.

3.1.5 Review of Safety

The subjects' safety will be monitored on an ongoing basis as described fully in Section 6. In addition, a BMS medical surveillance team (MST) routinely reviews safety signals across the entire nivolumab program. A Data Monitoring Committee (DMC) will also be established to provide oversight and safety and efficacy considerations in protocol CA209459 (see Section 7.1).

3.1.6 Treatment beyond progression

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop disease progression by conventional response criteria before demonstrating clinical objective responses and/or stable disease (see Section 1.2.6). This phenomenon was observed in the Phase I study of nivolumab, CA209003 and confirmed in multiple phase 3 studies (ie, lung CA209017[45]; melanoma CA209037[47], CA209066[47], and CA209067[48]). Two hypotheses explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent.

Similarly there are data to suggest that sorafenib administration beyond first radiological PD could continuously suppress HCC growth and may have survival benefit (See Section 1.2.6.2).

Therefore, subjects will be allowed to continue study therapy after an initial investigator-assessed RECIST 1.1-defined progression (Appendix 1) as long as they meet the following criteria:

- Investigator assessed clinical benefit, and
- Subject is tolerating the study drug (nivolumab or sorafenib)

These criteria aim to ensure the risk/benefit for continuing treatment will continue to favor the subjects. The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. Palliative local therapy for isolated lesions may be permitted if the patient is considered to have progressed and is discussed with the BMS Medical Monitor. All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records. Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least

10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

3.2 Post-Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to BMS supplied study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

c) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented

2. Target Population

a) Subjects with advanced hepatocellular carcinoma

i) disease not eligible for curative surgical and/or locoregional therapies, OR

ii) progressive disease after surgical and /or locoregional therapies

Note: Surgical and/or locoregional therapy to reduce overall tumor burden prior to study entry is not allowed.

b) No prior systemic therapy for hepatocellular carcinoma

c) Histologic confirmation of hepatocellular carcinoma.

i) Subjects with only a radiologic diagnosis of HCC may be enrolled for screening in the study but histological confirmation is mandatory prior to the start of study therapy.

ii) Tumor tissue (formalin-fixed, paraffin embedded archival or recent acquisition) must be received by the central vendor (1 block or 15 unstained slides) for correlative studies outlined in Section 5.6.1 in order to conduct the randomization call in the IVRS (the tissue submitted will be assessed for quality with a H&E stain and only those subjects who have meet tissue quality thresholds can be randomized). If archived samples are not available, subjects must consent to a pre-treatment fresh biopsy as a condition of protocol participation. (Note: Fine needle aspiration (FNA) and bone metastases samples are not acceptable for submission).

d) At least one RECIST 1.1 measurable untreated lesion. All subjects must have at least one previously untreated, unidimensionally measurable lesion by contrast-enhanced spiral computed tomography (CT) ≥ 10 mm or contrast enhanced dynamic magnetic resonance imaging (MRI) scan ≥ 10 mm (malignant lymph nodes must be ≥ 15 mm on short axis) (additional details are included in Appendix 1).

   i) The lesion can be accurately measured uni-dimensionally according to RECIST 1.1 criteria

   ii) The lesion has not been previously treated with surgery, radiotherapy, and/or locoregional therapy (eg: radiofrequency ablation [RFA], percutaneous ethanol [PEI] or acetic acid injection [PAI], cryoablation, high-intensity focused ultrasound [HIFU], transarterial chemoembolization [TACE], transarterial embolization [TAE], etc.)

e) For subjects who progressed after locoregional therapy, the locoregional procedure must have been completed at least 4 weeks prior to the baseline scan. In addition, all acute toxic effects of the locoregional procedure must have resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 Grade ≤ 1.

f) Cirrhotic status of Child-Pugh Class A (Appendix 2)

g) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. See Appendix 3 for ECOG Performance Status scale

h) Subjects are eligible to enroll if they have non-viral-HCC, or if they have HBV-HCC, or HCV-HCC defined as follows:

   i) HBV-HCC: Resolved HBV infection (as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen) or Chronic HBV infection (as evidenced by detectable HBV surface antigen or HBV DNA). Subjects with chronic HBV infection must have HBV DNA < 100 IU/mL and must be on antiviral therapy.

   ii) HCV-HCC: Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody

i) Screening laboratory values must meet the following criteria, without continuous supportive treatment such as growth factor administration, blood transfusion, coagulation factors and/or platelet transfusion, or albumin transfusion, and should be obtained within 14 days prior to randomization)

   i) Adequate hematologic function:

      (1) WBC ≥ 2000/μL

(2) Neutrophils ≥ 1500/μL

(3) Platelets ≥ 60 x 10^3/μL

(4) Hemoglobin ≥ 8.5 g/dL

ii) Prothrombin time (PT)-international normalized ratio (INR) ≤ 2.3 or Prothrombin time (PT) ≤ 6 seconds above control

iii) Adequate hepatic function as documented by:

(1) serum albumin ≥ 2.8 g/dL

(2) total bilirubin ≤ 3 mg/dl, and

(3) AST ≤ 5 times the institutional upper limits of normal

(4) ALT ≤ 5 times the institutional upper limits of normal

iv) Adequate renal function with a serum creatinine of < 1.5x ULN or a creatinine clearance > 50 mL/min (Cockcroft-Gault formula)

j) Adequate cardiac function with a left ventricular ejection fraction (LVEF) > 50% as measured by 2-D echocardiography

3. Age and Reproductive Status

a) Males and Females, ages ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug.

c) Women must not be breastfeeding

d) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception as indicated in the informed consent form, for the duration of treatment with study drug(s) [nivolumab or sorafenib] plus approximately 5 half-lives of the study drug(s) [nivolumab or sorafenib] plus 30 days (duration of ovulatory cycle):

i) Subjects randomized to nivolumab: total of 5 months post-treatment completion

ii) Subjects randomized to sorafenib: total of 40 days post-treatment completion

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as indicated in the informed consent form, for the duration of treatment with study drug (s) [nivolumab or sorafenib] plus approximately 5 half-lives of the study drug(s) [nivolumab or sorafenib] plus 90 days (duration of sperm turnover):

i) Subjects randomized to nivolumab: total of 7 months post-treatment completion

ii) Subjects randomized to sorafenib: total of 100 days post-treatment completion

f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC

b) Prior liver transplant

c) History of hepatic encephalopathy

d) Clinically significant ascites as defined by:

i) Any ascites by physical examination at screening or

ii) Prior ascites that required treatment and require on-going prophylaxis OR current ascites requiring treatment

e) Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 6 months

f) Active brain metastases or leptomeningeal metastases. Subjects with treated brain metastases are eligible if the following criteria are fulfilled:

i) The brain lesions have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete and within 28 days prior to randomization. (If an MRI is contraindicated, a CT scan is acceptable after discussion with the study Medical Monitor.)

ii) There is no requirement for immunosuppressive doses of corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration

iii) The case is discussed with the study Medical Monitor

2. Medical History and Concurrent Diseases

a) Infections:

i) Active co-infection with:

(1) Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and HCV RNA, OR

(2) Hepatitis D infection in subjects with hepatitis B

ii) Subjects with a history of coinfection with both hepatitis B and C, including, but not limited to:

(1) HBV DNA positive or HBV surface antigen positive subjects with detectable HCV antibody, OR

(2) HCV RNA positive subjects with resolved HBV infection as evidenced by detectable HBV surface antibody, detectable HBV core antibody, undetectable HBV DNA, and undetectable HBV surface antigen OR

(3) Any positive test for HBV excluding HBV surface antibody indicating chronic or resolved HBV infection (positive HBV core antibody, positive HBV surface antigen, or detectable HBV DNA) and any positive test for HCV indicating chronic or resolved infection (positive HCV antibody or detectable HCV RNA)

iii) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

iv) Active bacterial or fungal infections requiring systemic treatment within 7 days prior to study drug dosing

b) Interstitial lung disease that is symptomatic or may interfere with the detection and management of suspected drug-related pulmonary toxicity

c) History of active cardiac disease as evidenced by the following:

i) Uncontrolled hypertension which is defined as systolic blood pressure > 150 mmHg or diastolic blood pressure > 90 mmHg despite optimal medical management

ii) Congestive heart failure NYHA (New York Heart Association) class > 2 (Appendix 4)

iii) Active coronary artery disease, unstable or newly diagnosed angina or myocardial infarction < 6 months prior to study entry

iv) Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin

v) Valvular heart disease > CTCAE Grade 2

vi) QTc (Fridericia) > 450 msec on two consecutive ECGs (baseline ECG should be repeated if QTc is found to be > 450 msec)

d) Thrombotic or embolic events (except HCC tumor thrombus) within the past 6 months, such as cerebrovascular accident (including transient ischemic attacks), pulmonary embolism

e) Any other hemorrhage/bleeding event ≥ CTCAE Grade 3 within 8 weeks except for esophageal or gastric varices (Exclusion criteria 1.e.)

f) History of non-healing wounds or ulcers, within 3 months of study entry. Bone fractures at risk of bleeding, within 3 months of study entry, are also excluded.

g) Major surgical procedure, open biopsy, or significant traumatic injury within 4 weeks prior to start of investigational product administration or those who receive minor surgical procedures (eg, core biopsy) within 1 week prior to the start of investigational product.

h) Prior organ allograft or allogeneic bone marrow transplantation

i) Subjects who are unable to swallow tablets, requiring intravenous alimentation, malabsorption syndrome, or any conditions affecting gastrointestinal absorption; or active peptic ulcer disease.

j) Pre-existing thyroid abnormality with thyroid function that cannot be maintained in the normal range with medication.

k) Subjects with any active, known, or suspected autoimmune disease, with the following exceptions:

i) Subjects with vitiligo, type 1 diabetes mellitus, resolved childhood asthma or atopy are permitted to enroll.

ii) Subjects with suspected autoimmune thyroid disorders may be enrolled if they are currently euthyroid or with residual hypothyroidism requiring only hormone replacement.

iii) Subjects with psoriasis requiring systemic therapy must be excluded from enrollment

l) Prior malignancy active within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast.

m) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg/day prednisone equivalent) or other immunosuppressive medications within 14 days of study administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg/day prednisone equivalents are permitted in the absence of active autoimmmune disease, with the exception of criteria 1f, ii

n) Any serious or uncontrolled medical disorder that in the opinion of the investigator may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

3. Prior and Current Therapies

a) Subjects with history of life-threatening toxicity related to prior immune therapy (eg. with anti-CTLA-4 or anti-PD-1/PD-L1 treatment) except those that are unlikely to re-occur with standard countermeasures (eg. Hormone replacement after adrenal crisis); VEGF inhibitors, Raf-kinase inhibitors, MEK inhibitors, Farnesyl transferase inhibitors or other immunotherapy agents for HCC

b) Prior use of systemic investigational agents for HCC

c) Treatment with strong CYP3A4 inducers within 7 days of study entry, including rifampin (and its analogues) or St. John's wort.

d) Current anticoagulation therapy

e) Treatment with anti-platelet therapy (aspirin at dose ≥ 300 mg/day, clopidogrel at dose ≥ 75 mg/day)

f) Radiotherapy within 4 weeks prior to start of study drug. Palliative radiotherapy for symptomatic control is acceptable (if completed at least 2 weeks prior to study drug administration) and no additional radiotherapy for the same lesion is planned.

4. Physical and Laboratory Test Findings

a) Positive pregnancy test

b) Baseline serum sodium < 130 mmol/L

c) Baseline serum potassium < 3.5 mmol/L (potassium supplementation may be given to restore the serum potassium above this level prior to study entry)

5. Allergies and Adverse Drug Reaction

a) Known or suspected allergy to nivolumab or sorafenib or study drug components

b) History of severe hypersensitivity reaction to any monoclonal antibody

6. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

7. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone, (FSH) level > 40mIU/mL to confirm menopause.

*Females treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40 mIU/ml at any time during the washout period, the woman can be considered postmenopausal:

- 1 week minimum for vaginal hormonal products (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products

3.4 Concomitant Treatments

3.4.1 Permitted Therapy

3.4.1.1 Antiviral therapy

Subjects on antiviral therapy for hepatitis B or C should continue the treatment during the study. Changing of dosage and regimens of antiviral therapy will be at the discretion of the investigator.

If a subject has a > 1 log IU/mL increase in HBV DNA, then virologic breakthrough should be considered and HBV DNA confirmed. Adherence to current antiviral therapy should be assessed, and resistance testing performed according to local practices. If a subject has documented virologic

breakthrough due to antiviral resistance, then this should be managed based on standardized regional guidelines and treatment with nivolumab temporarily held. The subject may resume treatment with nivolumab once virologic control is reestablished (HBV DNA < 100 IU/mL).

For any subject who continues to be HCV RNA positive after receiving nivolumab, current guidelines for management of chronic HCV infection, including those from AASLD, EASL, or APASL may be consulted. Initiation of direct acting antivirals (DAAs) for HCV is allowed at the discretion of the investigator after discussion with the BMS medical monitor.

3.4.1.2 Steroids

For subjects randomized to **nivolumab,** steroid therapy is permitted as follows:

- Topical, ocular, intranasal, intra-articular, and inhalational corticosteroids (with minimal systemic absorption).
- Adrenal replacement steroid doses including doses > 10 mg daily prednisone equivalent in the absence of active immune disease.
- Immunosuppressive doses (eg, prednisone > 10 mg/day or equivalent) in the context of treating adverse events.
- A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen).

Steroid restrictions **do not apply** to subjects randomized to **sorafenib** treatment.

3.4.1.3 Vaccines

The use of any live / attenuated vaccine (eg varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) during treatment and until 100 days post last dose of nivolumab is prohibited.

3.4.1.4 Other Systemic Therapy

- Hormone replacement therapy - subjects may continue to receive hormonal replacement therapy if initiated prior to randomization.
- Biphosphonates and RANK-L inhibitors
  - For subjects randomized to nivolumab, these are allowed for bone metastases
  - For subjects randomized to sorafenib, please follow local guidelines when combining biphosphonates and RANK-L inhibitors with anti-angiogenesis agents[49,50,51]

3.4.1.5 Palliative Local Therapy

Palliative local therapy for clinically symptomatic tumor sites (eg, bone pain), including palliative (limited-field) radiation therapy and palliative surgical resection may be considered if the following criteria are met:

- The subject is considered to have progressed at the time of palliative local therapy and meets the criteria to continue with treatment beyond progression. (Section 3.1.6)
- The lesion for palliative local therapy is a non-target lesion.
- The case is discussed with the BMS Medical Monitor prior to the initiation of palliative local therapy.

The potential for overlapping toxicities with radiotherapy and nivolumab currently is not known; however, anecdotal data suggests that it is tolerable. As concurrent radiotherapy and nivolumab have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade < 1 prior to resuming nivolumab.

Tumor lesions requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy.

Palliative therapy must be clearly documented in the source records and electronic case report form. Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events.

3.4.2 Prohibited and/or Restricted Treatments

3.4.2.1 All subjects

The following are prohibited for all subjects during the study:

- Loco-regional therapy for HCC
- Any concurrent antineoplastic therapy such as chemotherapy, molecular targeted therapy, hormonal therapy, immunotherapy, botanical formulations with an approved indication for cancer treatment (eg, traditional Chinese medicines) radiation therapy (except for palliative radiation therapy described in Section 3.4.1.5)
- Immunosuppressive agents (except to treat a drug-related adverse event)
- Investigational agents for the treatment of cancer

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

3.4.2.2 Subjects randomized to nivolumab treatment

Systemic corticosteroids > 10 mg daily prednisone equivalent are not permitted, except as stated in Section 3.4.1.2 or to treat a drug-related adverse event.

3.4.2.3 Subjects randomized to sorafenib treatment

- Medications contraindicated with sorafenib treatment (refer to the package insert, summary of product characteristics (SmPC) or similar document)[52]

3.4.3 Other Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on subject attributes (eg, allergy history, diabetic history and renal status), the appropriate imaging modality and contrast regimen for each subject. Imaging contraindications and contrast risks should be considered in this assessment. Subjects with renal insufficiency should be assessed as to whether or not they should receive contrast and if so, what type and dose of contrast is appropriate. Specific to MRI, subjects with severe renal insufficiency (ie, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m2) are at increased risk of nephrogenic systemic fibrosis. MRI contrast should not be given to this subject population. In addition, subjects are excluded from MRI if they have tattoos, metallic implants, pacemakers, etc.

The ultimate decision to perform MRI in an individual subject in this study rests with the site radiologist, the investigator and the standard set by the local Ethics Committee.

3.5 Discontinuation of Subjects following any Treatment with Study Drug

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Specific criteria for discontinuation of study drugs are outlined for nivolumab in Section 4.5.1.5 and for sorafenib in Section 4.5.3.3.
- Disease progression unless the subject is eligible for treatment beyond progression (Section 4.5.1.6 for nivolumab and Section 4.5.3.4 for sorafenib)

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug a discussion between the investigator and the BMS Medical Monitor/designee must occur.

All subjects who discontinue study drug should comply with protocol specified follow-up procedures as outlined in Section 5. The only exception to this requirement is when a subject withdraws consent for all study procedures including post-treatment study follow-up or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post-Study Drug Study Follow up

In this study, overall survival is the primary endpoint. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study. Subjects who discontinue study drug for reasons other than disease progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-2 and Table 5.1-3 until progression.

BMS may request that survival data be collected on all treated subjects outside of the protocol window (Table 5.1-4). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow up.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes, or emails as well as lack of response by subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and cause of death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains

lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

Table 4-1: Study Drugs for CA209459:

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	IP	Open Label	10 mL per vial (5 or 10 vials/carton) Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8° C. Protect from light and freezing
Sorafenib Tablets[b]	200 mg	IP	Open Label	Wallet/blister card containing 28 film-coated tablets. Red and round with the Bayer cross on one side and "200" on the other side.	Store at 15°C to 25°C

[a] May be labeled as either BMS-936558-01 or Nivolumab

[b] These products may be obtained by the investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or summary of product characteristics (SmPC)

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational products are: BMS-936558 (nivolumab) and Sorafenib.

4.2 Non-investigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as non-investigational products.

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab).

4.3 Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.3.1 Nivolumab (BMS-936558)

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab).

BMS-936558 (nivolumab) is to be administered as an IV infusion over 30 minutes. At the end of the infusion, flush the line with a sufficient quantity of dextrose or normal saline.

4.3.2 Sorafenib

Please refer to the SmPC for complete storage, handling and dispensing information for sorafenib[52].

4.4 Method of Assigning Subject Identification

CA209459 is a randomized, open-label study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth
- Viral status at time of enrollment, if known

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria will be ready to be randomized through IVRS. The following information is required for site entry in the IVRS prior to subject randomization:

- Subject number
- Date of birth
- Vascular invasion and/or extrahepatic spread (present or absent)

Additional information will be automatically transferred to the IVRS by the Central Lab and must be available prior to subject randomization:

- Etiology (HCV vs non-HCV)
- Confirmation of tumor tissue sample receipt and acceptability at Central Laboratory

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to nivolumab or sorafenib, stratified by the following factors:

- Etiology - HCV vs non-HCV
- Vascular invasion and/or extrahepatic spread (present or absent)
- Geography (Asia vs. Non-Asia)

The randomization procedures will be carried out via permuted blocks within each stratum. The exact procedures for using the IVRS will be detailed in the IVRS manual.

4.5 Selection and Timing of Dose for Each Subject

Dosing schedules for both arms are detailed in Table 4.5-1. The first dose of study drug is to be administered within 3 days of randomization. Treatment dosing details are described separately for each Arm below. All subjects will be monitored continuously for AEs while on study treatment. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and adverse event criteria, as described in Sections 4.5.1 and 4.5.3.

Table 4.5-1: Selection and Timing of Dose for Each Subject

Drug	Dose	Frequency of administration	Route of administration	Duration
Nivolumab	240 mg	Every 2 weeks	30 minute intravenous (IV) administration	Until progression, unacceptable toxicity, or discontinuation from study
Sorafenib	400 mg (2 x 200 mg tablets)	Twice daily (BID)	PO	Until progression, unacceptable toxicity, or discontinuation from study

4.5.1 Nivolumab Dosing

4.5.1.1 Nivolumab Dose and Schedule

Subjects randomized to nivolumab will receive treatment with nivolumab at a dose of 240 mg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 2 weeks, until progression, unacceptable toxicity, withdrawal of consent, or study end, whichever occurs first.

Subjects may be dosed no less than 12 days between doses. Subjects may be dosed up to 3 days after the scheduled date if necessary. A dose given more than 3 days after the intended dose date will be considered a delay. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

4.5.1.2 Dose Modifications for Nivolumab

No dose modifications for nivolumab are allowed.

4.5.1.3 Dose Delay Criteria for Nivolumab

Nivolumab administration should be delayed for the following:

- Any Grade $\geq$ 2 non-skin drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality with the following exceptions:

  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
- Dose delay for changes in AST or ALT as follows:
  - If a subject has a baseline AST or ALT that is within normal limits, delay dosing for drug-related Grade $\geq$ 2 toxicity (2 grade shift)
  - If a subject has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related Grade $\geq$ 3 toxicity (2 grade shift)
  - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for a two-fold drug-related increase in AST or ALT or for AST or ALT values 8x ULN (whichever is lower).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated. It is recommended to monitor elevations in AST or ALT approximately every 3 days till levels peak or begin to decline. Nivolumab dosing can be resumed when re-treatment criteria are met (Section 4.5.1.4).

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

4.5.1.4 Criteria to Resume Dosing for Nivolumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade $\leq$ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline Grade 1 AST, ALT, or total bilirubin who require dose delays for reasons other than a drug-related hepatic event may resume treatment in the presence of Grade 2 AST, ALT, or total bilirubin.
- Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for permanent discontinuation are not met (Section 4.5.1.5).
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. If treatment is delayed > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.1.5 and Section 4.5.1.6. Please see also Appendix 5 (Algorithms for Management of Side Effects) for

guidance on appropriate management and follow-up of adverse events. For hepatic AE management, see Section 4.5.2.2.

4.5.1.5 Treatment Discontinuation Criteria for Nivolumab

Treatment with nivolumab should be permanently discontinued for the following

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days or recurs, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Hepatotoxicity as evidenced by the following:
  - AST or ALT > 10 x ULN for > 2 weeks,
  - AST or ALT > 15 x ULN irrespective of duration,
  - Total bilirubin > 5 x ULN for those with normal total bilirubin at entry or > 8 x ULN for subjects with elevated bilirubin at study entry, irrespective of duration.
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia < 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The BMS Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances or abnormalities that are not associated with clinical sequelae and are corrected with supplementation and appropriate management within 72 hours of their onset.
  - Grade 4 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
- Any dosing delay lasting > 6 weeks with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue

as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Investigator assessed disease progression according to RECIST 1.1 (unless subject meets criteria as specified in Section 4.5.1.6)

Tumor assessments for all subjects should continue as per protocol even if study drug dosing is discontinued.

4.5.1.6 Treatment Beyond Progression for Nivolumab

As described in Section 3.1.6 accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease.

Subjects will be permitted to continue with nivolumab treatment beyond initial RECIST 1.1-defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Subject is tolerating nivolumab treatment
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving any additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records.

If the decision is taken to continue nivolumab treatment beyond progression, the subject will remain on the trial and continue to be treated and monitored according to the Time and Events Schedule on Table 5.1-2.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden SLD (sum of longest diameters) from

time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm). Nivolumab treatment should be discontinued permanently upon documentation of further progression.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

For subjects discontinuing treatment because of global deterioration of health status without objective evidence of disease progression at that time, progression should be reported as "symptomatic deterioration". Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

[redacted]

[redacted]

4.5.3 Sorafenib Dosing

The criteria presented in this section are based on the sorafenib Summary of Product Characteristics (SmPC).[52]

4.5.3.1 Sorafenib Dose and Schedule

Subjects randomized to sorafenib will receive treatment with sorafenib. Sorafenib (Nexavar®) will be self-administered orally at the recommended dose of 400 mg sorafenib (two tablets of 200 mg) twice daily without food or with a low or moderate fat meal. If the subject intends to have a high-fat meal, sorafenib tablets should be taken at least 1 hour before or 2 hours after the meal. The tablets should be swallowed with a glass of water. Refer to the sorafenib SmPC for additional details[52].

Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, or study end, whichever occurs first. Provisions for treatment beyond progression are detailed in Section 4.5.3.4.

Trained personnel will dispense a 2 week supply of sorafenib to subjects on Day 1 of each new cycle (every two weeks). Each time study drug is dispensed, compliance will be evaluated and encouraged. Treatment compliance will also be monitored by drug accountability and recorded in the subject's medical record and eCRF. If the number of tablets returned does not agree with the expected number, the subject should be counseled and proper dosing reinforced.

Missed doses should be taken as soon as the subject remembers. However, if it is almost time for the next dose, the missed dose should be skipped and the subject should take his/her next dose as scheduled. A double dose should not be administered to make up for missed individual doses. Refer to the sorafenib SmPC for additional details.[52]

Subjects should be monitored continuously for adverse events while receiving study therapy and will be instructed to notify their physician immediately for any and all adverse events. Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy (Section 4.5.3.3). Dose modifications or delays may occur in the setting of a lower grade adverse event if the Investigator, in consultation with the Medical Monitor/sponsor, believes that it is in the interest of a subject's safety.

4.5.3.2 Dose Reductions for Sorafenib

When dose reduction is necessary during the treatment of HCC, the sorafenib dose should initially be reduced to two tablets of 200 mg sorafenib once daily. For further dose reductions, refer to the sorafenib SmPC or locally approved product label for additional details.[52]

4.5.3.3 Treatment Interruption or Discontinuation Criteria for Sorafenib

The decision to interrupt or discontinue sorafenib should follow local standards of care as guided by the locally approved product label or applicable SmPC.[52]

For any dose interruptions, re-initiation of study drugs therapy may be delayed for a maximum of 30 days to allow recovery from any adverse event. In exceptional cases where subjects are responding, re-initiation of therapy after missing > 30 consecutive days of treatment may be done on a case by case basis after confirmation with the BMS medical monitor.

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

4.5.3.4 Treatment Beyond Progression for Sorafenib

Subjects will be permitted to continue with sorafenib treatment beyond initial RECIST 1.1- defined progressive disease as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- Subject is tolerating sorafenib treatment
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent, at the next clinic visit, prior to receiving any additional sorafenib treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. The decision to continue treatment beyond initial investigator-assessed progression should be discussed with the BMS Medical Monitor and documented in the study records.

If the decision is taken to continue sorafenib treatment beyond progression, the subject will remain on the trial and continue to be treated and monitored according to the Time and Events Schedule on Table 5.1-3.

Subjects should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden (SLD: sum of the longest diameters) from time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm). Sorafenib treatment should be discontinued permanently upon documentation of further progression.

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

4.5.3.5 Management of Sorafenib Adverse Events

Toxicities attributable to sorafenib should be managed according to the locally approved product label or applicable SmPC.[52] Dose reductions are discussed in Section 4.5.3.2.

4.6 Blinding/Unblinding

Not applicable

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.8 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.9 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.10 Retained Samples for Bioavailability / Bioequivalence

Not applicable

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209459)

Procedure	Pre-Treatment (Baseline)	Notes
Eligibility Assessments		
Informed Consent	X	Original informed consent in screening for protocol participation. Study allows for re-enrollment of a subject that has discontinued the study as a pre-treatment failure. If re-enrolled, the subject must be re-consented and assigned a new subject number from IVRS.
Inclusion/Exclusion Criteria	X	Assessed during screening period and (re-enrollment if applicable).
Medical History	X	
Child-Pugh Score	X	
Safety Assessments		
Physical examination	X	Within 14 days prior to first dose
Physical Measurements	X	Height and Weight. Within 14 days prior to first dose
ECOG Assessment	X	
Vital Signs	X	Including BP, HR, temperature, respiratory rate. Obtain vital signs at the screening visit and within 72 hours prior to first dose.
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose
12 lead ECG	X	Within 14 days prior to first dose
2D Echocardiogram	X	2-D echocardiogram, performed locally, for valve and LVEF evaluation is to be done within 14 days prior to first dose and as clinically indicated.
Laboratory Tests	X	Performed locally, within 14 days prior to randomization to include CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), Alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase, Glucose, TSH, Free T4, Free T3

Table 5.1-1: Screening Procedural Outline (CA209459)		
Procedure	**Pre-Treatment (Baseline)**	**Notes**
Serology for Hep B, Hep C, Hep D	X	HepB surface antigen, HepB surface antibody, Hep B Core antibody, HepB DNA Viral load (PCR), Hep C viral load (PCR) and Hep C Antibody, Hep D antibody. Testing to be completed at the Central Laboratory within 28 days prior to randomization. ***In the event the Central Laboratory is unable to perform Hep D testing, local Hep D testing may be allowed <u>until</u> central lab testing resumes. Local testing requires approval from BMS along with supporting local laboratory documentation.***
Pregnancy test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done at screening visit and repeated within 24 hours of first dose of study therapy
SNP Sample	X	
Urinalysis	X	
Coagulation profile	X	Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead
Efficacy Assessments		
Baseline tumor imaging assessment	X	CT of the chest, CT or MRI of abdomen, and pelvis with IV contrast, including required tri-phasic CT of the liver should be performed at baseline (must be performed within 28 days prior to randomization). CT chest without contrast or MRI abdomen/pelvis is acceptable if CT is contraindicated. Modality (CT or MRI) used at baseline should be used across all imaging timepoints. Bone scan is required if clinically indicated. MRI brain within 28 days prior to randomization for subjects with a history of brain metastasis
Other Assessments		
Tumor tissue sample (biopsy)	X	A formalin-fixed, paraffin-embedded tumor tissue (FFPET) block (preferred) or minimum of 15 unstained slides of tumor tissue (archival or recent) for biomarker evaluation must be obtained. The tissue submitted will be assessed for quality with a H&E stain (100 tumor cells) and only those subjects who have met tissue quality thresholds can be randomized.
Extent of Disease & Risk Factors	X	

Table 5.1-1: Screening Procedural Outline (CA209459)		
Procedure	**Pre-Treatment (Baseline)**	**Notes**
Clinical Drug Supplies		
Register subject in IVRS	X	A call must be made to the IVRS to register subject after signing informed consent.

Table 5.1-2: On treatment Period Procedural Outline - Nivolumab (CA209459)		
Procedure	**During Treatment (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
Safety Assessments		
Targeted Physical examination	X	Targeted examination must include at a minimum the following body systems, performed within 72 hours prior to dosing: Cardiovascular Gastrointestinal Pulmonary Skin
Physical Measurements	X	Weight and ECOG performance status within 72 hrs prior to dosing.
Child-Pugh Score	X	
Vital Signs	X	Including BP, HR, temperature, and respiratory rate. Obtain vital signs within 72 hrs prior to dosing.
Adverse Events Assessment	X	
Review of Concomitant Medication	X	
Laboratory Tests	X	Performed locally within 72 hours prior to dosing to include CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase. In addition, the following tests every third cycle (3, 6, 9, etc.): glucose, TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available.)
[redacted]		

Table 5.1-2: On treatment Period Procedural Outline - Nivolumab (CA209459)		
Procedure	**During Treatment (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
		Testing to be completed at the Central Laboratory. See Table 5.6.2-1.
Pregnancy test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to first dose, and then monthly regardless of dosing schedule
Coagulation profile	X	Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead.
Efficacy Assessments		
Tumor imaging assessment	See note	Tumor imaging assessments will occur 8 weeks from the date of randomization (+/-1 wk), then every 8 weeks (+/- 1 wk) thereafter up to 48 weeks, then it will be every 12 weeks (+/- 1 week) until disease progression or treatment is discontinued (whichever occurs later). CT of the chest, CT or MRI of abdomen, and pelvis with IV contrast, including required tri-phasic CT of the liver should be performed. CT chest without contrast or MRI abdomen/pelvis is acceptable if CT is contraindicated. Modality (CT or MRI) used at baseline should be used across all imaging timepoints. Bone scan is required if clinically indicated. Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated
Other Assessments		
PK/IMG sampling	X	PK and IMG samples should be collected at predose C1D1, C3D1, C8D1, Day 1 of every 8th cycle thereafter. See Section 5.5.1
Serum sample (soluble factors)	See Note	See Table 5.6.2-1 for details.

Table 5.1-2: On treatment Period Procedural Outline - Nivolumab (CA209459)		
Procedure	**During Treatment (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
Peripheral blood mononuclear cells (PBMCs) and myeloid derived suppressor cells (MDSCs)	Cycle 1, Day 1	See sections 5.6.2.3 and 5.6.2.4, and Table 5.6.2-1 for details
Outcomes Research Assessment		Questionnaires should be administered at the start of the visit, before the subject sees the physician and before any study related procedures are done (with the exception of procedures completed 72 hours prior to visit).
EQ-5D-3L	See Note	To be completed on Cycle 1, Day 1, then every other cycle thereafter (Cycle 3, Day 1; Cycle 5, Day 1, etc.)
FACT-Hep	See Note	To be completed on Cycle 1, Day 1, then every other cycle thereafter Cycle 3, Day 1; Cycle 5, Day 1, etc.)
Health care resource use (HCRU)	X	
Clinical Drug Supplies		
Contact central randomization IVRS / Dispense Study Drug	X	Within 3 days from randomization, the subject must receive the first dose of study medication. Subjects may be dosed no less than 12 days between doses.

Table 5.1-3: On treatment Period Procedural Outline - Sorafenib (CA209459)		
Procedure	**During Treatment: (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
Safety Assessments		
Targeted Physical examination	X	Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Skin
Physical Measurements	X	Weight and ECOG performance status
Child-Pugh Score	X	
Vital Signs	X	Including BP, HR, temperature, and respiratory rate. BP monitoring frequency should follow local standards of care as guided by the locally approved sorafenib product label or applicable SmPC.[52]
2D Echocardiogram	See note	2-D echocardiogram, performed locally as clinically indicated.
Adverse Events Assessment	X	
Review of Concomitant Medication	X	

Table 5.1-3: On treatment Period Procedural Outline - Sorafenib (CA209459)		
Procedure	**During Treatment: (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
Laboratory Tests	See Note	Performed locally up to 72 hours prior to Day 1 (ie, day of clinic visit) of each cycle to include CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase. In addition, the following tests every third cycle (3, 6, 9, etc.): glucose, TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available.)
[redacted]		
Pregnancy test (WOCBP only)	X	Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) to be done within 24 hours prior to first dose, and then monthly regardless of dosing schedule
Coagulation profile	X	Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead.

Table 5.1-3: On treatment Period Procedural Outline - Sorafenib (CA209459)		
Procedure	**During Treatment: (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
Efficacy Assessments		
Tumor imaging assessment	See note	Tumor imaging assessments will occur 8 weeks from the date of randomization (+/-1 wk), then every 8 weeks (+/- 1 wk) thereafter up to 48 weeks, then it will be every 12 weeks (+/- 1 week) until disease progression or treatment is discontinued (whichever occurs later). CT of the chest, CT or MRI of abdomen, and pelvis with IV contrast, including required tri-phasic CT of the liver should be performed. CT chest without contrast or MRI abdomen/pelvis is acceptable if CT is contraindicated. Modality (CT or MRI) used at baseline should be used across all imaging timepoints. Bone scan is required if clinically indicated. Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated
Other Assessments		
Serum sample (soluble factors)	See Note	See Table 5.6.2-1 for details.
Peripheral blood mononuclear cells (PBMCs) and myeloid derived suppressor cells (MDSCs)	Cycle 1, Day 1	See Section 5.6.2.3 and Table 5.6.2-1 for details
Outcomes Research Assessment		Questionnaires should be administered at the start of the visit, before the subject sees the physician and before any study related procedures are done (with the exception of procedures completed 72 hours prior to visit).
EQ-5D-3L	See Note	To be completed on Cycle 1, Day 1, then every other cycle thereafter (Cycle 3, Day 1; Cycle 5, Day 1, etc.)
FACT-Hep	See Note	To be completed on Cycle 1, Day 1, then every other cycle thereafter

Table 5.1-3: On treatment Period Procedural Outline - Sorafenib (CA209459)		
Procedure	**During Treatment: (Cycle = 2 weeks)** **Cycle 1 - Day 1 (C1, D1), Cycle 2 - Day 1 (C2 D1), (and every cycle thereafter)**	**Notes**
		Cycle 3, Day 1; Cycle 5, Day 1, etc.)
Health care resource use (HCRU)	X	
Clinical Drug Supplies		
Contact central randomization IVRS / Dispense Study Drug	X	Within 3 days from randomization, the subject must receive the first dose of study medication. IVRS should be contacted at each visit for provision of 2 week supply of sorafenib.

Table 5.1-4: Follow-Up Procedural Outline - all subjects (CA209459)			
Procedure	**Follow Up, Visits 1 and 2 (X visits)[a]**	**Survival Follow Up Visits (Y visits)[b]**	**Notes**
Safety Assessments			
Targeted Physical examination	X		Targeted examination must include at a minimum the following body systems: Cardiovascular Gastrointestinal Pulmonary Skin
Adverse Events Assessment	X	X	
Review of Concomitant Medications	X		
Review of Subsequent Cancer Therapy	X	X	
Laboratory Tests	X		Performed locally: CBC w/differential and platelet count, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), alpha fetoprotein (AFP), BUN or serum urea level, albumin, creatinine, Ca+, Mg++, Na+, K+, Cl-, LDH, amylase, lipase, glucose, TSH (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available.) To be done at FU1. To be repeated at FU2 if study related toxicity persists.
[redacted]			
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG).

Table 5.1-4: Follow-Up Procedural Outline - all subjects (CA209459)			
Procedure	**Follow Up, Visits 1 and 2 (X visits)[a]**	**Survival Follow Up Visits (Y visits)[b]**	**Notes**
Coagulation profile	X		Include International Normalized Ratio (INR). If INR cannot be done by the local laboratory, then Prothrombin Time (PT) may be provided instead
Efficacy Assessments			
Tumor imaging assessment	See Note	See Note	Tumor imaging assessments during Follow Up and Survival Follow up is required for subjects that have discontinued treatment prior due to reason other than radiologic disease progression. Tumor imaging assessments will occur 8 weeks from the date of randomization (+/-1 wk), then every 8 weeks (+/- 1 wk) thereafter up to 48 weeks, then it will be every 12 weeks (+/- 1 week) until disease progression. CT of the chest, CT or MRI of abdomen, and pelvis with IV contrast, including required tri-phasic CT of the liver should be performed. CT chest without contrast or MRI abdomen/pelvis is acceptable if CT is contraindicated. Modality (CT or MRI) used at baseline should be used across all imaging timepoints. Bone scan is required if clinically indicated. Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks from the date of first dose, or sooner if clinically indicated
Other Assessments			
PK/IMG sampling	X		To be collected for nivolumab subjects only. See Section 5.5.1

Table 5.1-4: Follow-Up Procedural Outline - all subjects (CA209459)			
Procedure	**Follow Up, Visits 1 and 2 (X visits)[a]**	**Survival Follow Up Visits (Y visits)[b]**	**Notes**
Outcomes Research Assessment			The EQ-5D and FACT-Hep should be administered at the start of the visit, before the subject sees the physician and before any study related procedures are done
EQ-5D-3L	X	X	EQ-5D to be assessed during clinical visit or via a phone for survival follow-up visits
FACT-Hep	X	X	FACT-Hep to be assessed during clinical visit or via a phone for survival follow-up visits
Health care resource use (HCRU)	X		Health Care Resource Use (HCRU) to be assessed during clinical visit
Subject Status			
Survival Status		X	Every 3 months after FU 2; may be accomplished by visit or phone contact

[a] X visits occur as follows: X01 = 35 days ± 7 days from last dose, X02 = 80 days ± 7 days from X01

[b] S, Survival visits continue every 3 months after X visits

5.1.1 Retesting During Screening Period

Retesting of laboratory parameters and/or other assessments within any single Screening period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigator Brochure
- Sorafenib SmPC
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- Serious Adverse Events (or eSAE) case report forms
- EQ-5D-3L and FACT-Hep questionnaires
- CA209459 Imaging Manual

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include signs and symptoms, weight, height, ECOG Performance Status, BP, HR, temperature, respiratory rate, and should be performed within 14 days prior to first dose except where noted in Table 5.1-1. Concomitant medications will also be collected from within 14 days prior to first dose and through the follow up period (See Table 5.1-1, Table 5.1-2, Table 5.1-3and Table 5.1-4). Baseline laboratory assessments should be done within 14 days prior to randomization and include (see Table 5.1-1):

- CBC w/differential and platelet count,
- LFTs (ALT, AST, total bilirubin, alkaline phosphatase),
- alpha fetoprotein (AFP),
- BUN or serum urea level,

- albumin,
- creatinine,
- Ca+,
- Mg++,
- Na+,
- K+,
- Cl-,
- LDH,
- glucose,
- amylase,
- lipase,
- TSH, (Reflex to free T3 and free T4 if TSH abnormal. Total T3/T4 are acceptable if free T3/T4 are not available),
- coagulation profile (INR or PT), and
- urinalysis

Baseline serology should be obtained within 28 days prior to randomization and should include: Hep B surface antigen, Hep B surface antibody, Hep B core antibody, Hep B DNA viral load, Hep C viral load, Hep C antibody, and Hep D antibody.

Baseline 12-lead ECG and 2-D Echocardiogram are required, and should be performed locally within 14 days prior to first dose. Pregnancy testing for WOCBP (done locally) to be done at screening, within 24 hours prior to first dose, and then monthly regardless of dosing schedule, and at each safety follow up visit.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be performed continuously during the treatment phase. During the safety follow-up phase (Table 5.1-4) toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

On treatment weight, ECOG performance status, vital signs, laboratory tests and targeted physical examinations may be performed within 72 hours prior to nivolumab dosing, or during the Day 1 visit (ie, day of clinic visit) or subjects randomized to sorafenib. In addition, vital signs can also be taken as per institutional standard of care prior to; during and after the nivolumab infusion. The start and stop time of the nivolumab infusion should be documented. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

Blood pressure monitoring frequency for subjects randomized to sorafenib should follow local standards of care as guided by the locally approved sorafenib product label or applicable SmPC.[52]

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

If a subject shows pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity for subjects randomized to nivolumab can be found in Appendix 5.

Some of the previously referred to assessments may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.3.1 Imaging Assessment for the Study

Images will be submitted to an imaging core lab for central review. Sites will be trained prior to scanning the first study subject. Image acquisition guidelines and submission process will be outlined in the CA209459 Imaging Manual to be provided by the core lab.

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

- CT/MRI

Contrast-enhanced Computed Tomography (CT) scans acquired on dedicated CT equipment is preferred for this study. The CT with contrast of the chest, abdomen and pelvis including contrast-enhanced triphasic CT of the abdomen is to be performed for tumor assessments until disease progression is documented or treatment is discontinued (whichever occurs later). CT scans should be acquired with 5 mm slices with no intervening gap (contiguous).

Should a subject have a contraindication for IV contrast, a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen and pelvis may be obtained. MRIs should be acquired with slice thickness of < 5 mm with no gap (contiguous).

Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

- Note: Use of CT component of a PET/CT scanner:

  Combined modality scanning such as with FDG-PET/CT is increasingly used in clinical care, and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined FDG-PET/CT are of limited use in anatomically based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast enhanced CT scans for anatomically based RECIST measurements. However, if a site can document that the CT performed as part of a FDG-PET/CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast)

then the CT portion of the FDG-PET/CT can be used for RECIST 1.1 measurements. Note, however, that the FDG-PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- MRI Brain

  MRI of brain is required at screening in order to rule out active metastatic disease in subjects with a history of brain metastasis. Subjects with a history of brain metastasis may have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated. MRI brain scans during on-study treatment and follow up periods are required only if there is a prior history of lesions present at Screening, or as clinically indicated for new signs and symptoms that suggest central nervous system (CNS) involvement.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, and pelvis, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Baseline MRI for brain must be done for known or suspected disease. Subjects will be evaluated for tumor response beginning 8 weeks from the date of randomization (+/-1 wk), then every 8 weeks (+/- 1 wk) thereafter up to 48 weeks, then it will be every 12 weeks (+/- 1 week) until disease progression is documented or treatment is discontinued (whichever occurs later).

Tumor imaging assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria, see Appendix 1. For a BOR of CR or PR, the initial response assessment must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later. Responders are the subjects with BOR of confirmed CR or confirmed PR. In the case of stable disease (SD), measurements must have met the SD criteria at least once after randomization at a minimum of 7 weeks (49 days). All scans performed for study purposes will be submitted to an imaging core lab for a Blinded Independent Central Review (BICR) supporting primary and secondary efficacy endpoints.

5.4.1 Primary Efficacy Assessment

The primary endpoint for this study is OS. Every effort will be made to collect survival data on all subjects including subjects withdrawn from treatment for any reason who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

5.4.2 Secondary Efficacy Assessment

For the ORR secondary efficacy endpoint, all subjects will be monitored by radiographic assessment on an every 8-12 weeks schedule, to determine changes in tumor size according to Section 5.4.1. RECIST 1.1 criteria will be used for the assessment (see Appendix 1). For the PFS secondary efficacy endpoint, the same radiographic assessment is in place. In the case of stable

disease (SD), measurements must have met the SD criteria at least once after randomization at a minimum interval of 7 weeks, or approximately 8 weeks.

5.5 Pharmacokinetic Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab as described in Table 5.5.1-1. All time points are relative to the start of study drug administration. All on-treatment time points are intended to align with days on which study drug is administered, if dosing occurs on a different day, the PK and immunogenicity sampling should be adjusted accordingly. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

5.5.1 Pharmacokinetic and Immunogenicity Collection and Processing

A detailed schedule of PK and immunogenicity evaluations is provided in Table 5.5.1-1. Samples are required for subjects randomized to nivolumab only. PK samples will be analyzed for nivolumab by a validated ligand binding assay. Immunogenicity samples will be analyzed for anti-nivolumab antibodies by a validated immunogenicity assay; samples may also be analyzed for neutralizing antibodies by a validated method. Serum samples may be analyzed by an exploratory method that measures anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. Serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis if required (eg, insufficient volume for complete immunogenicity assessment or to follow up on suspected immunogenicity related AE).

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sampling Schedule (Nivolumab subjects only)

Study Day (1 Cycle = 2 Weeks)	Event (Relative to Start of Infusion)	Time (Relative to Start of Nivolumab Infusion) Hour:Min	Nivolumab PK Blood Sample	Nivolumab Immunogenicity Sample
Cycle 1 Day 1	predose[a]	00:00	X	X
Cycle 3 Day 1	predose[a]	00:00	X	X
Cycle 8 Day 1	predose[a]	00:00	X	X
Day 1 of every 8th cycle after Cycle 8 Day 1 until discontinuation of study treatment[b]	predose[a]	00:00	X	X
First 2 Follow-up visits- (approximately up to 100 days from the discontinuation of study drug)			X	X

[a] Predose samples should be taken just prior to the administration (preferably within 30 minutes). If the infusion is delayed and a pre-dose sample is already collected, there is no need to collect an additional pre-dose sample.

[b] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at follow-up visits

5.6.1 Tumor Tissue Specimens and Collection Details

Archival tumor specimens are acceptable. For subjects without available/acceptable archival tissue, new biopsies must be obtained. The tissue submitted will be assessed for quality with a H&E stain (100 tumor cells) and only those subjects who have meet tissue quality thresholds can be randomized. Subjects whose tissue fails the initial quality assessment can be screen failed and re-enrolled if they consent/agree to a new biopsy.

Biopsy samples should be excisional, incisional or core needle. If a core biopsy is taken, up to 4 cores are recommended with a minimum size 18 gauge needle and the length should be greater than 5mm. Fine needle aspirates or other cytology samples are not acceptable. An assessment of biopsy quality by a pathologist is encouraged at the time of the procedure. The tumor tissue that is obtained from these biopsies will be divided equally into a formalin fixed sample, which can be used for histologic confirmation of HCC and characterization of immune cell populations and tumor markers, and a RNAlater sample for DNA and RNA extraction for genomic analyses. Tumor samples obtained from bone metastases are not considered acceptable for PD-L1 testing because the PD-L1 assay does not include a decalcification step. For any cases where the only tumor tissue available is from a bone metastasis lesion, please discuss further with the study Medical Monitor.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the biopsy procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject. De-identified pathology report should be provided with tumor samples.

In addition to the assessments shown below, formalin fixed paraffin embedded tissue (FFPET) may also be evaluated by additional technologies including but not limited to FISH, genetic mutation detection methods, and QPCR for exploratory analyses of prognostic or predictive

molecular markers associated with hepatocellular carcinoma (eg, gene mutation, amplification or overexpression), to determine if these factors influence response or safety of nivolumab.

5.6.1.1 Characterization of tumor infiltrating lymphocytes (TILs) and tumor antigens

Immunohistochemistry (IHC) will be used to assess tumor markers as well as the number and composition of immune infiltrates in order to define the immune cell subsets present within formalin-fixed, paraffin embedded (FFPE) tumor tissue. These IHC analyses will include, but not necessarily be limited to, the following markers: CD4, CD8, CD3, FOXp3, PD-1, PD-L1, and PD-L2.

5.6.1.2 Whole Exome and Whole Transcriptome Sequencing

DNA and/or RNA extracted from tumor and/or blood provided may be subject to whole exome or transcriptome sequencing using next-generation sequencing or other technology to identify mutational load and transcriptional expression. RNA will also be extracted from tumor to assess expression of inflammation-related genes.

5.6.2 Peripheral Blood Assessments

A variety of factors that may impact the immunomodulatory properties and efficacy of nivolumab will be investigated in peripheral blood specimens taken from all subjects prior to or during treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety (adverse event) data. Several analyses will be completed and are described briefly below, and outlined in Table 5.6.2-1.

5.6.2.1 Single Nucleotide Polymorphisms (SNPs)

Whole blood will be collected from all subjects prior to treatment to generate genomic DNA for Single Nucleotide Polymorphism (SNP) analyses. Genes of interest include, but are not limited to, PD-1, PD-L1, IFN gamma, HLA, and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to nivolumab and/or with adverse events during treatment. Data from this study will be combined with SNP results from other studies to explore possible associations of SNPs and clinical activity or adverse events associated with nivolumab therapy.

5.6.2.2 Serum-Soluble Factors

Baseline and on-treatment serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include, but are not limited to ELISA or multiplex assays. Analytes may include, but are not limited to, IFN-γ, CXCL9, CXCL10, and soluble PD-L1.

5.6.2.3 Peripheral Blood Mononuclear Cells (PBMCs)

At participating sites, peripheral blood mononuclear cells in whole blood taken from subjects at Cycle 1 Day 1 will be analyzed by flow cytometry or other methods (eg, ELIspot) to assess immune cell activity. This blood collection may be canceled at the discretion of the sponsor.

5.6.2.4 Myeloid Derived Suppressor Cells (MDSCs)

Myeloid derived suppressor cells (MDSCs) are an immune cell population capable of suppressing T cell activation and proliferation. MDSCs will be measured at Cycle 1 Day 1 to assess pharmacodynamic changes or associations with outcome.

[redacted]

5.7 Outcomes Research Assessments

Subjects will be asked to complete the EQ-5D-3L and Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, before any clinical activities are performed during on-study clinic visits and at designated visits during the follow-up phase. The questionnaires will be provided in the subject's preferred language and may be administered by telephone during the follow-up phase. A standardized script will be used to facilitate telephone administration of the EQ-5D. A similar script does not exist for the FACT-Hep, though subjects will be provided with a hard copy of the FACT-Hep to take home and use as a visual aid during telephone interviews. Table 5.1-1, Table 5.1-2, Table 5.1-3 and Table 5.1-4 provide information regarding the timing of patient-reported outcomes assessments.

Subjects' reports of general health status will be measured using the EQ-5D. These data will be collected to assess the impact of nivolumab on generic health status and may be used to inform economic evaluations of nivolumab for the treatment of HCC.

The EQ-5D is a standardized instrument used to measure self-reports of health status and functioning. The instrument's descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no health problems," "moderate health problems," and "extreme health problems." A dimension for which there are no problems is said to be at level 1, while a dimension for which there are extreme problems is said to be at level 3. Thus, the vectors 11111 and 33333 represent the best health state and the worst health state, respectively, described by the EQ-5D. Altogether, the instrument describes $3^5 = 243$ health states. Empirically derived weights can be applied to an individual's responses to the EQ-5D descriptive system to generate an index measuring the value to society of his or her current health. Such preference-weighting systems have been developed for the UK, US, Spain, Germany, and numerous other populations. In addition, the EQ-5D includes a visual analog scale that allows respondents to rate their own current health on a 101-point scale ranging from "best imaginable" to "worst imaginable" health.

The FACT-Hep questionnaire will be used to assess the effects of HCC and its treatment on health-related quality of life (HRQL). As a generic cancer-related core, the questionnaire includes the FACT-General (FACT-G) to assess symptoms and treatment-related effects impacting physical well-being (PWB; seven items), social/family well-being (SWB; seven items), emotional well-being (EWB; six items), and functional well-being (FWB; seven items). In addition, the FACT-Hep includes an 18-item disease-specific hepatobiliary cancer subscale (HCS) that assesses back and stomach pain, gastrointestinal symptoms, anorexia, weight loss, and jaundice. Each item is rated on a five-point scale ranging from 0 (not at all) to 4 (very much). Scores for the PWB, FWB, SWB, and EWB subscales can be combined to produce a FACT-G total score, which provides an overall indicant of generic HRQL, while the FACT-G and HCS scores can be combined to produce a total score for the FACT-Hep, which provides a composite measure of general and targeted HRQL. Higher scores indicate better HRQL.

Minimally important differences (MIDs) have been estimated to be 2-3 points for the PWB, FWB, SWB, and EWB subscales; 5-6 points for the HCS subscale; 6-7 points for the FACT-G total score; and 8-9 points for the FACT-Hep total score.

Health care resource utilization data will be collected for all randomized subjects using an internal measure developed for use in previous trials. The questionnaire records information about medical care encounters, including hospital admissions and their duration, outpatient visits, diagnostic tests and procedures, concomitant medications, and reasons for encounters.

5.8 Other Assessments

Blood samples for immunogenicity analyses of nivolumab will be collected according to the schedule given in Table 5.5.1-1. Samples will be evaluated for development of Anti-Drug Antibody (ADA) for nivolumab by validated immunoassays. Samples may also be analyzed for neutralizing ADA response to nivolumab.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that

does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, second cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing. Subjects who are enrolled in the study but never treated with study drug must have SAEs collected for 30 days from the date of enrollment. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator must report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report must be completed for any event where doubt exists regarding its seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship must be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred

method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. In the event the electronic system is unavailable for transmission, paper forms must be used and submitted immediately. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): Refer to Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details.).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1 for reporting details). The following definition takes into account anticipated baseline compromise of liver function in patients with HCC.

Potential drug induced liver injury is defined as:

1) Concurrent ALT ≥ 10 x ULN, AND
2) Total bilirubin ≥ 2 times ULN or baseline value (if elevated bilirubin at study entry), AND
3) No other immediately apparent possible causes of ALT elevation and hyperbilirubinemia, including, but not limited to, tumor progression, acute viral hepatitis, cholestasis, pre-existing hepatic disease or the administration of other drug(s), herbal medications and substances known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

7.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to provide oversight and safety and efficacy considerations in protocol CA209459. The DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study.

The BMS clinical study leadership will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes to the study conduct are required. Adjudicated events will be submitted to the DMC and Health Authorities when required for review on a specified timeframe in accordance with the adjudication documentation.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

7.2 Blinded Radiology Review Committee

In addition to local tumor assessments, images from this study will undergo a blinded, independent central review (BICR) to assess response based on the RECIST 1.1 assessment criteria. The centrally reviewed response data will be used in the analyses of ORR, PFS, duration of objective response, and time to response. All final determinations on centrally reviewed image-based endpoints will be made based on the independent assessments for a uniform and unbiased assessment of outcome. Details of the procedures and the criteria for the central review are defined in a separate Imaging charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size determination of this study is based on OS comparison between subjects randomized to receive nivolumab and sorafenib. With a total of 726 subjects randomized in a 1:1 ratio to receive nivolumab or sorafenib, approximately 91.5% power will be achieved with an overall type I error 0.05. The sample size determination is based on simulation using R v3.2. Below are details of the sample size determination.

General assumptions:

- There are assumed 39% HCV-infected subjects among all randomized subjects.
- In the sorafenib arm, median OS is 10 months for non-HCV infected and 14 months for HCV infected.
- Exponential distribution is assumed for OS in each randomized arm.

Estimated cumulated enrollment of randomized subjects is available in the SAP.

Sample size determination for OS

Based on simulations under the assumptions stated above, approximately 726 subjects will be randomized and followed until at least 520 OS events are observed in order to provide 91.5% power for a hazard ratio of 0.74 with a two-sided type I error of 0.05. This accounts for a group sequential testing procedure with one interim analysis and one final analysis.

The interim analysis will be conducted when 80% OS events are observed. The alpha allocation for the interim and final analyses is based on the Lan-DeMets alpha spending function approach using an O'Brien-Fleming stopping boundary controlling for a two-sided overall type 1 error of 5%. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis and the final analysis. However, if the interim analysis is performed exactly when 80% OS events are observed, then 0.024 alpha will be used for the interim analysis and 0.043 alpha will be used for the final analysis.

It is projected that an observed hazard ratio of 0.80 or less would result in a statistically significant improvement of nivolumab at the interim analysis of OS; and an observed hazard ratio of 0.84 or

less would result in a statistically significant improvement of nivolumab at the final analysis of OS.

Analysis Timing Projections

As stated above, approximately 726 subjects will be randomized to the two treatment arms in a 1:1 ratio.

- It will take approximately 13 months to complete the randomization.
- OS interim analysis is projected to occur when there are at least 416 deaths (80% of target events) among approximately 726 randomized subjects, approximately 25 months after the first subject's randomization date (13 months for randomization and 12 months for survival follow-up).
- OS final analysis is projected to occur when there are at least 520 deaths among approximately 726 randomized subjects, approximately 33 months after the first subject's randomization date (13 months for randomization and 20 months for survival follow-up).

8.2 Populations for Analyses

All analyses will be performed using the treatment group as randomized (intent-to-treat) with the exception of extent of exposure (dosing) and safety, for which the treatment group as treated will be used. If a subject is randomized to nivolumab and receives at least 1 dose of nivolumab during the study, then the subject's treatment group is considered nivolumab. Similarly, if a subject is randomized to sorafenib and receives at least 1 dose of sorafenib, then the subject's treatment group is considered sorafenib. The following population datasets will be analyzed:

- **Enrolled Subjects:** Subjects who signed an informed consent form and were registered into the IVRS.
- **Randomized Subjects:** Subjects who were randomized to any treatment group in the study. This is the dataset for analyses of study conduct, study population and efficacy.
- **Treated Subjects:** Subjects who received at least one dose of nivolumab or sorafenib. This is the dataset for analyses of exposure and safety.
- **PK Subjects:** Subjects with available serum time-concentration data from randomized subjects dosed with nivolumab.
- **PD-L1 Measurable Subjects:** Randomized subjects with a measurable PD-L1 expression result (ie, excludes indeterminate and unknown)

8.3 Endpoints

8.3.1 Primary Endpoint

- Overall Survival (OS)

  OS is the primary endpoint for this study. It is defined as the time from the date of randomization to the date of death due to any cause in all randomized subjects. Subjects who are alive will be censored at the last known alive dates.

8.3.2 Secondary Endpoint(s)

- Objective Response Rate (ORR)

  ORR is defined as the proportion of subjects whose best overall response (BOR) is either a CR or PR. BOR is defined as the best response designation, as determined based on BICR-assessed tumor response according to RECIST 1.1, recorded between the date of randomization and the date of first objectively documented progression or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For a BOR of CR or PR, the initial response assessment must be confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

- Progression-Free Survival (PFS)

  PFS is defined as the time from the date of randomization to the date of the first objectively documented tumor progression as assessed by BICR according to RECIST 1.1 or death due to any cause in all randomized subjects. Subjects who die without a reported prior progression and without initiation of subsequent anti-cancer therapy will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last tumor assessment. Subjects who did not have baseline tumor assessment will be censored on the date they were randomized. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to subsequent anti-cancer therapy.

- PD-L1 expression

  The objective of evaluating the relationship between PD-L1 expression and efficacy will be measured by efficacy based on PD-L1 expression. Definition of PD-L1 expression will be described in the SAP.

[redacted]

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Analysis of OS

A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses (overall alpha=0.05). The distribution of OS will be compared in the two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by the stratification factors using allocated alpha based on Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary. The hazard ratio and the corresponding 100x (1-adjusted alpha)% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the KM product limit method. The two-sided 95% CIs for median OS will be computed by Brookmeyer and Crowley method (using log-log transformation). In additional, survival rates at select milestones will be computed as well as the corresponding two-sided 95% CIs using the log-log transformation.

8.4.2.2 Analysis of ORR

ORR based on BICR assessment per RECIST 1.1 between the two randomized arms will be compared using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by the stratification factors. The associated odds ratio and CI will also be calculated. ORR along with its 95% exact CI will be provided for each randomization arm. Hierarchical testing of ORR will be performed upon demonstration of superiority in OS at OS interim or final analyses for all randomized subjects.

8.4.2.3 Analysis of PFS

Hierarchical testing of PFS will be performed upon demonstration of superiority in ORR at OS interim or final analyses **for all randomized subjects**. Details of timing for the analysis and alpha allocated will be described in the SAP.

PFS will be compared using a two-sided stratified log-rank test. The hazard ratio and the corresponding two-sided CIs will be estimated in a Cox proportional hazards model using treatment as a single covariate, stratified by the stratification factors. PFS curves will be estimated using the KM product-limit method. The two-sided 95% CIs for median PFS will be computed by Brookmeyer and Crowley method (using log-log transformation). In additional, PFS rate at select milestone will be computed as well as the corresponding two-sided 95% CIs using the log-log transformation.

8.4.2.4 Analysis of Association between PD-L1 Expression and Efficacy Measures

Analyses of PD-L1 expression will be descriptive. Distribution of PD-L1 expression will be examined PD-L1-measurable subjects. Potential associations between PD-L1 expression and primary efficacy measure OS will be assessed. OS curves for each randomized arm will be estimated using the Kaplan-Meier product-limit method for each PD L1 Expression subgroup. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method. If there is an indication of a meaningful association, future work will evaluate PD-L1 expression as a predictive biomarker, including selection of an optimal PD-L1 expression cut-off to classify subjects as PD-L1 positive or PD-L1 negative. Cut-off selection and validation may be conducted across studies. More detailed analysis including potential associations between PD-L1 expression and secondary efficacy measures will be described in the SAP.

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All on-treatment AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

8.4.4 Pharmacokinetic Analyses

The nivolumab concentration data obtained in this study may be combined with data from other studies in the clinical development programs to develop or refine a population PK model. These models may be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure. In addition, model determined exposures may be used for exposure-response analyses. Results of population PK and exposure-response analyses will be reported separately.

[redacted]

8.4.6 Outcomes Research Analyses

The analysis of EQ-5D and FACT-Hep data will be performed in all randomized subjects who have an assessment at baseline (Day 1, assessment prior to administration of drug on day of first dose) and at least 1 subsequent assessment while on treatment. Questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number, will be calculated and summarized at each assessment point.

EQ-5D data will be described by treatment group as randomized in the following ways:

- EQ-5D index scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).
- EQ-VAS scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of subjects reporting no, moderate, or extreme problems will be presented for each of the 5 EQ-5D dimensions at each assessment time point. Subjects with missing data will be excluded from the analysis.
- A by-subject listing of the level of problems in each dimension, corresponding EQ-5D health state (ie, 5-digit vector), EQ-5D index score, and EQ-VAS score will be provided.

FACT-Hep data will be described by treatment group as randomized in the following ways:

- FACT-Hep total scores will be summarized at each assessment time point using descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).
- Changes from baseline in FACT-Hep total scores will be summarized at each post-baseline assessment time point using descriptive statistics (ie, N, mean with standard deviation and 95% CI, median, first and third quartiles, minimum, maximum).
- The proportion (N) of subjects achieving a change of ≥ 8 points (ie, MID) in FACT-Hep total score will be summarized at each post-baseline assessment time point.

8.4.7 Other Analyses

Methodology for exploratory analyses including immunogenicity is described in the statistical analysis plan.

8.5 Interim Analyses

A formal interim analysis for the OS is planned after 416 deaths have been observed, which is expected to occur approximately 25 months after the first subject's randomization date. This formal comparison of OS will allow for early stopping for superiority. Lan-DeMets alpha spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. However, if the analysis is performed exactly when 416 deaths are observed, the study can be stopped by the DMC for

superiority if the p-value is < 0.024. An independent statistician from external to BMS will perform the analysis.

If the study continues beyond the interim analysis, the nominal significance level for the final look after 520 deaths would be 0.043. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol (520 deaths), final boundary will not be recalculated using updated information fraction at interim. In addition to the formally planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment.

Details will be included in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Regulatory Authority (ies), if required by local regulations, of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them

with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label identification number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- nonstudy disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and

who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Involvement in trial design
- Subject recruitment (eg, among the top quartile of enrollers)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 LIST OF ABBREVIATIONS

Term	Definition
1L	first line
AASLD	American Association for the Study of Liver Diseases
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
BICR	blinded independent central review
BID, bid	bis in die, twice daily
BMS	Bristol-Myers Squibb
BOR	best overall response
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
Cmax	maximum observed concentration
Cmin	trough observed concentration
CNS	Central nervous system
CR	complete response
CRF	Case Report Form, paper or electronic

Term	Definition
CYP	cytochrome p-450
DCR	disease control rate
dL	Deciliter
DOR	duration of response
EASL	European Association for the Study of the Liver
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Eg	exempli gratia (for example)
FACT-Hep	Functional Assessment of Cancer Therapy-Hepatobiliary
FDA	Food and Drug Administration
FHSI	Functional Assessment of Cancer Therapy–Hepatobiliary Symptom Index
FSH	follicle stimulating hormone
G	gram
GCP	Good Clinical Practice
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotrophin
HCV	hepatitis C virus
HCRU	healthcare research utilization
HIFU	cryoablation, high-intensity focused ultrasound
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products

Term	Definition
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K+	potassium
kg	kilogram
KM	Kaplan-Meier
L	liter
LDH	lactate dehydrogenase
MDSCs	myeloid derived suppressor cells
mg	milligram
Mg++	magnesium
min	minute
mL	milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
Ng	nanogram
NIMP	non-investigational medicinal products
NSCLC	Non-small-cell lung cancer
ORR	objective response rate
OS	overall survival
PAI	acetic acid injection
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PD-1	Programmed death receptor-1

Term	Definition
PEI	percutaneous ethanol injection
PFS	progression free survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PR	partial response
PT	prothrombin time
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RFA	radiofrequency ablation
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SLD	sum of the longest diameters
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedures
TACE	transarterial chemoembolization
TAE	transarterial embolization
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
T-HALF	Half life
Treg	T regulatory cell
TTP	time to progression
TTR	time to response
WBC	white blood cell
WOCBP	women of childbearing potential

APPENDIX 1 RECIST 1.1

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of Tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of Assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

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

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

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

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

(i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be constituted PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor Markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time Point Response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Appendix Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: Summary of the Overall Response Status Calculation [Time point response: patients with target (+/-) non-target disease]

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

4.2 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Best Overall Response - All Timepoints

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Appendix Table 2. In the case of stable disease (SD), measurements must

have met the SD criteria at least once after study entry at a minimum interval of 7 weeks, or approximately 8 weeks.

Table 2: Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall response
CR	CR	CR
CR	PR	SD, PD, PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients

is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1 and Table 2.

For equivocal findings of progression (eg. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that Disappear and Reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

Reference:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. (2009);45:228-247.

APPENDIX 2 CHILD-PUGH SCORE

Score	Points
Child-Pugh A	5 - 6
Child-Pugh B	7 - 9
Child-Pugh C	> 9

Scoring

	Score		
Measure	1 Point	2 Points	3 Points
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dl)	< 2.0	2.0 - 3.0	> 3.0
Serum albumin (g/dl)	> 3.5	2.8 - 3.5	< 2.8
PT prolongation or INR	< 4 sec < 1.7	4 - 6 sec 1.7 - 2.3	> 6 sec > 2.3
Encephalopathy grade	None	1 - 2	3 - 4

Encephalopathy Grading

Encephalopathy Grade	Clinical Definition
Grade 0	Normal consciousness, personality, and neurological examination
Grade 1	Restless, sleep disturbed, irritable/agitated, tremor, and impaired handwriting
Grade 2	Lethargic, time-disoriented, inappropriate, asterixis, and ataxia
Grade 3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, and rigidity
Grade 4	Unrousable coma, no personality/behavior, decerebrate

APPENDIX 3 ECOG PERFORMANCE STATUS

These scales are used by doctors and researchers to assess how a patient's disease progressing, assess how the disease affects the dailing living abilitiesof the patient and determine appropriate treatment and prognosis. They are included here for health care professionsals to assess.

ECOG PERFORMANCE STATUS	
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Toxicity and Response Criteria of the Eastern Cooperative Oncology Group.

APPENDIX 4 NYHA CLASSIFICATION

NYHA Classification

Class I	patients with no limitation of activities; they suffer no symptoms from ordinary activities
Class II	patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	patients with marked limitation of activity; they are comfortable only at rest.
Class IV	patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.