Official Title of Study:

A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naïve to Systemic Therapy

NCT Number: NCT01658878

Document Date (Date in which document was last revised): October 26, 2016

Protocol Number: CA209040
IND Number: 126,406
Ex-US Non-IND
EUDRACT Number 2012-001514-42
Date: 25-May-2012
Revised Date: 26-Oct-2016

Clinical Protocol CA209040

A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy

Revised Protocol Number: 05
Incorporates Administrative Letters 05 and 06, and Amendment 14

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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 05	26-Oct-2016	Incorporates Administrative Letter 05, Administrative Letter 06, and Amendment 14
Amendment 14	26-Oct-2016	Modify the 1L Nivolumab vs Sorafenib Cohort efficacy analysis from a comparison of ORR to an estimation of ORR for both nivolumab and sorafenib arms.
Administrative Letter 06	24-Jun-2016	Change of Medical Monitor
Administrative Letter 05	23-Mar-2016	Clarified that SAE reporting to Ono Pharmaceutical Co., Ltd. is no longer required.
Revised Protocol 04	31-Jul-2015	Incorporates Administrative Letter 03, Administrative Letter 04, and Amendment 08
Amendment 08	31-Jul-2015	Changes include addition of two new treatment arms to the study: 1. 1L nivolumab vs sorafenib, 2. nivolumab plus ipilimumab combination, as well as other minor clarifications and edits
Administrative Letter 04	15-Jul-2015	Update the pharmacokinetic sampling schedule for subjects in the expansion cohorts.
Administrative Letter 03	28-Apr-2015	The FDA issued a new IND number for the indication of hepatocellular carcinoma for nivolumab.
Revised Protocol 03	29-Oct-2014	Incorporates Amendment 04
Amendment 04	29-Oct-2014	Changes include addition of an expansion phase to the study, introduction of the possibility to re-initiate treatment after treatment discontinuation, to be treated beyond progression in certain conditions, switch of tumor evaluation criteria from mRECIST to RECIST 1.1, introduction of a quality of life questionnaire (EQ-5D) in the expansion phase, updates to the WOCBP and pregnancy wording and other minor clarifications and edits.
Administrative Letter 02	15-Apr-2014	Change in Study Director/Medical Monitor
Administrative Letter 01	15-Oct-2013	Change in Study Director/Medical Monitor
Revised Protocol 02	06-Sep-2013	Changes include updated text for antiviral medications for HCV and HBV arms; expanded laboratory and Child-Pugh ranges for inclusion/exclusion criteria; added new safety information concerning virally infected subjects treated with checkpoint inhibitors; added a 10 mg/kg dose group to all three arms (uninfected, HCV infected, and HBV infected); minor clarifications and edits.
Amendment 03	06-Sep-2013	
Revised Protocol 01	18-Mar-2013	Incorporates Amendment 02.
Amendment 02	18-Mar-2013	Changes include updated text for pre-clinical toxicology finding, addition of a reference for this finding, updated suggested language for contraception based on this finding and updated Medical Monitor information, protocol title in synopsis edited to be consistent with protocol.

Document	Date of Issue	Summary of Change
Original Protocol	25-May-2012	Not applicable

SYNOPSIS

Clinical Protocol CA209040

Protocol Title: A Phase 1/2, Dose-escalation, Open-label, Non-comparative Study of Nivolumab or Nivolumab in Combination with Ipilimumab in Advanced Hepatocellular Carcinoma Subjects with or without Chronic Viral Hepatitis; and a Randomized, Open-label Study of Nivolumab vs Sorafenib in Advanced Hepatocellular Carcinoma Subjects who are Naive to Systemic Therapy.

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

In the Dose Escalation Phase Cohort: Intravenous (IV) infusion of nivolumab at doses of 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg q2week.

In the Expansion Phase Cohort: IV infusion of nivolumab at a dose of 3 mg/kg q2week.

In the 1L Nivolumab vs Sorafenib Cohort: Subjects will be randomized 1:1 to receive open-label

- IV infusion of nivolumab at a flat dose of 240 mg q2week or
- Sorafenib 400 mg po BID.

In the Nivolumab plus Ipilimumab Combination Cohort: Subjects will be randomized 1:1:1 to receive

- Arm A--nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week
- Arm B--nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV q3week x 4, followed by nivolumab 240 mg IV q2week
- Arm C--nivolumab 3 mg/kg IV q2week plus ipilimumab 1 mg/kg IV q6week.

All subjects upon activation of amendment 8 are to be treated until toxicity or disease progression. Prior to activation of amendment 8, subjects in the Dose Escalation Phase were treated until either a confirmed CR, completion of 2 years of therapy, toxicity, or disease progression.

Study Phase: 1/2

Research Hypothesis:

There is no formal hypothesis in the Dose Escalation Phase to be tested statistically. The purpose of the Dose Escalation Phase is to evaluate the safety profile, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) following IV infusion at doses of 0.1, 0.3, 1, 3, and 10 mg/kg of nivolumab administered every 14 days in subjects with advanced hepatocellular carcinoma (HCC).

In the Expansion Phase, treatment with nivolumab monotherapy will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response in subjects with advanced HCC who have been previously treated with sorafenib.

In the 1L Nivolumab vs Sorafenib Cohort, nivolumab administration in subjects with advanced hepatocellular carcinoma (HCC) who are naive to systemic therapy will improve ORR compared with sorafenib.

In the Nivolumab plus Ipilimumab Combination Cohort, treatment with nivolumab plus ipilimumab will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response in subjects with advanced HCC who are previously treated with sorafenib. In addition, the purpose of the cohort is to evaluate the safety profile of the combination in subjects with advanced HCC who have been previously treated with sorafenib.

Objective(s):

Primary Objective:

- **Dose Escalation Phase**: To establish the safety, tolerability, dose limiting toxicities (DLT) and maximum tolerated dose (MTD) for nivolumab administered every 14 days to subjects with advanced HCC.
- **Expansion Phase**: To estimate the ORR and duration of response of nivolumab monotherapy in subjects with advanced HCC who are naive to sorafenib or have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
- **1L Nivolumab vs Sorafenib Cohort**: To estimate overall response rate (ORR) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1..
- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To establish the safety and tolerability of nivolumab plus ipilimumab in subjects with advanced HCC.
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

Secondary Objectives:

- **Escalation and Expansion Phase**:
  - To assess antitumor activities (Time to Progression (TTP) and Progression Free Survival (PFS)) based on results of BICR and/or investigators using RECIST 1.1.
  - To evaluate overall survival (OS) in subjects treated with nivolumab monotherapy.
  - To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.
  - To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC (Dose Escalation Phase only).
  - To assess the immunogenicity of nivolumab in subjects with advanced HCC (Dose Escalation Phase only).
- **1L Nivolumab vs Sorafenib Cohort:**
  - To estimate TTP and PFS of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy.
  - To evaluate the overall survival (OS) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy.
  - To evaluate the relationship between PD-L1 expression and efficacy.
- **Nivolumab plus Ipilimumab Combination Cohort**
  - To assess antitumor activities (TTP and PFS) based on results of BICR and/or investigators using RECIST 1.1.
  - To evaluate overall survival (OS) in subjects treated with nivolumab plus ipilimumab.
  - To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.

Exploratory Objectives:

- **Escalation Phase**:
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To investigate the pharmacodynamic (PD) activity of nivolumab on antiviral immunologic biomarkers including HBV or HCV specific immune response in peripheral blood and cell phenotyping by flow cytometry.

- To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load, quantitative Hepatitis surface antigen (HBsAg) levels, quantitative Hepatitis e antigen (HBeAg) levels, Hepatitis B surface antibody (HBsAb), and Hepatitis B e antibody (HBeAb).
- To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
- To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
- To assess the relationship between nivolumab exposure and measures of hepatic dysfunction.

- **Expansion Phase**
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To investigate the pharmacodynamic (PD) activity of nivolumab on antiviral immunologic biomarkers including HBV or HCV specific immune response in peripheral blood and cell phenotyping by flow cytometry.
  - To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load, quantitative Hepatitis surface antigen (HBsAg) levels, quantitative Hepatitis e antigen (HBeAg) levels, Hepatitis B surface antibody (HBsAb), and Hepatitis B e antibody (HBeAb).
  - To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
  - To assess the relationship between nivolumab exposure and measures of hepatic dysfunction.
  - To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC.
  - To assess the immunogenicity of nivolumab in subjects with advanced HCC.
  - To assess self-reported health problems as measured using the descriptive system of the 3-level version of the EQ-5D (EQ-5D-3L) questionnaire.
  - To assess changes in societal utility for self-reported health as measured using the EQ-5D-3L index score.
  - To assess changes in subject ratings of own health as measured using the EQ-5D-3L visual analog scale (EQ-VAS) score.
- **1L Nivolumab vs Sorafenib Cohort**
  - To evaluate the safety of nivolumab and sorafenib.
  - To estimate overall response rate (ORR) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy. ORR will be determined with blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
  - To assess antitumor activities of nivolumab vs sorafenib based on results of BICR using mRECIST for HCC.
  - To evaluate disease control rate (DCR), duration of disease control, and time to response of nivolumab and sorafenib.
  - To evaluate overall survival in subjects who have intrahepatic vs extrahepatic progression for nivolumab and sorafenib.
  - To evaluate overall survival in subjects with baseline AFP < 400 ng/mL vs > 400 ng/mL for nivolumab and sorafenib.
  - To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
  - To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood in subjects with HCC.
  - To investigate the potential association between selected biomarker measures in tumor tissue specimens and blood samples and clinical efficacy measures including overall survival.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
  - To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC.

- To assess the immunogenicity of nivolumab in subjects with advanced HCC.
- To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
- To assess the subject's cancer-related QoL using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.

- **Nivolumab plus Ipilimumab Combination Cohort**
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To describe the effects of nivolumab plus ipilimumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
  - To investigate the pharmacodynamic activity of nivolumab plus ipilimumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
  - To assess the relationship between nivolumab plus ipilimumab exposure and measures of hepatic dysfunction.
  - To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
  - To characterize the pharmacokinetics of nivolumab and ipilimumab in subjects with advanced HCC.
  - To assess the immunogenicity of nivolumab and ipilimumab in subjects with advanced HCC.

Study Design:

The **Dose Escalation Phase** will consist of an open label, ascending, multi-dose, sequential 3-arm Phase I study. Subjects with differing underlying risk factors for the development of HCC will be evaluated in three separate dose escalation cohorts; HCC subjects with no active hepatitis virus infection (uninfected HCC), subjects with HCC due to chronic hepatitis C virus infection (HCC-HCV), and subjects with HCC due to chronic hepatitis B virus infection (HCC-HBV). Dose escalation will be performed independently in each group because of the concern that virally infected subjects may have a toxicity profile that is more severe. HBV infected subjects are thought to have the highest risk because viral DNA sequences can be found in virtually all hepatocytes even in subjects with complete viral clearance as assayed by standard methods. PD-1 blockade may stimulate antigen-specific T cell responses to produce hepatotoxicity. The study will open with subjects with non-viral HCC and HCC-HCV treated in parallel dose cohorts simultaneously. The initial dose employed in the HCC-HBV cohort will be lower than that employed in the other two cohorts.

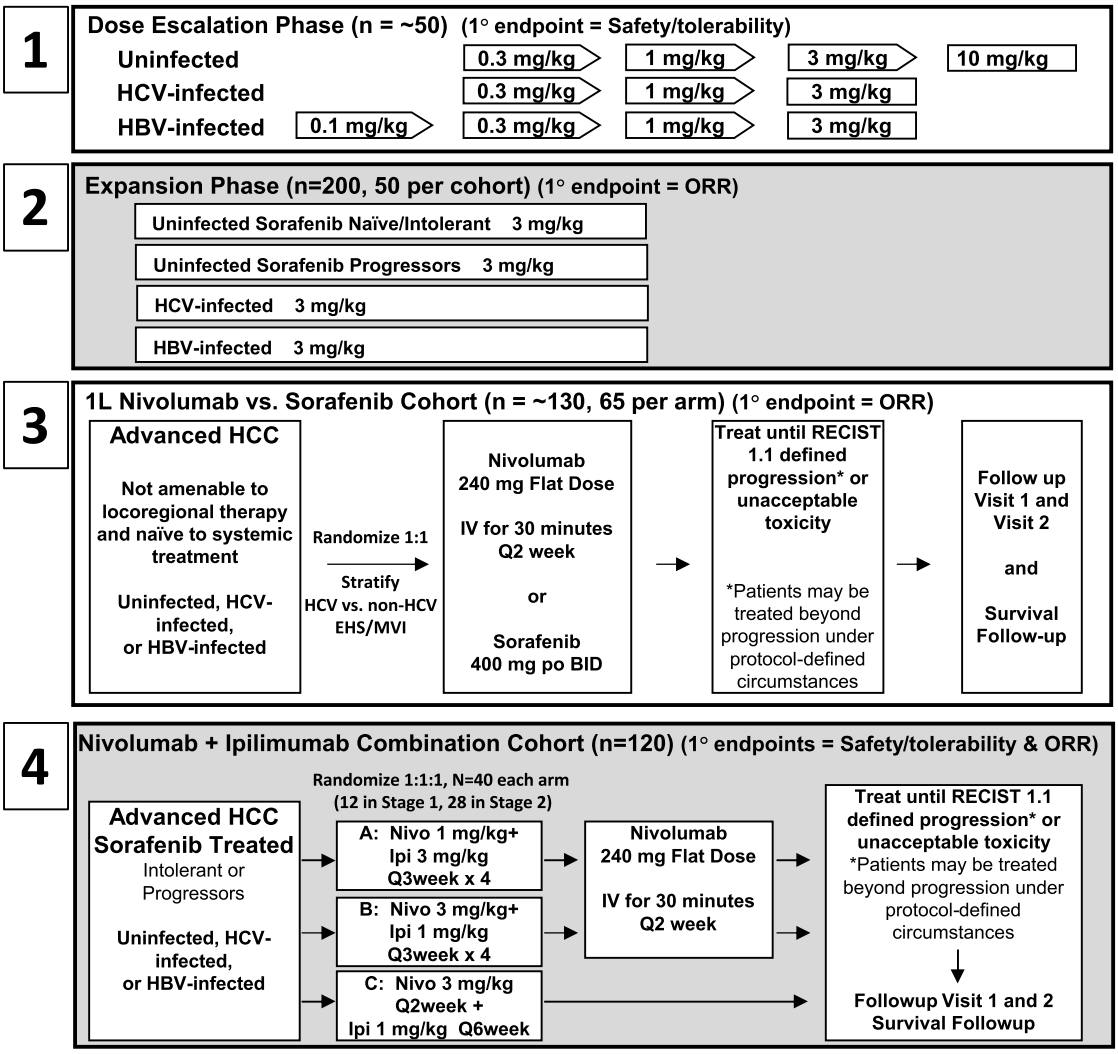
The **Expansion Phase** will consist of treatment of approximately an additional 100 uninfected HCC subjects at the 3 mg/kg dose level based on the established safety of the 10 mg/kg dose level in this cohort, observed preliminary anti-tumor activity, and preliminary PK analysis of a subset of subjects from CA209040 indicating exposures within the expected range of subjects from other tumor types. To further characterize nivolumab safety and activity in the hepatitis virus cohorts, approximately 50 subjects each will be dosed at the 3 mg/kg dose level for the HCV- and HBV-infected cohorts. This will be in keeping with the selected dose and schedule for expansion of the uninfected HCC cohort. The viral cohorts will no longer be dose escalated to 10 mg/kg.

The **1L Nivolumab vs Sorafenib Cohort** will consist of approximately 130 advanced HCC subjects who are naive to systemic therapy (uninfected, HCV-infected, or HBV-infected) who will be randomized 1:1 to receive open label flat dose nivolumab 240 mg Q2 week IV (Arm A) or sorafenib 400 mg po BID (Arm B) until unacceptable toxicity or RECIST 1.1 disease progression or study discontinuation for any other reason. Uninfected, HCV-infected, or HBV-infected subjects will be enrolled. Subjects will be stratified by viral status (HCV vs non-HCV [HBV infected or uninfected]) and presence of macrovascular invasion (MVI) or extrahepatic spread (EHS). Subjects with resolved HCV infection will be stratified into the HCV group.

The **Nivolumab and Ipilimumab Combination Cohort** will consist of up to 120 subjects. Uninfected, HCV-infected, or HBV-infected subjects with advanced HCC and previous treatment with sorafenib will be randomized 1:1:1 into 3 different dose arms:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3 week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm C--nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week until toxicity or disease progression (n = 40).

A 2-stage design will be employed for each of the 3 dose arms. Twelve subjects in each dose arm will undergo a safety and tolerability assessment at Week 13 (or prior to Week 13 if discontinued). The safety evaluation (Section 3.1.4) will be conducted independently for each dose cohort based on criteria described in Discontinuation Criteria (Sections 4.1.18 for nivolumab and 4.2 for ipilimumab). No additional subjects will be enrolled until the safety evaluation at Week 13 occurs. After completion of Stage 1, enrollment in Stage 2 of the subsequent 28 subjects can occur in each dose arm and is contingent upon the results of the safety evaluation.



Tumor response will be evaluated using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). It is recognized that there may be delayed responses following disease progression with nivolumab and other agents in this class. In these cases, subjects may continue treatment provided that they experience no clinical deterioration. These subjects will continue to be evaluated by RECIST 1.1.

Duration of Study: The study is expected to accrue over a period of approximately 5 years. The study will end when survival follow-up collection has concluded. The last visit will be defined as the latest survival visit included in the final analysis of OS (ie. the latest subject death, loss to follow up, or withdrawal of consent).

Number of Subjects: Approximately 500 subjects including the Dose Escalation Phase (~ 50 subjects), Expansion Phase (200 subjects), 1L Nivolumab vs Sorafenib Cohort (~130 subjects), and Nivolumab plus Ipilimumab Combination Cohort (120 subjects).

Study Population: The study population will include men and women age 18 or older with advanced HCC. Advanced HCC is HCC not appropriate for management with curative intent by surgery or local therapeutic measures. All subjects must have measurable disease at baseline.

Statistical Considerations:

Sample Size Determination

Dose Escalation: Sample size at each dose level depends on the observed toxicity and is not based on statistical considerations. Three to 6 subjects will be evaluated at each dose level.

Expansion Phase: In order to better estimate efficacy of nivolumab, approximately an additional 100 uninfected subjects (50 Sorafenib progressors and 50 Sorafenib naive or intolerant), 50 HCV-infected subjects, and 50 HBV-infected subjects will be dosed at the 3 mg/kg dose level. If 50 subjects are treated at 3 mg/kg dose level in any of the four additional expansion arms and 10 of 50 subjects (20%) are responders (BOR of PR or CR), the lower bound of 95% confidence interval of the response rate is 10% using the Clopper-Pearson Method.

1L Nivolumab vs Sorafenib Cohort:

The sample size of about 130 for this cohort is considered to provide a reasonably reliable estimate of ORR for both nivolumab and sorafenib arm. Table 1 summarizes the exact 95% CIs and 90% lower bound for a sample size of 65 subjects per arm when observed ORRs are 3.1% (2/65), 4.6% (3/65), 15.4% (10/65), and 20.0% (13/65) respectively.

Table 1: Observed ORR and CI under Sample Size of 65 per Arm

Observed ORR	Exact 95% CI	90% Lower Bound
3.1%	(0.4%, 10.7%)	0.8%
4.6%	(1.0%, 12.9%)	1.7%
15.4%	(7.6%, 26.5%)	9.8%
20.0%	(11.1%, 31.8%)	13.7%

Nivolumab plus Ipilimumab Combination Cohort: The sample size of each arm is decided based on safety and efficacy considerations. An initial total of 36 subjects will be randomized 1:1:1 (n=12) into one of three arms within stage 1 to assess safety and tolerability. An additional 28 subjects will be enrolled into each arm that remains open within stage 2 to further establish efficacy and safety. With sufficient follow up for a total of 40 subjects in an arm, this will allow a stable estimate of ORR, adequate safety follow up, as well as information on duration of response. The maximum width of the exact 2-sided 95% confidence interval (CI) is 31.8% when the ORR is in the 20% to 40% range. Table 2 summarizes the exact 95% CIs and 90% lower bound for a sample size of 40 per arm when observed ORRs are 20% to 40%, respectively.

Table 2:	Observed ORR with Exact 95% CI and 90% Lower Bound	
Observed ORR	**Exact 95% CI**	**90% Lower Bound**
20%	(9.1%, 35.7%)	12.0%
25%	(12.7%, 41.2%)	16.2%
30%	(16.6%, 46.5%)	20.5%
35%	(20.6%, 51.7%)	24.9%
40%	(24.9%, 56.7%)	29.4%

Primary Endpoint

Dose Escalation Phase

- The primary objective is safety and tolerability of nivolumab as evaluated by the following endpoints:
  - Incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, and deaths.
  - Incidence of clinical laboratory test abnormalities.

Expansion Phase

- ORR, based on assessments by BICR under RECIST 1.1 criteria, is the primary endpoint. It is defined as the proportion of all treated subjects whose BOR is CR or PR. BOR is the best response designation per subject over the study prior to subsequent anti-cancer therapy. For a BOR of CR or PR, the initial response assessment must have been confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

1L Nivolumab vs Sorafenib Cohort

- ORR, based on Investigator assessments under RECIST 1.1 criteria, is the primary endpoint. It is defined as the proportion of all randomized subjects whose BOR is CR or PR. For a BOR of CR or PR, the initial response assessment must have been confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

Nivolumab plus Ipilimumab Combination Cohort

- The primary objective is safety and tolerability of nivolumab plus ipilimumab as evaluated by the following endpoints.
  - Incidence of adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation, and deaths.
  - Incidence of clinical laboratory test abnormalities.
- ORR, as assessed by Investigator under RECIST 1.1 criteria, is the co-primary endpoint. It is defined as the proportion of all treated subjects whose BOR is CR or PR. For a BOR of CR or PR, the initial response assessment must have been confirmed by a consecutive assessment no less than 4 weeks (28 days) later.

Secondary Endpoints

The secondary efficacy endpoints for assessing antitumor activities include objective response rate (ORR) (Dose Escalation Phase only), CR rate, disease control rate (DCR), duration of response (DOR), TTR (time to response), TTP (time to progression), TTP Rate and PFS (progression free survival), all of which are based on BICR or investigator assessed response evaluation according to RECIST 1.1. These endpoints, as well as OS (overall survival) and OSR (overall survival rate), will be applied to all cohorts for treatment groups either as randomized (in

1L Nivolumab vs Sorafenib Cohort) or as treated (for all other cohorts). Definitions of the above secondary efficacy endpoints are available in Section 8.3.2.

The following pharmacokinetic parameters of nivolumab derived from serum concentration time profile of subjects in the dose escalation phase will be included for PK analysis: Cmax, Tmax, AUC(TAU), Ctrough, Ceoinf, AI_Cmax, AI_AUC, and Effective T-Half.

- Cmax: Maximum observed serum concentration
- Tmax: Time of maximum observed serum concentration
- AUC(TAU): Area under the serum concentration time curve in the dosing interval
- Ctrough: Serum concentration achieved at the end of dosing interval (trough concentration)
- Ceoinf: Serum concentration achieved at the end of the infusion
- AI_Cmax: Cmax at Cycle 3/ Cmax at Cycle 1
- AI_AUC: AUC(TAU) at Cycle 3/ AUC(TAU) at Cycle 1
- Effective T-Half will be calculated by using formula below for AI>1 with AI being AI_AUC

$$Effective\ \ T-HALF = \frac{\tau \ln(2)}{\ln\left[\frac{AI}{AI-1}\right]}$$

The secondary endpoints (for Dose Escalation and Expansion Phase) to assess the immunogenicity of nivolumab are incidence of subject ADA status, which include baseline ADA-positive, ADA-positive, and ADA-negative. Definitions of ADA status are described in the SAP.

Exploratory Endpoint(s)

Exploratory endpoints include, but are not limited to, BOR or ORR based on BICR assessed response evaluation according to mRECIST for HCC, AFP summary statistics, viral load, EQ-5D and FACT-Hep summary statistics. Detailed descriptions of the above exploratory endpoints are seen in Section 8.3.3.

Analyses

Only safety analysis and primary efficacy endpoint analysis are described below. Please refer to Section 8 for complete descriptions of statistical analyses.

Safety Analysis

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment arm. Adverse events, 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, chemistry, liver function and renal function will be summarized using worst grade per NCI CTCAE v.4.0 criteria.

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1 INTRODUCTION AND STUDY RATIONALE

Programmed Cell Death-1 (PD-1; CD279) is a cell surface signaling molecule that delivers inhibitory signals that regulate the balance between T cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). It is a 55 kD type I transmembrane protein that is a member of the CD28 family of T-cell costimulatory receptors, which also includes cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Inducible COStimulator (ICOS), and B- and T-lymphocyte attenuator (BTLA).[1] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). PD-1 is primarily expressed on activated T, B, and myeloid cells.[2] Its ligands, PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[3,4] PD-1 delivers a negative signal by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[5,6]

Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy and a lupus-like syndrome with arthritis and nephritis.[7,8,9] The emergence of autoimmunity is dependent upon the genetic background of the mouse strain; many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[10,11,12] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. This suggests that host mechanisms limit the antitumor response.[13,14,15,16,17,18]

In humans, PD-L1 is constitutively expressed on macrophage-lineage cells, activated T cells, lung, vascular endothelial cells, and placental syncitiotrophoblasts.[19] Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.[20,21,22,23,24,25,26] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[27] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[28] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness. Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression.[29] In multivariate analysis, high expression of PD-L1

in melanoma is an independent predictor of vertical growth of primary melanomas and of worse outcome.[30]

BMS-936558 (nivolumab) is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of `both proliferation and IFN-γ release in the MLR.[31] The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner.

1.1 Study Rationale

1.1.1 Rationale for Nivolumab in Hepatocellular Carcinoma

Expression of PD-L1 by malignant tumor cells and by other cells in the tumor microenvironment including infiltrating T cells, dendritic cells, and monocytes, has the potential to interact with tumor specific T cells that express PD-1. The interaction of PD 1 on tumor specific cytotoxic T cells with its ligands PD-L1 and PD-L2 causes a decrease in the ability of these cells to proliferate and exert cytotoxic effects, increases their apoptotic rate and alters the functional characteristics of the cells to produce a tolerogenic phenotype. This study will evaluate the effects of PD-1 blockade by nivolumab in subjects with hepatocellular carcinoma (HCC).

There is a strong preclinical rationale for blocking PD-1 signaling in HCC. Lymphocyte homeostasis is closely regulated by the differential effects of cytokines and an array of cell surface signaling molecules that exert opposing actions on T cell proliferation.[32,33,34] One of the primary molecules responsible for T cell expansion in response to antigenic stimulation is CD28. The interaction of CD28 on the T cell with B7.1 or B7.2 on the antigen presenting cell stimulates T cell proliferation and survival through increased expression of bcl2 family members, increased production of IL-2 and decreases the threshold of T cell receptors required for activation.[35] CD28 ligation also increases production of interferon gamma.[36] By necessity a mechanism for elimination of antigen stimulated T cells is required following control of the antigenic challenge to maintain the viability of the host. One important regulator of T cell contraction following antigen stimulation is CTLA4.[37] CTLA4 expression on T cells is increased following antigen stimulation and has an affinity for B7.1 and B7.2 that is 10-fold greater than CD28. Upon control of an antigenic challenge CTLA4 preferentially interacts with the antigen presenting cell to inhibit proliferation of T cells and helps to effect the contraction of the expanded T cell population. Mice that are deficient in CTLA4 die within one month of birth due to massive organ infiltration with lymphocytes as a result of the lack of this inhibitory signaling pathway.[38] A second member of this family of molecules that regulates T cell contraction is PD-1 and like CTLA4 its expression is increased following antigen stimulation.

Following most viral infections the host is capable of eliciting an effective innate and adaptive immune response to eliminate the virus and prevent reinfection. However, both in animals and

man there are examples of viral infections that are not eliminated following infection but instead a chronic viral infection is established. Examples include lymphocytic choriomeningitis virus (LCMV) in mice and hepatitis B and C in man. In chronic LCMV infection, antigen specific CD8 T cells demonstrate increased expression of PD-1.[39] These T cells have been termed "exhausted" due to their inability to control the infecting virus. Administration of an antibody that prevents PD-1 interaction with its ligands restores the ability of the cells to eliminate the virus infection.

PD-L1 is expressed in tumor biopsies from subjects with HCC. There is some controversy over the cell type that expresses PD-L1 and variability may exist between subjects with different stages of disease, etiologic factors associated with HCC, or immunologic response of the host to the tumor.[40,41,42,43] Hepatocytes and hepatoma cell lines express PD-L1 and its expression is increased by interferon gamma exposure.[44] This implies that the malignant cell may be the source of PD-L1 expression in some tumors but its expression has variably been observed on the malignant cells in patient samples. Some reports identify the hepatoma cells as PD-L1 positive whereas others show them to be negative for its expression. Instead, PD-L1 is observed on the mononuclear cells at the periphery of the malignant cells, potentially acting as a barrier for entry of PD-1 positive T cells. As in renal cell carcinoma and melanoma, expression of PD-L1 in the tumor is associated with an adverse outcome.[45,46] In a study of 265 subjects with HCC, the median disease free survival (DFS) was 14.9 for PD-L1-positive subjects but was not reached for PD-L1-negative subjects. Overall survival (OS) was also worse in subjects with PD-L1 positive tumors, 29.6 months versus 59.4 months.

Hepatocellular carcinoma is diagnosed in more than 500,000 people globally and is the fifth most common cancer in men and seventh in women.[47] There is an uneven distribution of HCC throughout the world with a higher incidence in Asia and Africa. This is related primarily to the differential rates of hepatitis B infection throughout the world and hepatitis B infection is found as a predisposing feature in about 50% of cases. In the United States about 20,000 cases of HCC are diagnosed per year and the incidence is predicted to increase by 81% by 2020. Risk factors for initiation of HCC are related to liver injury and repair particularly in association with liver cirrhosis. Viral infection or other inflammatory insults to the liver account for most cases of HCC. The risk factors for the development of HCC in hepatitis B carriers is highest in Asian men older than 40, Asian women over the age of 50, and in those with liver cirrhosis or a family history of HCC. In subjects with chronic hepatitis B infection but without cirrhosis, HCC is dependent upon viral genotype, replication and the presence of inflammation. Most other cases of HCC are associated with liver cirrhosis due to a variety of agents that damage the liver. Hepatitis C infection is found as the underlying etiology in about 25% of cases and is increasing significantly in the United States. Virtually any cause of liver damage that leads to cirrhosis can predispose to HCC. The most common associated disorders include alcohol-induced liver disease, fatty liver disease, aflatoxin exposure, primary biliary cirrhosis, or genetic predisposition to liver damage including hemochromatosis, alpha-1 antitrypsin deficiency or Wilson's disease.

Advances in the treatment of HCC have been related to improved disease control due to early detection. Early detection permits a curative surgical approach or use of local therapies such as radiofrequency ablation or cryotherapy as a curative option for management. Unfortunately up to 70% of subjects will recur. Liver transplantation is another curative treatment for HCC.

HCC is diagnosed at an advanced stage in more than 80% of subjects thus precluding potentially curative treatment approaches. The prognosis of advanced HCC largely depends not only on the characteristics of the tumor but also on the severity of the underlying chronic hepatic disease, as well as the patient's general condition.[48,49,50] Although chemotherapy has demonstrated activity against HCC, the current standard of care for subjects with advanced HCC is sorafenib.[51] A randomized double-blind, placebo-controlled trial of sorafenib administered at a dose of 400 mg twice daily showed a 2.8 month improvement in median overall survival from 7.9 months to 10.7 months (hazard ratio in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; $P < 0.001$). The median time to radiologic progression was also improved in the sorafenib group from 2.8 months to 5.5 months. There was however no significant difference in median time to symptomatic progression in those treated with sorafenib. Following sorafenib progression there is currently no standard of care agents that demonstrate a survival advantage.

1.1.2 Study Design Rationale for Dose Escalation Phase

PK data from subjects with normal hepatic function (804 subjects) and those with mild hepatic impairment (92 subjects), indicate that nivolumab clearance is not affected by mild hepatic impairment (< 20% effect on clearance). Exposures in mild hepatic impairment subjects that received nivolumab Q2W were comparable with normal subjects. Thus, mild hepatic impairment had no effect on nivolumab clearance and exposure, suggesting that no dose adjustment is needed for subjects with mild hepatic impairment. However, PK data were not available for subjects with moderate and severe hepatic impairment.[52]

HCC generally occurs in the setting of an underlying cirrhosis and impaired liver function. In addition, nivolumab is known to have potential hepatic adverse events (Section 1.4.2). For this reason, this study was initially designed to specifically assess the safety and tolerability of multiple doses of nivolumab in subjects with HCC.

Furthermore, there were additional concerns for HCC subjects with on-going active hepatitis virus infections. Stimulation of the immune system could potentially result in immune related viral clearance due to a cytolytic viral-specific response and additional hepatic toxicity. This was of particular concern in subjects with chronic hepatitis B infection who tend to have a higher number of infected hepatocytes expressing viral-specific antigens than subjects with chronic hepatitis C infection. In addition, the potential for ALT flares due to complex and poorly characterized changes in viral-host interactions is a well-described phenomenon in subjects with chronic HBV infection which can result in significant morbidity and mortality. Therefore, there was a significant concern that the immunostimulatory effect of nivolumab could result in a greater frequency of hepatic adverse events in virally-infected HCC subjects, with HBV-infected subjects perceived to have the greatest risk.

For these reasons, the study was initially designed with 3 separate HCC cohorts: an uninfected HCC cohort (no active hepatitis virus infection), an HCV-HCC cohort (with active HCV infection), and an HBV-HCC cohort (with active HBV infection). Dose escalation was planned to proceed independently within each cohort. In addition, the HBV-HCC cohort was started at 0.1 mg/kg (one dose level below the starting dose of 0.3 mg/kg in the uninfected and HCV-HCC cohorts).

1.1.3 Rationale for Expansion of Uninfected Cohorts in Expansion Phase

Preliminary data from this study has demonstrated the safety and tolerability of nivolumab in uninfected HCC up to 10 mg/kg administered every 14 days. As of 7-Oct-2014, nineteen uninfected HCC subjects have been treated in the current study at doses of 0.1 mg/kg (n = 1), 0.3 mg/kg (n = 3), 1.0 mg/kg (n = 3), 3.0 mg/kg (n = 3), and 10.0 mg/kg (n = 9). Preliminary anti-tumor activity from 17 evaluable uninfected subjects has been observed with 1 complete response (CR) at 1 mg/kg, 1 CR at 3 mg/kg, and 1 partial response (PR) at 10 mg/kg. In addition, a BMS-assessed best overall response (BOR) of stable disease (SD) has been observed in 6 subjects (with durable responses over 15 months). These data are promising especially when compared to historical data with ORR of 2% to 7% and median TTP of 2.8 to 4.1 months in the first line setting with sorafenib and warrants further exploration.

The uninfected HCC cohort in the dose escalation phase is a heterogeneous population of subjects who have progressed following or intolerant of at least one line of therapy or refused sorafenib treatment. Sorafenib is the only approved drug for the treatment of HCC and is the current standard of care for HCC patient not amenable to curative local therapy. Of note, the majority (21 of 28 [75%]) of subjects with evaluable responses in CA209040 have had prior sorafenib exposure, including all subjects (uninfected, HCV, or HBV cohorts) with either CR (n = 2) or PR (n = 4). In addition, 9 of 12 subjects with SD have had prior sorafenib exposure. Sorafenib has been shown to have limited effects on antitumor immunity. Low dose sorafenib may promote effector CD4+ T-cell function in peripheral blood mononuclear cells obtained from patients with HCC. Sorafenib has also been reported to decrease Th2 and Treg cells in peripheral blood from patients with HCC.[53] The tumor immunobiology may therefore be different between subjects who fail sorafenib and those with inadequate or no exposure to sorafenib. Two expansion cohorts will therefore be added to further understand nivolumab's effects in an uninfected cohort of HCC subjects who failed sorafenib and in an uninfected cohort of HCC subjects who are sorafenib naive or sorafenib intolerant.

In the nivolumab clinical development program, the recommended nivolumab monotherapy dose and schedule of 3 mg/kg Q2W is the same across tumor-types. This was based on the observed clinical safety and efficacy from the 306 subjects treated in CA209003 across different dose levels and tumor types (non-HCC: metastatic castrate resistant prostate cancer, renal cell carcinoma, colorectal adenocarcinoma, malignant melanoma, and non-small cell lung cancer). The multiple dose safety profile of nivolumab monotherapy is acceptable, in the context of the observed clinical activity, and manageable. The nature, frequency, and severity of AEs were similar across tumor types and dose levels. In the Phase 1 setting, dose escalation up to 10 mg/kg (0.1 to 10 mg/kg) was achieved without reaching a MTD. In addition, an integrated assessment

of data from in vitro, preclinical, and clinical studies and exposure-response in multiple tumor types was used to support the dose selection. In exposure analysis for steady-state trough concentration and best overall response, a trend was observed for each tumor type, but appeared to plateau at ≥ 3 mg/kg Q2W doses for all tumor types.

Preliminary clinical safety data from this study indicates that the profile of nivolumab in subjects with advanced HCC is generally consistent with the safety profile from other tumor types. Subjects in the uninfected cohort were safely dosed up to 10 mg/kg Q2W. Preliminary pharmacokinetic data in the uninfected HCC cohort indicate consistency with observations from other tumor types. As of 07-Oct-2014, responses in 28 evaluable subjects (across all 3 cohorts) have been observed at all dose levels ranging from 0.1 to 10.0 mg/kg; two CRs have been observed at 1.0 and 3.0 mg/kg, whereas 4 PRs have been observed at 0.1, 0.3, 1.0, and 10.0 mg/kg. Based on the observed safety and efficacy of nivolumab from CA209003 and CA209040, in conjunction with clinical pharmacology profiles, 3 mg/kg IV Q2W was selected as the nivolumab monotherapy dose and schedule for expansion of the uninfected cohorts. The selected dose and schedule provides for unified monotherapy dosing across the nivolumab development program.

1.1.4 Rationale for Expansion of Hepatitis Virus Infected Cohorts in Expansion Phase

As of 07-Oct-2014, the 2 hepatitis virus infected cohorts were in the dose escalation period. At that time, eight subjects each had been treated in the HCV or HBV cohorts. In both arms, preliminary anti-tumor activity has been observed. In 7 evaluable subjects in the HCV arm, there have been two PRs at 0.3 mg/kg and 1.0 mg/kg, 4 subjects with SD (2 at 0.3 mg/kg and 2 at 1 mg/kg), and 1 PD at 1.0 mg/kg; in 4 evaluable subjects in the HBV arm at 0.1 mg/kg, there has been 1 PR, 1 SD, and two subjects with PD. Thus, preliminary efficacy data indicate anti-tumor effects regardless of viral etiology.

In addition to the anti-tumor effects, preliminary results also suggest anti-viral activity. In the HCV cohort, 3 subjects have experienced significant HCV RNA declines ranging from 1.0 $\log_{10}$ to > 4 $\log_{10}$. Of these 3 subjects with evidence of significant antiviral activity, one had a transient decline in HCV RNA to < LOQ (limit of quantification); however, virologic rebound occurred and the subject has returned to baseline. In the HBV cohort, none of the subjects has had a significant change in viral biomarkers at the lowest dose tested of 0.1 mg/kg.

In summary, preliminary data indicate anti-tumor as well as anti-viral effects in HCC subjects with viral hepatitis. Nivolumab in this setting has also demonstrated an acceptable safety profile. Thus, the amendment 4 proposes to expand both HCV and HBV cohorts to enroll additional subjects and further characterize the safety, anti-tumor, and anti-viral properties of nivolumab.

The uninfected HCC cohort has been safely dose escalated to the 10 mg/kg dose level. This cohort will be expanded at the 3 mg/kg dose level in keeping with monotherapy dosing across the nivolumab program. As such, the HCV and HBV viral cohorts (currently dosing at 3 mg/kg and 1 mg/kg, respectively, without any safety concerns) will no longer be dose escalated to the 10 mg/kg dose level. These expansions will take place at the 3 mg/kg dose level if no DLTs are

observed at this dose. This will be in keeping with the selected dose and schedule selected for expansion of the uninfected HCC cohort. If however, the MTD is established at a lower dose level, expansions will take place at that lower dose level.

1.1.5 Rationale for the 1L Nivolumab vs Sorafenib Cohort

Based on an interim analysis with a data cutoff of 12-Mar-2015, 47 subjects with advanced HCC had been treated with nivolumab at doses ranging from 0.1 mg/kg to 10 mg/kg. As outlined in Section 1.4.6, there have been 42 subjects with evaluable responses. Antitumor activity has been observed in uninfected and viral-infected subjects, and at dose levels ranging from 0.1 mg/kg to 10 mg/kg. Overall, investigator-assessed responses by RECIST1.1 have been observed in 8 of 42 subjects (19%) with evaluable response data, including 2 CRs and 6 PRs, and median OS for all treated subjects is approximately 15 months. These data are promising especially when compared to historical data of sorafenib (the only agent approved for treatment of subjects with advanced HCC) in the **first line** setting (subjects naive to systemic treatment) with ORR of 2% to 7% by RECIST and 9% by mRECIST, median TTP of 2.8 to 4.1 months, and median OS of 6.5 to 10.7 months in patients with previously untreated HCC.[54,55,56,57,58] In addition to preliminary anti-tumor activity, nivolumab has demonstrated an acceptable safety profile for subjects with advanced HCC as outlined in Section 1.4.6.

Currently, there is only one approved agent for subjects with advanced HCC (sorafenib), and there are no approved therapies for patients with advanced HCC who are intolerant to sorafenib or have progressed after sorafenib treatment. As described in Sections 1.1.2 and 3.1.3, study CA209040 was initially designed as a Phase 1 dose-escalation study to investigate the safety, immunoregulatory activity, pharmacokinetics, and preliminary anti-tumor activity of nivolumab in advanced HCC subjects with or without chronic viral hepatitis. Given the preliminary yet promising antitumor activity of nivolumab in advanced HCC as outlined in Section 1.4.6 in CA209040, a predominantly 2L (post-sorafenib) patient population, BMS proposes a randomized cohort to explore efficacy of nivolumab vs sorafenib in 1L (systemic therapy naive) HCC patients.

Despite the demonstrated benefits of sorafenib in advanced HCC, the prognosis of patients with advanced HCC has not been radically improved.[59] 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.[55,56] Furthermore, the landmark sorafenib trials also failed to demonstrate symptomatic improvement or improvement in quality of life.[60] GIDEON, the largest real-life study conducted on the use of sorafenib, reported sorafenib-related adverse events in 64% of patients, 23% of which were Grade 3 or 4 AEs. In 28% of patients, AEs resulted in permanent discontinuation of sorafenib.[61] Overall, the most common adverse events were diarrhea (25%), hand-foot skin reaction (24%), fatigue (14%), rash/desquamation (12%), anorexia (9%), hypertension (7%), and alopecia (7%). Asians further experience more hand-foot-skin reactions (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. Predictive biomarkers for sorafenib benefit that could refine the risk-benefit ratio for therapy have not yet been validated.[60,62] These data

highlight the continued unmet medical need for advanced HCC subjects in the 1L setting. Thus, given the efficacy and safety data observed in CA209040 as outlined in Section 1.4.6, nivolumab monotherapy may offer improved benefit to subjects in the 1L setting.

1.1.6 Rationale for Open Label Design for 1L Nivolumab vs Sorafenib Cohort

This cohort is an open-label randomized controlled trial design. Nivolumab and sorafenib belong to two different drug classes with key differences in the mechanism of adverse events. The adverse event profiles of nivolumab and sorafenib have events like skin-, gastrointestinal-, and thyroid-related signs and symptoms that have different approaches to management. In particular, there are different approaches to dose reductions and delays and the use of immunosuppressants. An open-label design ensures that adverse events are appropriately identified and managed according to the study therapy the subject is receiving.

Because of the open label design, response-related endpoints for all randomized subjects will be determined by an Independent Radiologic Review of tumor assessments.

1.1.7 Rationale for Stratification Factors in 1L Nivolumab vs Sorafenib Cohort

Stratification factors for this cohort will include:

- HCV vs non-HCV, and
- Presence of investigator-assessed vascular invasion or extrahepatic spread (VI/EHS) vs absence of VI/EHS.

The rationale for these 2 stratification factors is based on the following information summarized below.

Randomized phase 3 trials in HCC that followed after the sorafenib pivotal trials have all failed to demonstrate positive outcomes. These include 4 phase 3 trials in the first-line setting with sunitinib, brivanib, linifanib, and erlotinib.[57,58,63,64] The reasons for trial failure are considered heterogeneous and include lack of understanding of critical drivers of tumor progression/dissemination, liver toxicity, flaws in trial design, or marginal tumor potency.[11] With respect to trial design, publications have cited potential imbalances in prognostic baseline factors.

The randomized Phase 3 trials mostly stratified by the presence or absence of vascular invasion and/or extrahepatic spread (VI/EHS), region, and ECOG performance status (PS). Despite stratification and randomization, there are notable differences in the outcomes. Subset analysis of the 2 pivotal sorafenib trials showed differences in the outcomes of patients who had VI/EHS compared to those who did not have VI/EHS. Subjects who had VI/EHS had worse outcomes than subjects without VI/EHS.[65,66,67] This study will therefore stratify by VI/EHS.

An important issue that has emerged from the recent HCC trials is evidence that suggests that the benefits of angiogenesis inhibition may vary in patients with different etiologies. Greater improvement in survival in the HCV-HCC subjects with both sorafenib and sunitinib

(14 vs 8.7 months and 17.6 vs 9.2 months, respectively.[57] Literature has long cited that clinicopathologic features and prognoses differ among the different etiologies of HCC.[68] To date, most international clinical trials allow recruitment of HCC patients with different etiologies resulting in difficulties with data interpretation in a heterogeneous population. The linifanib trial was the only large trial that stratified by etiology, ie, HBV+ HCC vs HBV- HCC. No significant differences were observed in overall survival outcomes. In the meta-analysis of the sorafenib trials, the synthesized hazard ratio for HCV-HCC patients was significantly lower than that for HCV(-) patients. Differences in overall survival outcomes for HBV-HCC and non-viral HCC (uninfected HCC) have not been distinctly difference. This study will therefore stratify by etiology, specifically HCV-HCC vs non-HCV-HCC.

No clear differences in regional outcomes emerged from the 2 pivotal sorafenib trials or from the erlotinib, brivanib, and sunitinib trials. There was a trend toward better outcomes in Japan compared to the rest of Asia and the non-Asian regions in the linifanib trial. A recent meta-analysis of 6 randomized controlled sorafenib trials did not find any differences between the Asian and non-Asian subjects.[69] Therefore, this study will not stratify by region.

Lastly, trial outcomes in the sorafenib pivotal trials and the sorafenib comparative trials did not differ by ECOG PS. The meta-analysis of sorafenib trials also did not demonstrate significantly different hazard ratios for patients with different ECOG PS.[69] ECOG PS will therefore not be a stratification factor in this trial.

1.1.8 Rationale for Nivolumab plus Ipilimumab Combination Cohort

Immune checkpoint blockade is a rapidly advancing therapeutic approach in the field of immuno-oncology and treatment with investigational agents targeting this mechanism has induced regressions in several types of cancer. Programmed death 1 (PD-1) receptor and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) are two important cellular targets that play complementary roles in regulating adaptive immunity. Whereas PD-1 contributes to T-cell exhaustion in peripheral tissues, CTLA-4 inhibits at earlier points in T-cell activation. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone.[70]

Ipilimumab is a fully humanized IgG1 monoclonal antibody binding to the anti-cytotoxic T-cell lymphoma-4 antigen (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma [Yervoy® Prescribing Information, 2011] and has demonstrated improved overall survival as monotherapy and in combination with dacarbazine.[71,72] Ipilimumab has been studied in combination with multiple standard of care (SOC) therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer.

Phase 3 studies are ongoing in NSCLC, SCLC, and prostate carcinoma.[73]

Preliminary data in patients with advanced HCC support the continued development of Immuno-Oncology (IO) agents in this tumor type. In a Phase 2, non-controlled, open-label, multicenter trial, tremelimumab, a monoclonal antibody that blocks CTLA-4, was administered

at a dose of 15 mg/kg IV every 90 days in 20 subjects with advanced HCC and chronic HCV.[74] In terms of antitumor responses, this pilot study in HCV-HCC patients treated with a CTLA-4 blocking antibody, reported a partial response rate (PR) of 17.6%, a disease control rate (DCR) of 76.4%, and a time to progression of 6.48 months, which compares favorably with sorafenib data as outlined above in Section 1.1.3. A rise in serum transaminases was observed after the first dose in more than half of the subjects. Five of 20 subjects (25%) experienced a Grade 3 or higher elevation in ALT. However, in all cases, the transaminitis was transient, not associated with a decline in liver function, did not require steroid management, and did not recur with subsequent doses. An HCC clinical trial is currently on-going for tremelimumab in combination with chemoembolization or ablation.[75]

In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[63]

Combining immunotherapeutic agents with different mechanisms of action offers the possibility of an additive to synergistic response. PD-1 and CTLA-4 are both co-inhibitory molecules, but evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity. In a Phase 1 study of the combination of nivolumab plus ipilimumab in advanced melanoma (CA209004), there was a 41% response rate, including a 17% complete response rate (CR).[76] A randomized Phase 2 study (CA209069) comparing nivolumab plus ipilimumab versus ipilimumab showed an objective response rate of 61%, including a 22% complete response rate, in previously untreated, advanced melanoma patients with BRAF wild-type mutation status, versus 11 % for ipilimumab alone.[77] In addition, the combination regimen decreased the risk of melanoma progression or death compared to ipilimumab alone by 60%.

In a Phase 3 trial of combined nivolumab and ipilimumab or monotherapy in untreated melanoma (CA209067), nivolumab alone or combined with ipilimumab resulted in significantly longer progression-free survival than ipilimumab alone. The median progression-free survival was 11.5 months (95% confidence interval [CI], 8.9 to 16.7) with nivolumab plus ipilimumab, as compared with 2.9 months (95% CI, 2.8 to 3.4) with ipilimumab (hazard ratio for death or disease progression, 0.42; 99.5% CI, 0.31 to 0.57; $P < 0.001$), and 6.9 months (95% CI, 4.3 to 9.5) with nivolumab (hazard ratio for the comparison with ipilimumab, 0.57; 99.5% CI, 0.43 to 0.76; $P < 0.001$). In patients with PD-L1–negative tumors, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone.[78] Additional efficacy and safety results demonstrating the potential for a combination IO approach are outlined in Sections 1.4.4 and 1.4.5.

Taken together, the preliminary monotherapy data of CTLA4 and PD-1 pathway inhibition in HCC demonstrate antitumor activity and manageable safety profiles. Given the increased efficacy observed with combination approaches in other tumor types, nivolumab plus ipilimumab may offer subjects with advanced HCC, who have been previously treated with sorafenib and have no other approved treatment options, the potential for benefit.

1.1.9 Rationale for Objective Response Rate as Primary Endpoint in 1L Sorafenib vs Nivolumab Cohort and Nivolumab plus Ipilimumab Combination Cohort

As outlined in Section 1.4.6, the response rate for nivolumab in predominantly 2L advanced HCC subjects of 19% (8 of 42 subjects) in the Dose Escalation Phase of CA209040 and preliminary 1 year survival of 61% compares favorably to sorafenib in the 1L setting as outlined in Section 1.1.5 Antitumor activity has been observed in uninfected and viral-infected subjects, and at dose levels ranging from 0.1 mg/kg to 10 mg/kg. Overall, responses as assessed by RECIST1.1 have been observed in 8 of 42 subjects (19%) with evaluable response data, including 2 CRs and 6 PRs. In addition to preliminary anti-tumor activity, nivolumab has demonstrated an acceptable safety profile for subjects with advanced HCC (Section 1.4.6).

Objective Response Rate (ORR) as estimated by RECIST 1.1 assessments from a blinded independent central review (BICR) is the primary endpoint for the randomized 1L Nivolumab vs Sorafenib Cohort and the Nivolumab plus Ipilimumab Combination Cohort.

The primary analysis of ORR will be performed at least 6 months after the last patient first dose date. Six months follow-up is thought to be sufficient to characterize durable clinical benefit because in the dose escalation cohorts of CA209040, the majority of responses to nivolumab occurred early (by Week 12) in 7 of 8 subjects; the median duration of response (DOR) was approximately 12 months; and in 1L trials with sorafenib the median time to progression is usually < 4 months. This will allow sufficient follow up for ORR to have a stable estimate, adequate safety follow up, as well as information on duration of response in the 1L Nivolumab vs Sorafenib Cohort and Nivolumab plus Ipilimumab Combination Cohort. Furthermore, in advanced HCC subjects who received a systemic multikinase inhibitor, brivanib (BRISK-PS), ORR has been shown to be an independent predictor of OS with median OS of 16.4 months in brivanib responders vs 8.3 months for brivanib non-responders (hazard ratio 0.28; 95% CI 0.14 - 0.55, P < 0.01).[79]

1.2 Research Hypothesis

The purpose of the Dose Escalation Phase of this study is to evaluate the safety profile, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) following IV infusion at doses of 0.1, 0.3, 1, 3, and 10 mg/kg of nivolumab in subjects with advanced hepatocellular carcinoma (HCC) administered every 14 days.

In the Expansion Phase, treatment with nivolumab monotherapy will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response in subjects with advanced HCC who have been previously treated with sorafenib.

In the 1L Nivolumab vs Sorafenib Cohort, nivolumab administration in subjects with advanced hepatocellular carcinoma (HCC) who are naive to systemic therapy will improve ORR compared with sorafenib.

In the Nivolumab plus Ipilimumab Combination Cohort, treatment with nivolumab plus ipilimumab will lead to clinical benefit as demonstrated by a clinically meaningful objective response rate (ORR) and duration of response in subjects with advanced HCC who are previously treated with sorafenib. In addition, the purpose of the cohort is to evaluate the safety profile of the combination in subjects with advanced HCC who have been previously treated with sorafenib.

1.3 Objectives(s)

1.3.1 Primary Objectives

- **Dose Escalation Phase**: To establish the safety, tolerability, dose limiting toxicities (DLT) and maximum tolerated dose (MTD) for nivolumab administered every 14 days to subjects with advanced HCC.
- **Expansion Phase**: To estimate the ORR and duration of response of nivolumab monotherapy in subjects with advanced HCC who are naive to sorafenib or have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
- **1L Nivolumab vs Sorafenib Cohort**: To estimate overall response rate (ORR) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.
- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To establish the safety and tolerability of nivolumab plus ipilimumab in subjects with advanced HCC.
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with Investigator assessed tumor response based on RECIST 1.1.

1.3.2 Secondary Objectives

- **Escalation and Expansion Phase**:
  - To assess antitumor activities (Time to Progression (TTP) and Progression Free Survival (PFS)) based on results of blinded independent central review (BICR) and/or investigators using RECIST 1.1.
  - To evaluate overall survival (OS) in subjects treated with nivolumab monotherapy.
  - To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.

- To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC (Dose Escalation Phase only).
- To assess the immunogenicity of nivolumab in subjects with advanced HCC (Dose Escalation Phase only).

- **1L Nivolumab vs Sorafenib Cohort**:
  - To estimate TTP and PFS of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy.
  - To evaluate the overall survival (OS) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy.
  - To evaluate the relationship between PD-L1 expression and efficacy.
- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To assess antitumor activities (TTP and PFS) based on results of BICR and/or investigators using RECIST 1.1.
  - To evaluate overall survival (OS) in subjects treated with nivolumab plus ipilimumab.
  - To investigate the potential association between selected biomarker measures, such as PD-L1 expression, and clinical efficacy measures including overall survival.

1.3.3 Exploratory Objectives

- **Escalation Phase**:
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To investigate the pharmacodynamic (PD) activity of nivolumab on antiviral immunologic biomarkers including HBV or HCV specific immune response in peripheral blood and cell phenotyping by flow cytometry.
  - To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load, quantitative Hepatitis surface antigen (HBsAg) levels, quantitative Hepatitis e antigen (HBeAg) levels, Hepatitis B surface antibody (HBsAb), and Hepatitis B e antibody (HBeAb).
  - To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
  - To assess the relationship between nivolumab exposure and measures of hepatic dysfunction.
- **Expansion Phase**:
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To investigate the pharmacodynamic (PD) activity of nivolumab on antiviral immunologic biomarkers including HBV or HCV specific immune response in peripheral blood and cell phenotyping by flow cytometry.

- To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load, quantitative Hepatitis surface antigen (HBsAg) levels, quantitative Hepatitis e antigen (HBeAg) levels, Hepatitis B surface antibody (HBsAb), and Hepatitis B e antibody (HBeAb).
- To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
- To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
- To assess the relationship between nivolumab exposure and measures of hepatic dysfunction.
- To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC.
- To assess the immunogenicity of nivolumab in subjects with advanced HCC.
- To assess self-reported health problems as measured using the descriptive system of the 3-level version of the EQ-5D (EQ-5D-3L) questionnaire.
- To assess changes in societal utility for self-reported health as measured using the EQ-5D-3L index score.
- To assess changes in subject ratings of own health as measured using the EQ-5D-3L visual analog scale (EQ-VAS) score.

- **1L Nivolumab vs Sorafenib Cohort**:
  - To evaluate the safety of nivolumab and sorafenib.
  - To estimate overall response rate (ORR) of nivolumab and sorafenib in subjects with advanced HCC who are naive to systemic therapy. ORR will be determined with blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
  - To assess antitumor activities of nivolumab vs sorafenib based on results of BICR using mRECIST for HCC.
  - To evaluate disease control rate (DCR), duration of disease control, and time to response of nivolumab and sorafenib.
  - To evaluate overall survival in subjects who have intrahepatic vs extrahepatic progression for nivolumab and sorafenib.
  - To evaluate overall survival in subjects treated with nivolumab or sorafenib with baseline AFP < 400 ng/mL vs > 400 ng/mL.
  - To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
  - To investigate the pharmacodynamic activity of nivolumab on antitumor immunologic biomarkers in peripheral blood in subjects with HCC.
  - To investigate the potential association between selected biomarker measures in tumor tissue specimens and blood samples and clinical efficacy measures including overall survival.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.

- To characterize the pharmacokinetics of nivolumab in subjects with advanced HCC.
- To assess the immunogenicity of nivolumab in subjects with advanced HCC.
- To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
- To assess the subject's cancer-related QoL using the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire.

- **Nivolumab plus Ipilimumab Combination Cohort**:
  - To estimate the ORR and duration of response for nivolumab plus ipilimumab combination therapy in subjects with advanced HCC who have been previously treated with sorafenib. ORR will be determined with a blinded independent central review (BICR) assessed tumor response based on RECIST 1.1.
  - To assess antitumor activities based on results of BICR using mRECIST for HCC.
  - To describe the effects of nivolumab in subjects infected with hepatitis B virus (HBV) or hepatitis C virus (HCV) whether positive or negative as assessed by HCV or HBV viral load.
  - To investigate the pharmacodynamic activity of nivolumab plus ipilimumab on antitumor immunologic biomarkers in peripheral blood and tumor tissue in subjects with advanced HCC.
  - To explore the association of oncologic and antiviral clinical activity and safety measures with SNPs.
  - To assess the relationship between nivolumab plus ipilimumab exposure and measures of hepatic dysfunction.
  - To assess the subject's overall health status using the EQ-5D-3L index and visual analog scale.
  - To characterize the pharmacokinetics of nivolumab and ipilimumab in subjects with advanced HCC.
  - To assess the immunogenicity of nivolumab and ipilimumab in subjects with advanced HCC.

1.4 Product Development Background

A summary of the nonclinical pharmacology, toxicology, pharmaceutical and metabolism data is provided in this section. Additional information can be found in the Investigator Brochures for nivolumab[80] and ipilimumab.[81]

1.4.1 Pharmacology

1.4.1.1 Nonclinical Pharmacology

Nivolumab is an IgG4 antibody which binds to PD-1 (CD279) with nanomolar affinity and shows a high degree of specificity for PD-1, blocking binding of PD-1 to PD-L1 and PD-L2. nivolumab binds to human PD-1 and not to other members of the CD28 family, such as ICOS, CTLA-4 or BTLA.

1.4.1.2 Metabolism and Excretion

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals, no tissue distribution studies with nivolumab have been conducted in animals. However, the low volume of distribution in cynomolgus monkeys (0.046 to 0.060 L/kg) indicates that there is little extravascular distribution of the drug.

In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals no metabolism studies with nivolumab have been conducted in animals. The expected in vivo degradation of monoclonal antibodies (mAbs) is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes. In accordance with regulatory guidelines for biotechnology-derived pharmaceuticals, no mass balance studies with nivolumab have been conducted in animals.

1.4.1.3 Clinical Pharmacokinetics of Nivolumab

The pharmacokinetics (PK) of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, tumor type, baseline tumor size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab.

Full details on the clinical pharmacology aspects of nivolumab can be found in the Investigator Brochure.

1.4.1.4 Clinical Pharmacokinetics of Ipilimumab

The PK of ipilimumab has been extensively studied in subjects with melanoma, at the 3 mg/kg and 10 mg/kg doses administered as a 1.5 h IV infusion. The PK of ipilimumab was characterized by population PK (PPK) analysis and was determined to be linear and time invariant in the dose range of 0.3 mg/kg to 10 mg/kg. The mean CL (± standard deviation [SD]) value after IV administration of 10 mg/kg was 18.3 ± 5.88 mL/h, and the mean steady-state volume of distribution (Vss) (± SD) value was 5.75 ± 1.69 L. The terminal T-HALF determined from PPK analysis was 15.4 days. CL of ipilimumab in subjects with mild and moderate hepatic impairment was similar to that of subjects with normal hepatic function. PK within Japanese

subjects is comparable and consistent with previous PK results reported within non-Japanese subjects.

1.4.2 Nivolumab Safety Summary

In clinical trials, nivolumab has demonstrated an acceptable benefit-risk across multiple tumor types, including advanced melanoma, RCC, NSCLC, and some lymphomas. Overall, the safety profile is quite similar across multiple tumor types and is discussed further in the sections below, including overviews from studies CA209003 and CA20937.

CA209003 is a completed Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. A total of 306 subjects were treated with nivolumab in the dose range of 0.1 - 10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303 (99.0%) subjects have at least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3 - 4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and diarrhea (1%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3 - 4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%).

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reactions. Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. Most high grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively. In conclusion, the safety profile at 3 mg/kg (n = 54) was similar to safety profile across the dose ranges from 0.1 mg/kg to 10 mg/kg (n = 306).

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

CA209037 is an ongoing Phase 3, open-label study of nivolumab (3 mg/kg administered by intravenous [IV] infusion every 2 weeks [Q2W]) vs investigator's choice therapy in subjects with previously-treated advanced melanoma. As of 30-Apr-2014, 268 subjects have been treated with 3 mg/kg IV nivolumab in CA209037 with safety results as outlined below (source document interim CSR, DCN930081508)[82] that are consistent with the Phase 1 experience of CA209003.

In CA209037, nivolumab related AEs of any grade occurred in 67.5% of subjects. Of the 268 subjects treated with nivolumab, 255 (95.1%) subjects had at least 1 reported AE regardless of causality. The most frequently reported treatment-related AEs were fatigue (25.0%), pruritus (16.0%), diarrhea (11.2%), and nausea (9.3%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3 - 4) AEs were reported in 24 (9.0%) of subjects. The most common treatment-related high grade AEs were fatigue (0.7%), anemia (0.7%), diarrhea (0.4%), and vomiting (0.4%). Drug-related SAEs occurred in 4.5% of subjects. Grade 3 - 4 drug-related SAEs reported in at least 2 subjects included diarrhea (2 subjects, 0.7%). In addition, drug-related SAE of hyperglycemia occurred in 0.7%.

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) are:

- Skin (29.1%) including pruritus (16.0%) and rash (9.3%)
- GI (11.6%) including diarrhea (11.2%) and colitis (1.1%)
- Endocrine (7.8%) including hypothyroidism (7.8%) and hyperthyroidism (1.9%)
- Hepatic (4.5%) including AST increased (4.1%) and ALT increased (2.6%)
- Pulmonary (2.2%) including pneumonitis (1.9%)
- Hypersensitivity/infusion reaction (1.9%)
- Renal (1.5%) including increased creatinine (0.7%), increased urea (0.4%), and tubulointerstitial nephritis (0.4%).

In general, these select AEs were considered by the investigator to be related to study drug, except for AEs in the hepatic and renal select AE categories. There were few high-grade select adverse events (n = 20), and the majority of high-grade events (13 of 20) subsequently resolved, including those for which immunosuppressive therapy was not initiated.

Treatment-related AEs leading to discontinuation were reported in 6 (2.2%) of the 268 treated subjects in CA209037 including single events of colitis, pancreatitis, increased ALT, increased lipase, autoimmune neuropathy, and demyelination. There were no deaths due to drug-related toxicity in CA209037.

Taken together, these data from studies from CA209003 and CA209037 highlight the acceptable safety profile with similar trends in AEs in the 574 subjects treated with nivolumab in these 2 studies. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

In addition to the clinical safety data outlined above, preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[83] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with BMS-936558 (nivolumab) during pregnancy.

1.4.3 Summary of Nivolumab Clinical Activity

As of July 2015, > 8,600 subjects have received nivolumab in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies).

In **CA209003**, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg). In CA209003, a total of 306 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on RECIST 1.1 criteria,[84] has been reported at all dose levels.

In NSCLC, the most active doses were 3 and 10 mg/kg. The overall ORR of 17% was reported with a 48-week progression-free survival rate (PFSR) of 22% (95% CI: 15 - 30%), and a 24-month overall survival rate of 24% (95% CI: 16 - 32%). Only a single response (1/33) was reported at 1 mg/kg. Durable responses were observed in both squamous and non-squamous subtypes. Historically, ORR of 5% to 10% and median PFS (mPFS) of 2 to 3 months has been reported with docetaxel treatment in previously-treated NSCLC subjects.

A complete response (CR) or partial response (PR) was reported in 31% (95% CI: 22% - 41%) of the 107 response-evaluable subjects with melanoma treated with nivolumab monotherapy Q2W at doses ranging from 0.1 to 10 mg/kg in CA209003. The responses were durable with a PFSR at 24 weeks of 38% (95% CI: 28 - 47%) and OS at 24 months of 48% (95% CI: 38 - 57%).

Of the 34 response evaluable RCC subjects in CA209003, responses were reported in both the 1 mg/kg (5 of 18 subjects, 27 %) and 10 mg/kg (5 of 16 subjects, 31%) treatment groups. PFSR at 24 weeks was 33% (95% CI: 14 - 55%) in the 1 mg/kg and 37% (95% CI: 14 - 61%) in the 10 mg/kg nivolumab treatment groups. OS at 24 months was 51% (95% CI: 30 - 64%) and 44% (95% CI: 20 - 66) in the 1 mg/kg and 10 mg/kg groups, respectively.

In **CA209037**, the ongoing Phase 3 study for subjects with previously-treated advanced melanoma of nivolumab (3 mg/kg administered by intravenous [IV] infusion every 2 weeks [Q2W]) vs investigator's choice therapy, as of 30-Apr-2014, 120 nivolumab-treated and 47 subjects in the investigator's choice arm are available for determination of the ORR using RECIST 1.1 criteria. As determined by imaging plus clinical review by a blinded independent central review (BICR), the ORR for nivolumab vs the reference arm is 31.7% vs 10.6%, respectively. Four subjects in the nivolumab arm had a CR, whereas no subjects in the reference arm had a CR. Median progression-free survival was 4.7 months (95% CI: 2.3 - 6.5) vs

4.2 months (95% CI: 2.1 - 6.3) with a 6-month PFS rate of 48% (95% CI: 38 - 56) vs 34% (95% CI: 18 - 51) in the nivolumab (n = 122) vs reference arm (n = 60), respectively.

In addition, recent clinical trial data in MEL **(CA209066)**, and NSCLC **(CA209017 and CA209057)** have demonstrated OS benefit:

- In **CA209066**, a Phase 3 study of 418 previously untreated metastatic melanoma patients without a BRAF mutation, 1 year overall survival was 72.9% (95% CI: 65.5 to 78.9) in the nivolumab group as compared to 42.1% (95% CI: 33.0 to 50.9) in the dacarbazine group (P < 0.001). The median progression-free survival was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P < 0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P < 0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1).[85] Additional supportive data for the clinical activity of nivolumab in advanced melanoma has been shown in a cohort of 107 advanced melanoma subjects in an outpatient setting who enrolled between 2008 and 2012. In 107 patients with advanced MEL treated with nivolumab**,** objective responses were observed in 31% of patients. Median OS (62% with two to five prior systemic therapies) was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively. Median progression-free survival was 3.7 months (95% CI, 1.9 to 9.1 months), with 1- and 2-year progression-free survival rates of 36% (95% CI, 27% to 46%) and 27% (95% CI, 17% to 36%), respectively.[86]
- In **CA209017**, a Phase 3 trial in 272 patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy, subjects were randomized to nivolumab 3 mg/kg IV q2 week (n = 135) or docetaxel (n = 137) at 75 mg/m^2 every 3 weeks. Median OS was 9.2 months in the nivolumab group (95% CI: 7.3 - 13.3) vs 6.0 months in the docetaxel group (95% CI: 5.1 - 7.3) (HR of 0.59, P = 0.00025).
- A Phase 3 clinical trial of nivolumab vs docetaxel in Non-squamous NSCLC (**CA209057**), nivolumab monotherapy demonstrated superior OS compared with docetaxel, with a clinically meaningful and statistically significant improvement observed (HR=0.73 [95.92% CI: 0.59, 0.89]; stratified log-rank test p-value = 0.0015). The median overall survival was 12.2 months (95% confidence interval [CI], 9.7 to 15.0) with nivolumab versus 9.4 months (95% CI, 8.1 to 10.7) with docetaxel. Results of secondary endpoints of ORR, DOR, and TTR further support the antitumor activity of nivolumab in this population. Pre-study (baseline) PD-L1 expression was predictive for benefit from nivolumab for all efficacy endpoints. Interaction p-values reported for PD-L1 expression subgroups by each of the pre-defined expression levels suggested a clinically important signal of a predictive association. In PD-L1 positive subjects, the nivolumab group showed improved efficacy vs docetaxel across all efficacy endpoints (OS, ORR, and PFS). In contrast, there were no meaningful differences in efficacy between the treatment groups in the PD-L1 negative subgroups by any expression level.[87]

1.4.4 Summary of Nivolumab plus Ipilimumab Safety Data

Several doses of nivolumab and ipilimumab are currently being explored in ongoing clinical trials. Although the optimal doses have not yet been defined across multiple tumor types, the largest studies to date have been done in melanoma at a dose of nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W. These studies include subjects with previously untreated unresectable or metastatic melanoma in **CA209067** (313 subjects) and **CA209069** (94 subjects) (a total of 407 subjects). Based on the pooled analyses, nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg administered IV Q3W for 4 doses followed by nivolumab 3 mg/kg IV Q2W has an acceptable safety profile, as demonstrated by the frequency, severity, and types of AEs, drug-related deaths, SAEs, and AEs leading to discontinuation as described below. Additional details on safety and clinical activity of nivolumab plus ipilimumab combinations are described in the IB.[80]

The following were the key safety findings for these pooled subjects:

- The most frequently reported drug-related AEs of any grade (≥ 15% of subjects) were diarrhea (43.0%), fatigue (35.4%), pruritus (33.4%), rash (31.0%), nausea (24.8%), pyrexia (18.7%), ALT increased (18.2%), AST increased (16.7%) and decreased appetite (16.2%). The most frequently reported drug-related Grade 3 - 4 AEs (≥ 5% of subjects) were colitis (9.6%), diarrhea (8.80%), ALT increased (8.4%), lipase increased (8.4%), and AST increased (5.9%).
- The majority of drug-related SAEs were Grade 3 - 4 in severity. The most frequently reported drug-related SAEs of any grade (≥ 2% of subjects) were colitis (11.1%), diarrhea (8.8%), pyrexia (3.7%), pneumonitis (2.7%), hypophysitis (2.2%), transaminases increased (2.2%), and adrenal insufficiency (2.0%). The majority of drug-related SAEs were Grade 3 - 4. The most frequently reported drug-related Grade 3 - 4 SAEs (≥ 2% of subjects) were colitis (8.8%), diarrhea (5.7%), and transaminases increased (2.2%).
- Drug-related AEs leading to discontinuation occurred in 36.4% of subjects. The majority of drug-related AEs leading to discontinuation of study drug were Grade 3 - 4 in severity. The most frequently reported drug-related AEs of any grade leading to discontinuation of study drug (≥ 2% of subjects) were colitis (10.1%), diarrhea (7.4%), ALT increased (4.7%), and AST increased (4.2%). These were also the most frequently reported drug-related Grade 3 - 4 SAEs leading to discontinuation of study drug (≥ 2% of subjects).
- The most frequently reported drug-related select AE categories with nivolumab + ipilimumab combination therapy were skin (61.9%), GI (46.4%), endocrine (29.7%), and hepatic (29.0%). The majority of select AEs were considered by the investigators to be related to study treatment.
- Drug-related select AEs were mostly Grade 1 - 2 in all categories with the exception of hepatic select AEs where the majority was Grade 3 - 4.
- Across categories, the majority of high-grade events subsequently resolved, including those for which immunosuppressive medication was not initiated.
- The majority of deaths (80/105) were due to disease progression. Study drug toxicity was considered responsible for 2 deaths; 1 subject died of ventricular arrhythmia within 30 days of the last dose and the other died of pneumonitis between 31 and 100 days of the last dose.

- Abnormalities in select hematology assessments and liver/kidney function tests were primarily Grade 1 - 2 in severity.
- The immunogenicity of nivolumab was low and not clinically meaningful.

In general, the frequency of adverse events was lowest across AE categories in the nivolumab monotherapy group and highest in the nivolumab + ipilimumab group. However, the types and frequency of AEs reported in the nivolumab + ipilimumab group were as expected based on the mechanism of action of the two agents and were consistent with previously reported data. Additional toxicity, including a higher frequency of Grade 3 - 4 AEs, was observed in the nivolumab+ipilimumab group relative to the ipilimumab group, leading to a higher frequency of discontinuation from study treatment. The most frequently reported select AE categories were skin, GI, endocrine, and hepatic. Select AEs belonging to these categories were reported more frequently in the nivolumab+ipilimumab group than the ipilimumab group. The majority of events were manageable. In summary, results to date suggest that the safety profile of nivolumab+ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.[80]

1.4.5 Summary of Nivolumab plus Ipilimumab Clinical Activity

Since PD-1 and CTLA-4 use distinct mechanisms to limit T cell activation, combining immunotherapeutic agents with different mechanisms of action offers the possibility of increased antitumor activity. Multiple studies suggest a higher response rate and antitumor activity with the combination of nivolumab plus ipilimumab:

- In a Phase 1 study of the combination of nivolumab plus ipilimumab in advanced melanoma (**CA209004**), there was a 42% response rate 22 of 53 subjects, including a 17% complete response rate (CR) in a pooled analysis of multiple doses (nivolumab 3 mg/kg and ipilimumab 1 mg/kg, and nivolumab 0.3 mg/kg, 1 mg/kg or 3 mg/kg combined with ipilimumab 3 mg/kg).[88]
- A randomized Phase 2 study (**CA209069**) comparing nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3week x 4 followed by nivolumab 3 mg/kg q2week versus ipilimumab q3 week x 4 showed an objective response rate of 61%, including a 22% complete response rate, in previously untreated, advanced melanoma patients with BRAF wild-type mutation status, versus 11 % for ipilimumab alone.[89] In addition, the combination regimen decreased the risk of melanoma progression or death compared to ipilimumab alone by 60%.
- In a randomized Phase 3 study (**CA209067**), 945 previously untreated subjects with unresectable melanoma were randomized 1:1:1 to receive nivolumab alone (3 mg/kg Q2weeks), nivolumab plus ipilimumab (nivolumab 1 mg/kg and ipilimumab 3 mg/kg Q3week x 4, followed by nivolumab 3 mg/kg Q2weeks), or ipilimumab alone (3 mg/kg Q3weeks x 4); median PFS for the three treatment arms were 6.9 months, 11.5 months, and 2.9 months, respectively, and demonstrated that the combination was more effective than either therapy alone.[90] Investigator-assessed response rates were also highest in the

combination arm: nivolumab (43.7%), nivolumab plus ipilimumab (57.6%), and ipilimumab (19.0%).

1.4.6 Summary of Preliminary Clinical Data from CA209040

In the current study (CA209040), as of 12-Mar-2015, 47 subjects have been dosed with nivolumab (including 43 subjects from the Dose Escalation Phase and 4 from the Expansion Phase): 25 uninfected, 11 HCV-infected, and 11 HBV-infected.

- In the uninfected arm, subjects have been dosed at concentrations of 0.1 mg/kg (n = 1), 0.3 mg/kg (n = 3), 1 mg/kg (n = 3), 3 mg/kg (n = 6), and 10 mg/kg (n = 12).
- In the HCV cohort, subjects have been dosed at concentrations of 0.3 mg/kg (n = 3), 1 mg/kg (n = 4), and 3 mg/kg (n = 4).
- In the HBV cohort, subjects have been dosed at 0.1 mg/kg (n = 5), 0.3 mg/kg (n = 3), and 1 mg/kg (n = 3).

To date, there has been one DLT in a subject at 10 mg/kg in the uninfected arm (as described in the SAE narrative below). No subsequent DLTs have occurred and no MTD in the uninfected cohort was defined. Dose escalation to 3 mg/kg has completed in the HCV cohort without any safety issues and no MTD identified. More recently, as of the end of June 2015, 3 HBV-infected HCC subjects have been dosed and have completed the DLT evaluation with no DLT observed. Therefore, at the beginning of July 2015, the cohort of HBV-infected subjects in the Expansion Phase has opened enrollment.

As of 12-Mar-2015 (data cutoff for interim analysis), there are 17 subjects continuing on-treatment in CA209040. Thirty subjects have been discontinued including 2 subjects with a confirmed complete response, 26 subjects with disease progression, 1 subject with a related event of hepatitis and increased AST/ALT (subject 3 - 19 described in Section 1.4.15), and 1 subject with unrelated increased bilirubin.

Two subjects have experienced drug-related SAEs:

- An uninfected subject with a Grade 2 SAE of liver decompensation who experienced a DLT at 10 mg/kg beginning on Day 17 after a single dose of nivolumab. The subject presented with new onset mild ascites and encephalopathy. Hepatic parameters were stable, including G1 ALT, G2 AST, and normal INR and bilirubin. CT imaging showed no evidence of disease progression. Mental status improved and the SAE resolved within 7 days; however, the subject experienced disease progression with increasing hip pain due to bone metastases and died 104 days after last study dose.
- A subject experienced a Grade 3 SAE of bullous pemphigoid in the 0.1 mg/kg HBV cohort. After 5 doses of study drug, the subject developed [redacted] without eye or oral involvement. Skin biopsy revealed subepidermal blistering process rich in eosinophils, and immunofluorescence with strong linear deposits of IgG and C3 at the dermal-epidermal junction, consistent with bullous pemphigoid. The subject was successfully managed with topical corticosteroids until resolution, and is now in the follow-up portion of the study.

There have been 17 on-treatment deaths (12 in the uninfected cohort, 1 in the HCV-cohort, and 4 in the HBV cohort) reported after administration of nivolumab. Nine deaths occurred within 100 days of last dose, and 8 subjects had deaths reported > 100 days after last dose. Fifteen subjects died due to disease progression; 1 subject died from GI bleeding unrelated to study drug 129 days after the last dose; and 1 subject died from a cerebral hemorrhage unrelated to study drug 399 days after the last dose.

Preliminary safety data indicate that the profile of nivolumab in subjects with advanced HCC is generally consistent with the safety profile from other tumor types, with the exception for an increased frequency of asymptomatic transaminitis. From the 47 treated subjects, the most frequent drug-related adverse events (≥ 5% of subjects) include: AST increased (19%), lipase increased (17%), rash (17%), ALT increased (15%), amylase increased (15%), pruritus (13%), hypoalbuminemia (9%), anemia (6%), asthenia (6%), diarrhea (6%), fatigue (6%), and hyponatremia (6%).

- Of note, transaminase elevations have generally been transient, with no dose dependency, without accompanying changes in other hepatic parameters, and occur in both the viral and non-viral cohorts. Some cases have resolved spontaneously while continuing nivolumab monotherapy, and only a single case required steroid intervention and improved to a Grade 1. Detailed narratives of drug-related hepatic events are provided in Section 1.4.15.
- Based on historical data, transaminase elevations are not uncommon in the setting of advanced HCC:
  - Treatment related increased AST and ALT was observed in 26% and 18% of subjects treated with sorafenib,[64] which is similar to nivolumab.
  - As discussed in Section 1.4.7 in the setting of HCV-infected HCC treated with the checkpoint inhibitor, tremelimumab, a rise in serum transaminases was observed in more than half of the subjects, with nearly half of subjects experiencing a Grade 3 or higher ALT. However, in all cases, the transaminitis was transient, not associated with a decline in liver function, did not require steroid management, and did not recur with subsequent doses.
  - Taken together, these data indicate that the overall safety profile of nivolumab (hepatic and non-hepatic events) is acceptable in subjects with advanced HCC.

In addition to the manageable safety profile of nivolumab in advanced HCC, preliminary antitumor activity is encouraging in this patient population. As of 12-Mar-2015, 42 subjects (all from the Dose Escalation Phase) have an investigator-assessed response by RECIST 1.1. Five subjects are not evaluable (4 who recently started the study and 1 subject who died prior to disease assessment). BOR is summarized below in Table 1.4.6-1. Eight of 42 subjects (19%) have had a BOR of either CR (n = 2) or PR (n = 6):

- Uninfected cohort (3 responders)--CR (1 mg/kg), CR (3 mg/kg), and PR (10 mg/kg)
- HCV-infected cohort (4 responders)--PR at 0.3 mg/kg, 1 mg/kg, and 3 mg/kg (n = 2)
- HBV-infected cohort (1 responder)--PR at 0.1 mg/kg.

Other efficacy data are also promising compared to historical data in the 2L and 1L setting:

- The current median TTP in CA209040 is 4.2 months which compares favorably to best supportive care in the 2nd line setting of 2.6 - 2.7 months.[54,91]
- Preliminary analysis of survival data indicate a 1 year survival rate of 62% in CA209040, which compares favorably to best supportive care in the 2L setting (approximately 30%),[54,91] and 30 - 44% for sorafenib in the 1L setting.[55,56,57,58,64]

In summary, preliminary anti-tumor activity has been observed in all 3 etiologic subtypes of the Dose Escalation Phase confirming biological activity regardless of HCC etiology and an acceptable safety profile in this patient population. These results are promising given the rarity of CRs (< 1%) across multiple Phase 3 studies with targeted agents; median TTP of < 3 months with best supportive care; overall survival of 30 - 44% with either best supportive care or sorafenib; and ORRs with sorafenib ranging from 2% to 7% by RECIST and 9% by mRECIST.[54,91,92,93,94,95,96]

Table 1.4.6-1: Investigator-assessed ORR and Best Overall Response (RECIST v1.1) by Nivolumab Dose - Response Evaluable Subjects - CA209040

	Nivolumab Dose					
	0.1 mg/kg (N = 6)	0.3 mg/kg (N = 9)	1 mg/kg (N = 10)	3 mg/kg (N = 6)	10 mg/kg (N = 12)	Total (N = 42)[a]
ORR, number (%) responders	1 (17)	1 (11)	2 (20)	3 (50)	1 (8)	8 (19)
Best overall response, number (%)						
Complete response (CR)	-	-	1 (10)	1 (17)	-	2 (5)
Partial response (PR)	1 (17)	1 (11)	1 (10)	2 (33)	1 (8)	6 (14)
Stable disease (SD)	3 (50)	5 (56)	5 (50)	2 (33)	5 (42)	20 (47)
Progressive disease (PD)	1 (17)	3 (33)	3 (30)	1 (17)	6 (50)	14 (33)

[a] Five subjects do not have disease assessments as of the database lock on 12-Mar-2015: One subject had death prior to disease assessment, and 4 subjects had recently started the study and were not yet available.

1.4.7 Nivolumab Experience in Hepatitis C Infected Subjects

A Phase 1 single-ascending dose escalation trial, CA209002, of nivolumab (anti-PD-1) was conducted in subjects with genotype 1 active hepatitis C infection.[97] Prior exposure to interferon was permitted. This was a double blind randomized trial with 45 subjects receiving nivolumab and nine subjects receiving placebo. Doses of 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg of nivolumab were administered, and subjects were followed 85 days post-dose.

In the primary efficacy population (Per-protocol Population), 5 subjects had a clinical response of repeatedly demonstrated ≥ 0.5 log HCV RNA decline (1 in the nivolumab 10 mg

IFN-experienced group, 3 in the nivolumab 10 mg/kg IFN-naïve group, and 1 in the placebo group). The duration of response was ≥ 8 weeks for all subjects except for 1 subject in the nivolumab group who had a duration of ≥ 4 to < 8 weeks. Three subjects who manifested a significant clinical response, all of whom received 10 mg/kg of study drug, experienced a ≥ 4-log decline in HCV RNA levels; 2 of these subjects were IFN-naive while 1 was IFN-experienced. Of note, one of the 3 subjects, a prior INF null responder, became undetectable for HCV RNA, and remained undetectable for more than 1 year after study completion. A single dose of nivolumab (up to 10 mg/kg) was generally well tolerated in subjects with active Hepatitis C infection. There were no deaths, SAEs, or withdrawals due to AEs occurring during the course of the study. The most commonly reported treatment-emergent AEs and treatment-related AEs were fatigue, headache, and diarrhea. Most were Grade 1 or 2 in severity and were evaluated as not related to study drug. One subject treated with 10 mg/kg of nivolumab experienced a transient, asymptomatic, 17 fold elevation in ALT/AST at Day 22 that coincided with peak HCV viral load decline. This transaminitis spontaneously and without any intervention reverted to baseline within 3 weeks, and this subject maintained normal LFTs for the remainder of the study. In addition, changes in thyroid function were observed in a few subjects with reports both of hypothyroidism and hyperthyroidism.

1.4.8 *Treatment Experiences with Other Immune Checkpoint Inhibitors in Subjects with Chronic Hepatitis*

In addition to the safety profile of nivolumab in subjects with chronic HCV as described in Section 1.4.7 above, there have been a few recent reports of other immune checkpoint inhibitors administered to oncology subjects with chronic hepatitis.

In a Phase 2, non-controlled, open-label, multicenter trial, tremelimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), was administered at a dose of 15 mg/kg IV every 90 days was been administered to 20 subjects with HCC and chronic HCV.[98] A total of 46 treatment doses were administered, and 13 subjects received at least 2 doses. Overall, there was a significant antiviral effect with a median reduction in HCV RNA of 0.76 log at Day 120 (P = 0.11) and 2.1 log at Day 210 (P = 0.017), and 3 subjects demonstrated a transient complete viral response during follow-up. A rise in serum transaminases was observed after the first dose in more than half of the subjects. Five of 20 subjects (25%) experienced a Grade 3 or higher elevation in ALT. However, in all cases, the transaminitis was transient, not associated with a decline in liver function, did not require steroid management, and did not recur with subsequent doses.

Since FDA approval of ipilimumab (anti-CTLA-4 mAb) for patients with metastatic melanoma in 2011, there have been recent case reports that highlight ipilimumab 3 mg/kg can be administered IV every three weeks safely to subjects with metastatic melanoma and chronic HCV (n = 2)[99] or chronic HBV (n = 1).[100] In the subject with metastatic melanoma and chronic hepatitis B, antiviral therapy with tenofovir was initiated to mitigate the potential risk of immune-mediated hepatotoxicity given the high frequency of HBV-infected hepatocytes in subjects with chronic HBV. HBV DNA levels were reduced from 2950 IU/mL to 41 IU/mL

with tenofovir prior to administration of ipilimumab, and the subject completed treatment without any hepatic events or change in LFTs.

In addition to the case report of ipilimumab administration to a single subject with melanoma and HBV as described above, a recent case series of 9 melanoma subjects (4 with chronic HCV and 5 with chronic HBV) has recently been published. Seven subjects had no changes in LFTs during the ipilimumab treatment cycles, 1 subject who had a Grade 2 AST/ALT subsequently normalized by Cycle 4; and 1 HCV-infected subject who had a Grade 1 AST/ALT at baseline developed a Grade 2 AST/Grade 3 ALT after Cycle 3. In summary, these data indicate that ipilimumab can be well tolerated without significant hepatotoxicity in subjects with chronic HCV or HBV.

Similar to the approach previously described[99] and reflective of guidance from an independent HBV/HCC expert panel (as discussed below in Section 1.4.10), subjects in the current study CA209040 are required to have a low HBV DNA level <100 IU/mL and be on antiviral therapy prior to administration of nivolumab to lower HBV viral load and reduce the risk of hepatotoxicity in the setting of nivolumab administration.

Taken together, the treatment experiences of nivolumab in subjects with chronic HCV (Section 1.4.7) and the treatment experiences of tremelimumab or ipilimumab in subjects with chronic hepatitis (Section 1.4.8) add to the growing safety profile of immune checkpoint inhibitors and suggest that nivolumab in virally-infected HCC subjects will be adequately tolerated. Specifically:

- Nivolumab in single ascending doses in chronic HCV is well tolerated with an acceptable safety profile.
- High grade transaminitis may occur with immune checkpoint inhibitors (tremelimumab) in subjects with chronic HCV+/- HCC; however, to date, these elevations are transient, without decline in hepatic synthetic function or hyperbilirubinemia, resolve spontaneously, and do not preclude repeat dosing.
- The safety profile of immune checkpoint inhibitors in the setting of chronic HCV or HBV is evolving; however, based on recent case reports with ipilimumab, immune checkpoint inhibitors can be given safely to subjects with chronic HCV or HBV.

As a result of this additional safety information, the CA209040 study team recommended in a previous amendment that the HBV arm initiate dosing at 0.1 mg/kg independent of the uninfected or HCV-infected arms (see study design Figure 3.1-1). For additional risk mitigation, a sentinel dosing paradigm was utilized in the first HBV cohort of 0.1 mg/kg; therefore, two weeks separated the first nivolumab dose for each subject in the 0.1 mg/kg cohort. However, in subsequent dose panels, a sentinel dosing strategy was not utilized. In addition, dose escalation in the HBV-HCC group was not planned to exceed the MTD in the other two arms of the study.

1.4.9 Definitions for Sorafenib Intolerance and Progression

In the Dose Escalation and Expansion Phase, 'sorafenib intolerance' is defined as:

- CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily)
- ≥ CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (to 400 mg once daily).

In the Dose Escalation and Expansion Phase subjects who failed sorafenib, ie 'sorafenib progressors' are defined as:

- Documented symptomatic OR radiographic progression during or after sorafenib therapy.

In the Nivolumab plus Ipilimumab Combination Cohort, 'sorafenib intolerance' is defined as:

- CTCAE Grade 2 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards AND 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (eg to 400 mg once daily)
- ≥ CTCAE Grade 3 drug-related adverse event which 1) persisted in spite of comprehensive supportive therapy according to institutional standards OR 2) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level (eg to 400 mg once daily).
- Requires a minimum of 14 days of sorafenib exposure (not necessarily consecutive).

In the Nivolumab plus Ipilimumab Combination Cohort, subjects who failed sorafenib, ie 'sorafenib progressors' are defined as:

- Documented radiographic progression during or after sorafenib therapy.

A decision on temporary or permanent sorafenib treatment interruption or sorafenib-dose reduction should have been based on the recommendations outlined in the sorafenib product label. Supportive therapies for sorafenib-related adverse events should have been administered according to institutional standards and may include but are not limited to treatments listed in the sorafenib product label:

- Dermatologic Toxicities: topical therapies for symptomatic relief

- Hypertension: institution of anti-hypertensive therapy
- Gastrointestinal Toxicities: with a minimal risk of severe nausea, vomiting, and diarrhea, supportive treatment may follow institutional standards.

Episodes of sorafenib-related toxicity (onset/end), supportive care measures, length of temporary sorafenib discontinuation and sorafenib dose reduction will be documented in the medical history section of the CRFs. If both disease progression and intolerance are observed at study entry, disease progression will be regarded as the entry criterion.

1.4.10 Rationale for Defining Dose Limiting Hepatic Toxicity in the Dose Escalation Phase

An advisory board panel was convened to discuss treatment of subjects with hepatitis B infection with or without hepatocellular carcinoma in August 2011. The potential for hepatic flare with antiviral therapy such as entecavir, lamivudine or tenofovir was discussed. It was the consensus of the panel members that the risk for this toxicity was low in subjects with low viral DNA loads who were on antiviral therapy for several months. As described above in subjects with hepatitis C infection, transient Grade 4 transaminase levels can be observed. The standard hepatic toxicity parameters used for BMS-936558 therapy are AST or ALT > 5 - 10 x ULN for > 2 weeks, AST or ALT > 10 x ULN irrespective of duration, T. bilirubin > 5 x ULN irrespective of duration, or concurrent AST or ALT > 3 x ULN and T. bilirubin > 2 ULN (potential Hy's Law case). Due to the potential for hepatic inflammation that could be greater due to viral infection the panel recommended that these parameters be adjusted to permit a higher level of hepatic toxicity with AST or ALT > 10 x ULN for >2 weeks, AST or ALT > 15 x ULN irrespective of duration, T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T. bilirubin at study entry, concurrent AST or ALT > 3 x ULN and T. bilirubin > 5 x ULN for subjects entering treatment with a normal bilirubin and up to 8 x ULN for subjects with elevated bilirubin, or clinical deterioration manifested by drug-related hepatic decompensation not identified above.

1.4.11 Rationale for Nivolumab Dose in Expansion Phase

Nivolumab monotherapy at 3 mg/kg was chosen for the expansion arms in the current amendment based on the following:

- Acceptable safety profile in the current study without correlation between dose and frequency or severity of AEs.
- Preliminary anti-tumor activity observed at dose levels of 0.1 mg/kg to 10 mg/kg in CA209040.
- Preliminary PK analysis of a subset of samples from CA209040 that indicate exposures are within the expected range of subjects from other tumor types.
- To align with the standard dose in the nivolumab program used in late stage studies that are based on the safety, efficacy, and exposure-response data in multiple other tumor types.

- In the large Phase 1 CA209003 study:
  - Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC, and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma.
  - The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above.
  - Results of the exposure-response analyses for these tumor types show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing.
  - A favorable risk/benefit profile demonstrated at 3mg/kg dose in other ongoing Phase 3 trials and the nivolumab label.

In addition, the uninfected HCC cohort has been safely dose escalated to the 10 mg/kg dose level. The HCV cohort has safely dose escalated to 3 mg/kg, and most recently at the end of June 2015, the HBV cohort has completed dose escalation to 3 mg/kg. The HCV and HBV viral cohorts will no longer be dose escalated to the 10 mg/kg dose level and the dose in the Expansion Phase will be 3 mg/kg for all cohorts.

In summary, across the nivolumab program, doses up to 10 mg/kg have been adequately tolerated, and based on the current data from CA209040 combined with CA209003 and CA209037, a dose of 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk in the additional planned expansions of the uninfected HCC subjects in CA209040.

1.4.12 Rationale for Nivolumab Flat Dosing in 1L Nivolumab vs Sorafenib Cohort and Nivolumab plus Ipilimumab Combination Cohort (Post Induction in Arms A and B)

The nivolumab dose of 240 mg every 2 weeks (Q2W) was selected based on clinical data and modeling and simulation approaches using population PK (PPK) and exposure-response analyses of data from studies in multiple tumor types (melanoma, non-small-cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) where body weight normalized dosing (mg/kg) has been used.

PPK analyses have shown that the PK of nivolumab is linear with proportional exposure over a dose range of 0.1 to 10 mg/kg, and no differences in PK across ethnicities and tumor types were observed. Nivolumab clearance and volume of distribution were found to increase as the body weight increases, but less than the proportional with increasing weight, indicating that mg/kg dosing represents an over-adjustment for the effect of body weight on nivolumab PK. The PPK model previously developed using data from NSCLC subjects has recently been updated, using data from 1,544 subjects from 7 studies investigating nivolumab in the treatment of melanoma, NSCLC, and RCC. In this dataset, the median (minimum - maximum) weight was 77 kg (35 kg - 160 kg) and thus, an approximately equivalent dose of 3 mg/kg for an 80 kg subject, nivolumab 240 mg Q2W was selected for future studies. To predict relevant summary exposures of nivolumab 240 mg Q2W, the PPK model was used to simulate 100 virtual trials, each

consisting of two arms, nivolumab 3 mg/kg Q2W and 240 mg Q2W. In the simulations, the simulated patient populations consisted of 1,000 subjects per treatment arm randomly sampled from aforementioned pooled database of cancer patients. Because no differences in PK were noted across ethnicities and tumor types, these simulated melanoma and NSCLC data will be applicable to patients with other tumor types. The simulated measure of exposure of interest, time-averaged concentrations (Cavgss) for 240 mg Q2W are predicted to be similar for all subjects in reference to 80 kg subjects receiving 3 mg/kg Q2W. Given the lower body weight in Japanese patients (median: 58.4 kg),[101] the exposures following 240 mg Q2W in the range of 50 to 70 kg were also simulated, and they are predicted to be approximately 16.8% greater when compared to the 3 mg/kg, 80 kg reference group.

Nivolumab is safe and well tolerated up to 10 mg/kg Q2W dose level. Adverse events have been broadly consistent across tumor types following monotherapy and have not demonstrated clear dose-response or exposure-response relationships. Additionally, the simulated median and 95th prediction interval of nivolumab summary exposures across body weight range (35 - 160 kg) are predicted to be maintained below the corresponding observed highest exposure experienced in nivolumab ie, 95th percentile following nivolumab 10 mg/kg Q2W from clinical study CA209003. Thus, while subjects in the lower body weight ranges would have greater exposures than 80 kg subjects, the exposures are predicted to be within the range of observed exposures at doses (up to 10 mg/kg Q2W) used in the nivolumab clinical program, and are not considered to put subjects at increased risk. For subjects with greater body weights, the simulated ranges of exposures are also not expected to affect efficacy, because the exposures predicted following administration of a 240 mg Q2W are on the flat part of the exposure-response curves for previously investigated tumors, melanoma and NSCLC.

Consistent with the nivolumab program and other tumor types, no MTD has been established in the dose escalation phase for the HCC cohorts. In addition, safety has been established up to 10 mg/kg in the uninfected-HCC cohort, and a similar safety profile has been observed regardless of HCC etiology at doses up to 3 mg/kg. As of 12-Mar-2015, 47 subjects had been treated in CA209040 as discussed in Section 1.4.6. In addition, as of 30-June-2015, 3 HBV-infected HCC subjects have received at least 3 doses of 3 mg/kg nivolumab q2 week. No DLT has been observed in the HBV cohort at 3 mg/kg, and the safety profile remains similar across each etiology and dose level. Given similar safety findings across the 3 uninfected, HCV-infected, and HBV-infected subjects in the Dose Escalation Phase, and similar PK observed from preliminary data in HCC, a flat dosing of 240 mg will be administered to all subjects in who will receive nivolumab monotherapy in the 1L Nivolumab vs Sorafenib Cohort and Nivolumab plus Ipilimumab Combination Cohort.

1.4.13 Rationale to Support Dose/Schedule of Nivolumab Combined with Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased

antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone.[102]

The combination of nivolumab and ipilimumab was evaluated in **CA209004** (MDX1106-04), a Phase 1b multiple ascending dose study in subjects with treatment-naive and previously treated advanced melanoma. Antitumor activity was observed in 5 different combination cohorts: nivolumab 0.3 mg/kg and ipilimumab 3 mg/kg (Cohort 1, n = 14), nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 2, n = 17), nivolumab 3 mg/kg and ipilimumab 1 mg/kg (Cohort 2a, n = 16), nivolumab 3 mg/kg and ipilimumab 3 mg/kg (Cohort 3, n = 6), and nivolumab 1 mg/kg and ipilimumab 3 mg/kg (Cohort 8, n = 41). From this study, it has been found that the 3 mg/kg nivolumab and 3 mg/kg ipilimumab combination regimen exceeded the maximum tolerated dose. Even though the drug-related discontinuation rates in combination cohorts were approximately 26 - 27%, the ORR in these cohorts were still higher compared to nivolumab monotherapy (42% - 44% versus 36%).

Additional studies have demonstrated the potential for IO combinations to improve antitumor responses across the nivolumab program.[80] An ORR of 62 - 65% has been observed in advanced melanoma (CA209067 and CA209069, N = 407) with a combination regimen of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg q3week x 4. In RCC patients (CA209016), both nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n = 21) and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (n = 23) showed antitumor activity with an ORR of 38%-40%. In NSCLC patients (CA209012), both combination regimens demonstrated a favorable efficacy profile with a response rate of 20% and a median OS of 11m for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg, and a response rate of 13% and median OS of 19.8 m for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg.

In summary, nivolumab and ipilimumab combinations have shown additive or synergistic activities across the tumor types investigated. To further improve the tolerability profile, other combination dosing regimens were also explored in the nivolumab development program. Less frequent dosing of ipilimumab at 1 mg/kg q6week when given with nivolumab 3 mg/kg q2week was found to have a similar discontinuation rate to that observed in nivolumab monotherapy (11% vs 10%) in preliminary data from CA209012.

Based on these data, the following three dose arms will be evaluated in CA209040:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q2 weeks;
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg, q3 weeks x4, followed by nivolumab 240 mg q 2weeks;
- Arm C--nivolumab 3 mg/kg q 2weeks + ipilimumab 1 mg/kg q 6weeks.

1.4.14 Rationale for Shorter Infusion Times With 240 mg Flat Dose Nivolumab and Ipilimumab

Long infusion times place a burden on patients and treatment centers. Establishing that nivolumab and ipilimumab can be safely administered using shorter infusion times of 30 minutes duration in subjects will diminish the burden provided no change in safety profile.

Previous clinical studies of nivolumab monotherapy and ipilimumab monotherapy and the combination of nivolumab and ipilimumab have used a 60 minute infusion duration for nivolumab and 90-minute infusion duration for ipilimumab (1 - 3 mg/kg dosing for both).

However, both nivolumab and ipilimumab have been administered at up to 10 mg/kg with the same infusion duration:

- Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg safely over long treatment duration. In Study CA209010, (a Phase 2, randomized, double blinded, dose-ranging study of nivolumab in subjects with advanced/metastatic clear cell RCC) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 - 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration.
- Similarly, ipilimumab at 10 mg/kg has been safely administered over 90 minutes. In the CA184022 study, where ipilimumab was administered up to a dose of 10 mg/kg, on-study drug related hypersensitivity events (Grade 1 - 2) were reported in 1 (1.4%) subject in the 0.3 mg/kg and in 2 (2.8%) subjects in the 10 mg/kg group. There were no drug-related hypersensitivity events reported in the 3 mg/kg group. Across the 3 treatment groups, no Grade 3 - 4 drug-related hypersensitivity events were reported and there were no reports of infusion reactions. Ipilimumab 10 mg/kg monotherapy has also been safely administered as 90 minute infusion in large phase 3 studies in prostate cancer (CA184043) and as adjuvant therapy for stage 3 melanoma (CA184029), with infusion reactions occurring in subjects. Administering 1 mg/kg of ipilimumab represents one-tenth of the 10 mg/kg dose.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab or ipilimumab clinical studies or the combination of nivolumab and ipilimumab. Furthermore, a 30-minute break after the first infusion for the combination cohort will ensure the appropriate safety monitoring before the start of the second infusion. Overall, a change in safety profile is not anticipated with 30-minute infusion of nivolumab, ipilimumab or combination.

1.4.15 Summary of Drug-related Hepatic Events in CA209040

Most subjects who enroll in nivolumab studies must have AST/ALT ≤ 3x ULN (Grade 1) or bilirubin ≤ 1.5x ULN (Grade 1). However, given the patient population in CA209040 with

advanced HCC, subjects may enroll with AST/ALT ≤ 5x ULN (Grade 2) or bilirubin ≤ 3x ULN (Grade 2). As a result, the CA209040 protocol when originally written made exceptions to the program standard DILI criteria (see Section 6.6) and dose discontinuation due to hepatotoxicity (see Section 4.1.18).

As of 12-Mar-2015, there have been 47 subjects treated with nivolumab and overall 19% of subjects have experienced a drug-related AST increase (11% Grade 3) and 15% have experienced a drug related ALT increase (9% Grade 3). These have occurred without changes in other hepatic parameters, are generally transient, and occur in both viral and non viral cohorts. Steroid intervention was required in only 1 of 5 Grade 3 elevations, and was adequately managed (see the narrative below).

As outlined in Section 1.4.8, in the setting of tremelimumab in HCC-HCV, a rise in serum transaminases was observed after the first dose in more than half of the HCC subjects with five of 20 subjects (25%) experiencing a Grade 3 or higher elevation in ALT.[98] However, in all cases, the transaminitis was transient, not associated with a decline in liver function, did not require steroid management, and did not recur with subsequent doses. In addition, in advanced HCC subjects treated with sorafenib, all-grade transaminase elevations have been observed in 26% of subjects with 17% Grade 3 or 4,[64] which is very similar to the observed hepatic profile of nivolumab to date.

Additional details for the 5 Grade 3 related hepatic events in CA209040:

- Subject [redacted] (uninfected) had a Grade 3 event of hepatitis and AST/ALT increased that began on study Day 71. At baseline, AST/ALT values were 1.2x ULN/<ULN, respectively, and peaked at 10x ULN/8.8x ULN, respectively. The event was managed by dose delay, steroid intervention, and resolved to Grade 1 after 127 days. The subject was discontinued permanently from nivolumab treatment.
- Subject [redacted] (HCV infected) had a 4-day AST/ALT elevation (baseline 3x ULN/<ULN) who peaked at 6x ULN/1.6x ULN, respectively. Onset was at Day 15 and was managed by dose delay. AST/ALT remained <1.5x ULN upon rechallenge, and the subject continued nivolumab without further hepatic issues.
- Subject [redacted] (HCV infected) had a Grade 3 increased AST/ALT at study Day 170. At baseline, AST/ALT were 3x ULN/4.1x ULN, respectively, and the subject peaked at 7x ULN/6.6x ULN, respectively. The subject continued on nivolumab and LFTs returned to baseline after 55 days.
- Subject [redacted] (HCV infected) had a Grade 3 increased AST/ALT at study Day 15. At screening AST/ALT were 3.5x ULN/4.3x ULN, respectively. At baseline AST/ALT were 4.2x ULN/5.2x ULN and peaked at 6x ULN/7.4x ULN, respectively, on Day 15. Nivolumab was continued and the event resolved after 7 days. The subject continued nivolumab without further hepatic issues.
- Subject [redacted] (Uninfected) had an 8-day event of Grade 3 AST/ALT increased, cholangitis, and increased bilirubin that occurred at study Day 428. AST/ALT/bilirubin at baseline were 1.3x ULN/<ULN/<ULN, respectively, and peaked at 3.5x/3.1x/2.2x ULN. After dose delay and treatment with antibiotics, the event resolved; however, the subject was

not rechallenged due to other ongoing adverse events including anemia requiring blood transfusions.

1.5 Overall Risk/Benefit Assessment

Subjects with advanced hepatocellular carcinoma have limited therapeutic options. Despite intensive efforts to develop new treatment paradigms while improving on the efficacy of current treatment options, the clinical management of HCC remains challenging. Systemic therapy with sorafenib is currently the only effective and approved first line therapy to prolong survival for subjects with advanced disease. For subjects progressing on or intolerant to sorafenib treatment, best supportive care or participation in clinical trials are the only remaining treatment options.

The development of new approaches for the management of advanced HCC is needed. Nivolumab has demonstrated clinical efficacy in a renal cell carcinoma, malignant melanoma, non-small cell lung cancer, and some lymphomas. There is a strong preclinical rationale for blocking PD-1 signaling in HCC. Nivolumab appears to have a manageable safety profile across multiple tumor types, and has been approved for metastatic melanoma and metastatic squamous non-small cell lung cancer. Adverse events associated with its use include liver toxicities, thyroiditis, pneumonitis, and diarrhea. Liver toxicities were observed in about 2% of subjects treated with nivolumab. In this study, it is possible that a higher percentage of subjects will experience liver toxicity because of the presence of pre-existing liver damage due to viral infection. A comprehensive algorithm is included in the protocol detailing the management of pneumonitis and other immune-related adverse events associated with nivolumab therapy (Appendix 1). Frequent monitoring of liver function tests during the study will help to identify liver injury at an early time point and permit initiation of treatment. Clinical activity with single agent nivolumab in other tumors that express PD-L1 support its clinical application.

This study will permit entry of subjects with impaired hepatic function and a history of viral hepatitis. The maintenance of stable disease in this population may be of benefit. Due to a concern that the potential toxicity of nivolumab in subjects with concurrent viral hepatitis, particularly those with chronic HBV, could be higher than those with other risk factors for HCC, dose escalation will be performed independently in each population. As an additional safety measure, the initial dose level of nivolumab in the HBV cohort will be one third of the other arms. Accrual to the arms of the study after that time will be independent and based on safety demonstration in the previous dose level for each arm. There is some risk associated with tumor biopsies, including bleeding and pain. While there will be no direct benefit to individual subjects that undergo these procedures, it is hoped that data generated from the analyses of these samples will guide the clinical development of this compound for the treatment of cancer. Given the strong scientific rationale based on the biological importance of inhibiting the PD-1/PD-L1 pathway the overall benefits far outweigh the potential clinical risks associated with this treatment.

Subjects in CA209040 from the Dose Escalation Phase include sorafenib-treated (32 of 47) and sorafenib-naive (15 of 47), and overall suggest the potential to improve clinical outcomes in a 1L

or 2L setting. However, the potential benefit of nivolumab monotherapy over sorafenib is not yet established. Sorafenib is the only approved agent for advanced HCC; however, it has a relatively low response rate vs placebo in the setting of frequent adverse events and drug discontinuations.[55,61] Based on the preliminary safety, tolerability, and activity of nivolumab in advanced HCC, the benefit-risk profile of nivolumab appears to favor nivolumab and warrants a randomized comparison. In order to assess the potential benefit and safety of nivolumab monotherapy over standard-of-care sorafenib, a randomized cohort comparing nivolumab monotherapy to sorafenib will be conducted. The overall risk-benefit assessment supports the conduct in CA209040. A DMC will be utilized to monitor the safety and activity of the treatments throughout the conduct of the 1L Nivolumab vs Sorafenib Cohort.

The combination of nivolumab plus ipilimumab has the potential for increased benefit compared to monotherapy targeting the PD-1 or CTLA-4 pathway. Current data from CA209040 demonstrate nivolumab has antitumor activity and an acceptable safety profile in subjects with advanced HCC. Similarly, in advanced HCC-HCV subjects, blockade of CTLA-4 pathway with tremelimumab is tolerable and also demonstrates antitumor activity. In addition to the potential for increased efficacy with a combination IO approach, there is also potential for increased frequencies of adverse events. The safety profile of nivolumab and nivolumab plus ipilimumab is characterized by immune-related toxicities, such as diarrhea, rash, pneumonitis, liver toxicity, and endocrinopathies. The frequencies and intensities of these events in the combination are variable and may depend on specific doses and schedules used, but may be increased over monotherapy. Sequelae have been manageable and reversible following intervention with existing algorithms using dose delays and/or with systemic steroid treatment. However, these AEs have the potential to be fatal if not detected early and managed per the established algorithms.

The following measures will be employed to ensure safety of the subjects in the Nivolumab plus Ipilimumab Combination Cohort:

- Two stage design with initial lead-in (n = 12) to establish the safety and tolerability of the combination before enrolling the entire cohort (n = 40).
- Toxicity monitoring to ensure the subjects' safety, including frequent safety conference calls during safety lead-in cohorts with investigators and representatives of the sponsor.
- BMS medical safety team (MST) to review ongoing safety signals across the entire nivolumab program, including all ongoing combinations with ipilimumab.

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) 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 (e.g., 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 (e.g., 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 (e.g., 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 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.

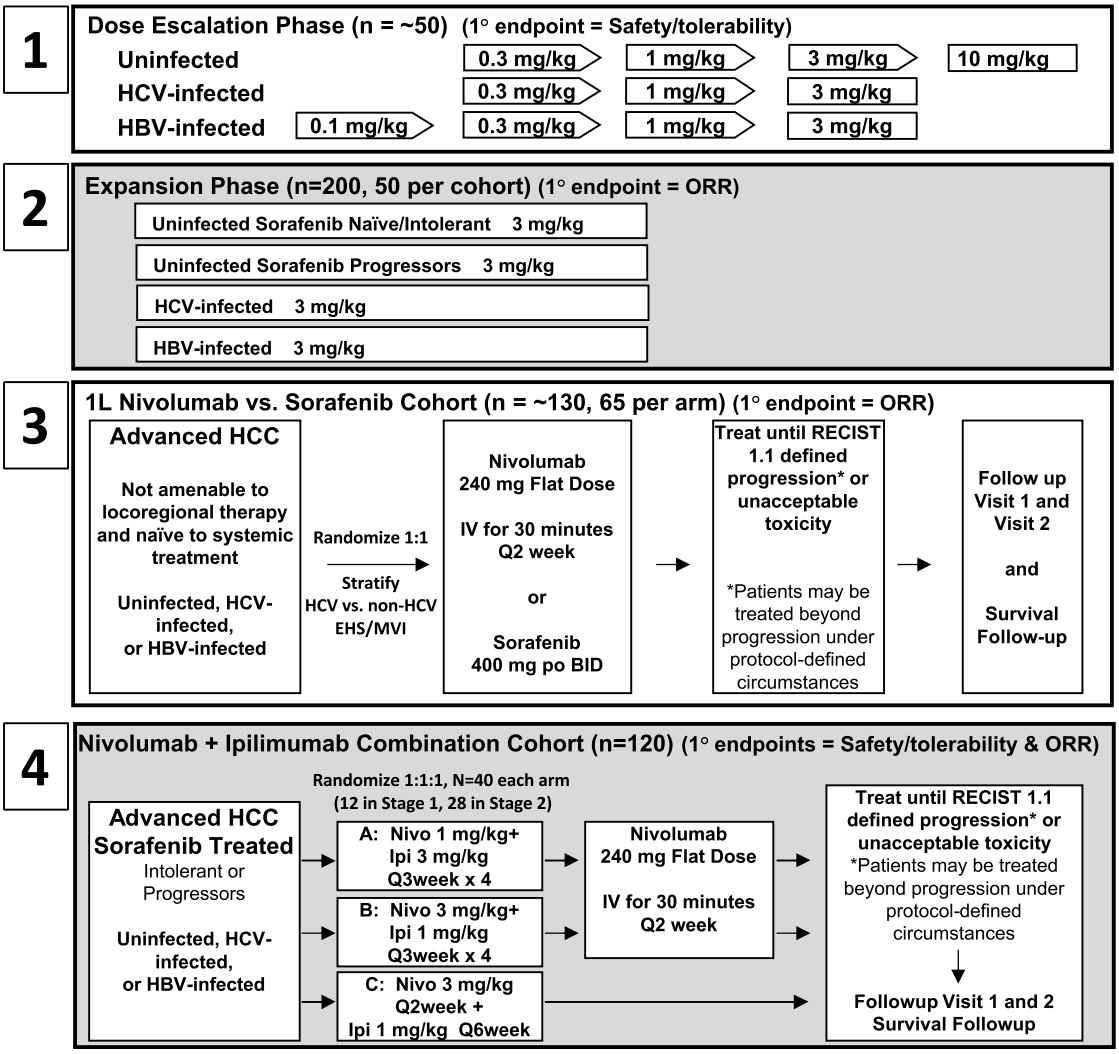
3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a phase 1/2, dose-escalation, open-label, non-comparative study of nivolumab or nivolumab in combination with ipilimumab in advanced hepatocellular carcinoma subjects with or without chronic viral hepatitis; and a randomized, open-label study of nivolumab vs sorafenib in advanced hepatocellular carcinoma subjects who are naive to systemic therapy.

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

Figure 3.1-1: Study Design of CA209040 and Cohorts 1 - 4



Three etiologic subtypes are included in the Dose Escalation Phase: uninfected HCC subjects, HCV-infected HCC subjects, and HBV-infected subjects.

The first part of the study is the Dose Escalation Phase designed to establish the safety of nivolumab at different dose levels (Section 3.1.3). The maximum dose level for the dose escalation phase is 10 mg/kg in uninfected HCC subjects and 3 mg/kg in HCV and HBV infected HCC subjects, respectively.

Upon activation of Amendment 4, the Expansion Phase (200 subjects) is designed to generate additional clinical data at specified doses in 4 cohorts (50 subjects per cohort) including uninfected sorafenib naive/intolerant subjects, uninfected sorafenib progressors (previously referred to as sorafenib failures in Amendment 4), HCV-infected, and HBV-infected subjects. Uninfected, HCV-infected, and HBV-infected subjects will receive a dose of 3 mg/kg Q2 week IV over 60 minutes. Prior to activation of amendment 8, nivolumab infusions were administered

over 60 minutes in the Dose Escalation Phase and Expansion Phase; however, upon activation of amendment 8 and based on rationale in Section 1.4.14, nivolumab infusions may be given over 30 minutes to align with the infusion times in the 1L Nivolumab vs. Sorafenib Cohort and Nivolumab plus Ipilimumab Combination Cohort.

Upon activation of Amendment 8, enrollment into the Expansion Phase will close (if not already completely enrolled), and the 1L Nivolumab vs Sorafenib Cohort will begin accrual. This is an open-label, randomized, cohort in adult (>18 years) male and female subjects with advanced HCC. Subjects must not be amenable for management with surgery or loco-regional therapy. Approximately 130 advanced HCC subjects who are naive to systemic therapy (uninfected, HCV-infected, or HBV-infected) will be randomized 1:1 to receive open label flat dose nivolumab 240 mg Q2 week IV over 30 minutes (Arm A) or sorafenib 400 mg po BID (Arm B) until unacceptable toxicity or RECIST 1.1 radiographic progression or study discontinuation for any other reason (Section 3.5). Uninfected, HCV-infected, or HBV-infected subjects will be enrolled. Subjects will be stratified by viral status (HCV vs non-HCV [HBV infected or uninfected]) and presence of macrovascular invasion (MVI) or extrahepatic spread (EHS). Subjects with resolved HCV infection will be stratified into the HCV group.

Upon activation of Amendment 8, enrollment into the Expansion Phase will close (if not already completely enrolled), and the Nivolumab and Ipilimumab Combination Cohort will begin accrual of up to 120 subjects. Uninfected, HCV-infected, or HBV-infected subjects with advanced HCC and previous treatment with sorafenib will be randomized 1:1:1 into 3 different dose arms:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3 week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3week x 4 followed by flat dose nivolumab 240 mg IV q2week until toxicity or disease progression (n = 40)
- Arm C--nivolumab 3 mg/kg q2week + ipilimumab 1 mg/kg q6week until toxicity or disease progression (n = 40).

Since the use of nivolumab and ipilimumab has not been previously studied in subjects with advanced HCC, a 2 stage design will be employed for each of the 3 dose arms. In Stage 1, 12 subjects will be enrolled in each dose arm, and will undergo a safety and tolerability assessment at Week 13 (or prior to Week 13 if discontinued) prior to enrollment of any additional subjects.

The safety evaluation (Section 3.1.4) will be conducted independently for each dose arm in Stage 1 based on criteria described in Discontinuation Criteria (Sections 4.1.18 for nivolumab and 4.2 for ipilimumab). No additional subjects will be enrolled until the safety evaluation at Week 13 occurs. Enrollment of the first 12 subjects in each dose cohort will be limited to select sites. After completion of Stage 1, enrollment in Stage 2 of the subsequent 28 subjects can occur in each dose arm and is contingent upon the results of the safety evaluation.

Number of Subjects: Approximately 500 subjects including the Dose Escalation Phase (~ 50 subjects), Expansion Phase (200 subjects), 1L Nivolumab vs Sorafenib Cohort (~ 130 subjects), and Nivolumab plus Ipilimumab Combination Cohort (120 subjects).

3.1.1 Treatment Flow

The study will consist of 4 phases: Screening, Treatment, Follow-up and Survival Follow-up.

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).
- 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 (for subjects in the 1L Nivolumab vs Sorafenib Cohort and Nivolumab plus Ipilimumab Combination Cohort).
- Screening assessments can be performed within 28 days of first dose.

Treatment Phase:

Nivolumab monotherapy will be given on an every two week schedule and one treatment cycle (42 days) is comprised of three doses in the Dose Escalation (at doses of 0.1 mg/kg to 10 mg/kg q2week) and Expansion Phase (3 mg/kg q2week). In the 1L Nivolumab vs Sorafenib Cohort, nivolumab monotherapy (240 mg IV) will be given on an every two week schedule with 1 dose = 1 cycle; sorafenib will be given 400 mg po BID. In the Nivolumab plus Ipilimumab Combination Cohort, the dosing will be as outlined above, with no less than 19 days between doses in Arms A and B during the q3week induction phase. In arm C, nivolumab doses may be given no less than 12 days between doses, and ipilimumab doses no less than 5 weeks between scheduled doses

All subjects except those in the 1L Nivolumab vs Sorafenib Cohort will undergo tumor assessments at every q6 week (± 2 days) for the first 48 weeks, and then q12 week (± 1 week) thereafter until disease progression. Subjects in 1L Nivolumab vs Sorafenib Cohort will undergo tumor assessments q8 week (± 1 week) for the first 48 weeks, and then q12week (± 1 week) thereafter until disease progression or treatment is discontinued (whichever occurs later). Imaging assessments should be scheduled regardless of dose delay or missed doses in all cohorts.

Prior to activation of Amendment 8, subjects in the Dose Escalation Phase were treated until either a confirmed CR, completion of 2 years of therapy, toxicity, or disease progression. However, upon activation of Amendment 8, all subjects are to be treated until toxicity, RECIST 1.1 defined progression (Appendix 2), unacceptable toxicity, or study discontinuation for any other reason (Section 3.5). Treatment may continue beyond progression under protocol defined.

Subjects will continue to receive nivolumab, sorafenib, or nivolumab plus ipilimumab until:

1. RECIST 1.1-defined radiographic progression or unacceptable toxicity.
2. Clinical deterioration (Section 3.1.4) suggesting that no further benefit from treatment is likely.
3. Meets criteria for discontinuation of study therapy as outlined in Sections 3.1.3.1 (Dose Limiting Toxicity), 3.5 (Discontinuation of Subjects from Treatment), 4.1.18 (Nivolumab Permanent Discontinuation Criteria), 4.1.12 (Treatment Interruption or Discontinuation for Sorafenib Treatment) or 4.2 (Ipilimumab Permanent Discontinuation Criteria)

Accumulating evidence indicates that the emergence of objective responses to agents that activate anti-tumor immune responses follows delayed kinetics of weeks or months, and can be preceded by initial apparent radiological progression or the appearance of new lesions or some enlarging lesions while certain target lesions are regressing ("mixed response"). It is thus reasonable, in the absence of clinical deterioration, to continue to treat these subjects until progression is both confirmed and found to have worsened at a subsequent imaging evaluation. Evidence of PD will be based on a comparison with baseline (or nadir) scans or other tumor evaluations. Additional details on treatment beyond progression are located in Sections 3.1.8 (for nivolumab and ipilimumab) and 4.1.13 (for sorafenib).

No subject receiving nivolumab or nivolumab plus ipilimumab will be permitted dose escalations or de-escalations. Sorafenib dose adjustments are described in Section 4.1.8 circumstances (Section 3.1.8). After discontinuation from study therapy, there are 2 follow-up visits required (on site visits), and additional survival follow-up (on-site or phone visits).

Follow Up Phase:

Follow-Up Visit 1 to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days).

Subjects who discontinue study drug for reasons other than radiographic progression or who continue treatment beyond progression will continue to have tumor assessments (if clinically feasible) according to the schedule in Table 5.1-8 and Table 5.1-9 and until progression or treatment discontinuation for subjects being treated beyond 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.

Survival Follow Up Phase:

Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit (please refer to Section 3.7.

3.1.2 Duration of Study

The study is expected to accrue over a period of approximately 4 years. The study will end when survival follow-up collection has concluded. The last visit will be defined as the latest survival visit included in the final analysis of OS (ie. the latest subject death, loss to follow up, or withdrawal of consent). 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.

3.1.3 Dose Escalation Phase

A 3+3 design with escalating doses will be used with this Phase 1/2 study starting at a dose of 0.3 mg/kg in the non-viral HCC and HCC-HCV arms. Escalations to 1 mg/kg, 3 mg/kg, and 10 mg/kg were originally planned for all cohorts, if safety is demonstrated. Accrual to the HCC-HBV infected arm will begin at 0.1 mg/kg. Subjects will be assigned to a dose level in the order of study entry. For additional risk mitigation, a sentinel dosing strategy will be utilized in the first HBV cohort of 0.1 mg/kg; therefore, two weeks will separate the first nivolumab dose for each subject in the 0.1 mg/kg cohort. However, in subsequent dose panels, a sentinel dosing strategy will not be utilized.

In Amendment 4, given the safety data for the uninfected HCC cohort at the 10 mg/kg dose level and a similar safety profile observed across each HCC etiology, 3 mg/kg dose was selected for Expansion Phase for the uninfected and HCV-infected HCC subjects, whereas a dose of 3 mg/kg or the MTD was planned for the HBV-infected HCC subjects. The HCV- and HBV-HCC cohorts in the dose escalation phase will no longer be escalated to the 10 mg/kg dose. More recently, the HBV 3 mg/kg dose escalation completed at the end of June 2015 with no DLT in any subject; therefore, the HBV expansion arm has opened in July 2015 at the 3 mg/kg dose.

3.1.3.1 Dose Limiting Toxicity in the Dose Escalation Phase

Dose limiting toxicity (DLT) will be determined based on the incidence and intensity of adverse events (AEs) occurring up to two weeks after the administration of the third dose of nivolumab (ie from C1D1-C1D42).

Dose Limiting Hematologic Toxicity

DLT will be defined as the need for platelet transfusion, platelet count < 10,000/μL, Grade 4 neutropenia of greater than 3 days duration or febrile neutropenia. The development of a transfusion requirement or an increase in transfusion requirement of more than two units of red blood cells every two weeks over a six week period will also be considered dose limiting unless an alternative cause is identified.

Dose Limiting Non-hematologic Toxicity

Dose limiting hepatic toxicity will be defined as

- Hepatotoxicity as evidenced by any of the following:
  - AST or ALT > 10 x ULN for > 2 weeks,

  - AST or ALT > 15 x ULN irrespective of duration,
  - T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T bilirubin at entry,
- Clinical deterioration manifested by drug-related hepatic decompensation not identified above (eg, encephalopathy etc.)
- Grade 2 or greater eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy or requires systemic treatment (eg encephalopathy etc.).
- Clinically relevant Grade 3 or greater non-hematologic toxicity excluding lymphopenia, asymptomatic lipase or amylase or laboratory abnormalities that correct to Grade 1 within 72 hours after treatment. Toxicity will be graded by CTCAE v 4.03.

No dose escalations or de-escalations are permitted within each subject's treatment. A subject who is withdrawn from the study before the completion of the first six weeks of treatment for a reason other than a DLT may be replaced. Subjects who experience dose limiting toxicity may resume treatment as per Section 4.1.16 upon resolution, providing that criteria for permanent discontinuation are not met (Section 4.1.18).

3.1.4 Safety Evaluation of Stage 1 of the Nivolumab plus Ipilimumab Combination Cohort

A total of 36 subjects will be randomized 1:1:1 (n=12) into one of the following 3 dose arms in Stage 1:

- Arm A--nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3week x 4 (Week 1, 4, 7, and 10) followed by nivolumab 240 mg q2week (beginning at Week 13)
- Arm B--nivolumab 3 mg/kg + ipilimumab 1 mg/kg q3 week x 4 (Week 1, 4, 7, and 10) followed by nivolumab 240 mg q2week (beginning at Week 13)
- Arm C--nivolumab 3 mg/kg q2 week (Week 1, 3, 5, 7, 9, 11, 13, etc) + ipilimumab 1 mg/kg q6week (Week 1, 7, 13, etc).

After enrollment of 36 subjects in Stage 1, no additional subjects will be enrolled until completion of the safety evaluation. Safety and tolerability will be determined when subjects reach week 13, or have been discontinued prior to this time point. However, tolerability beyond four doses may also be taken into consideration. All subjects will continue to be followed for safety, progression, and overall survival after discontinuation of study medication. The criteria used to advance to Stage 2 will be based on drug related adverse events leading to permanent discontinuation in the safety lead-in cohort (Stage 1, n = 12 per dose arm) (listed in Section 4.1.18 for nivolumab and 4.2 for ipilimumab) and include the following:

- If no more than one-third of the subjects in a given treatment arm permanently discontinue study medication prior to Week 13 due to treatment related adverse events, then this dose cohort will be deemed as tolerable and enrollment of an additional 28 subjects may proceed (Stage 2).
- If more than one-third of subjects in a treatment arm permanently discontinue study medication prior to Week 13 due to treatment-related adverse events, then the safety, tolerability, and efficacy of that treatment arm will be reviewed by the Sponsor and investigators prior to randomizing any additional subjects. A decision will be made by the sponsor whether to continue enrollment of an additional 28 subjects (Stage 2).

3.1.5 Evaluation of Risk/Benefit for a Cohort that does not meet Tolerability Criteria in the Nivolumab plus Ipilimumab Combination

In the event that more than 4 of 12 subjects (one-third) per dose arm in Stage 1 require permanent discontinuation due to treatment related adverse events prior to completion of the safety lead-in, the sponsor will review the risk/benefit profile from each cohort and determine whether or not to advance. In this event, the Sponsor will review all available data from Arms A, B, and C, and recommend continuation, modification or termination of a cohort. The rationale for further evaluation is that the most frequent severe drug-related AEs for the combination of nivolumab and ipilimumab have been asymptomatic and reversible (ie, LFTs and lipase laboratory changes) and there is preliminary evidence of deep and durable responses in advanced melanoma (CA209004, CA209067, and CA209069) despite these events. In particular, any assessment of the risk/benefit of a cohort not meeting tolerability will be triggered if the following criteria are met:

- A majority of subjects in the cohort have at least stable disease or a partial tumor response.
- All treatment related AEs leading to discontinuation are non-fatal, reversible and without severe sequela.
- A majority of the treatment related AEs are laboratory in nature, asymptomatic, and monitorable via routine blood draws.

If a decision is made to continue with a cohort because of a favorable risk/benefit profile (ie. non fatal AEs in subjects with at least stable disease or a partial tumor response) and despite meeting the 'not tolerable' criteria above, then the EC/IRBs must be notified.

Informed Consent forms updated, and discussion of the risk/benefit must be documented with all current and future subjects who are randomized to this regimen.

3.1.6 Stopping Rule for Dose Escalation Cohort

During the dose escalation phase, if more than one drug-related Grade 4 toxicity or drug-related death occurs at a dose level for a specific cohort, new subject accrual in that cohort at that dose level will be held. A discussion with investigators may be held to review the risk/benefit of this regimen. This discussion will be triggered if the following criteria are met:

- Majority of subjects who discontinue due to treatment related AEs have deep tumor response (ie, > 80% reduction)
- All treatment related AEs leading to discontinuation are non-fatal, reversible and without severe sequela (ie, GI perforation)
- Majority of the treatment related AEs are laboratory in nature, asymptomatic, and readily monitored with routine blood draws.

If a decision is made to continue with a dose level because of a favorable risk/benefit profile despite meeting the 'not tolerable' criteria ('more than one drug-related Grade 4 toxicity or drug-related death'), then IRBs must be notified, ICFs must be updated, and discussion of the risk/benefit must be documented with all future subjects who enroll on this regimen.

3.1.7 Stopping Rules for Clinical Deterioration

Clinical deterioration will be assessed to have occurred after a clinical event that, in the Investigator's opinion, is attributable to disease progression, is unlikely to reverse with continued study treatment and therefore indicates that the subject is not benefiting from study treatment and cannot be managed by the addition of supportive care (such as bisphosphonates and/or bone directed radiotherapy, thoracentesis or paracentesis of accumulating effusions). The decision to continue or stop treatment should be discussed with the BMS Medical Monitor and will be documented in the study files.

Examples of events that may, in the Investigator's opinion, indicate a lack of clinical benefit include, but are not limited to, the following:

- Performance status decrease of at least 2 points from baseline
- Skeletal related events defined by the following:
  - Pathologic bone fracture in the region of cancer involvement
  - Cancer related surgery to bone
  - Spinal cord or nerve root compression
- Bladder outlet or urethral obstruction
- Development of new central nervous system metastases or ≥ Grade 3 encephalopathy
- Any setting where the initiation of new anti-neoplastic therapy has been deemed beneficial to the subject.

3.1.8 Treatment Beyond Progression for Nivolumab or Nivolumab plus Ipilimumab

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. This phenomenon was observed in the Phase 1 study of nivolumab, CA209003, and confirmed in multiple Phase 3 studies (ie, lung CA209017; melanoma CA209037, CA209066, and CA209067). 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. Therefore, subjects will be allowed to continue study therapy after an initial investigator-assessed RECIST 1.1 (Appendix 2) defined progression as long as they meet the following criteria:

- Investigator assessed clinical benefit
- Subject is tolerating nivolumab or nivolumab plus ipilimumab
- 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 or nivolumab plus ipilimumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

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. 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 in Table 5.1-4, Table 5.1-5 and, Table 5.1-7.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden SLD 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.

3.2 Post Study Access 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. Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria. No exceptions will be granted.

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

3.3.1 Dose Escalation and Expansion Phase

3.3.1.1 Inclusion Criteria

1. Signed Written Informed Consent

a) The signed informed consent form prior to the performance of any study related procedures that are not considered part of standard of care.

2. Target Population

a) Subjects with advanced hepatocellular carcinoma not amenable for management with curative intent by surgery or local therapeutic measures.

b) Histological confirmation of hepatocellular carcinoma. Subjects with radiological diagnosis may be enrolled for screening in the study but histological confirmation is mandatory prior to initiation of study therapy.

c) Subjects must fulfill the criteria for prior therapy as follows:

i) For the dose escalation cohorts (uninfected, HCV-infected, and HBV-infected), subjects must have progressive disease following or be intolerant of at least one line of systemic therapy or refuse sorafenib treatment (refusal must be documented); subjects cannot be on active cancer therapy during the screening period.

ii) For the uninfected sorafenib progressors in the Expansion Phase, subjects must have had documented radiographic or symptomatic progression during or after sorafenib therapy

iii) For the uninfected sorafenib naive or intolerant subjects in the Expansion Phase, subjects must either have never received sorafenib treatment or were intolerant to sorafenib therapy as defined in Section 1.4.9.

iv) For the HCV and HBV cohorts in the Expansion Phase, subjects must have received sorafenib treatment and be either intolerant or have had documented radiographic or symptomatic progression during or after sorafenib therapy as defined in Section 1.4.9.

d) Subjects must have Child-Pugh scores as follows (Appendix 3):
   i) Dose Escalation Phase: Child-Pugh score of 7 points or less, ie, Child-Pugh A or Child Pugh B7.
   ii) Expansion Phase: Child-Pugh score of 6 points or less, ie, Child-Pugh A.

e) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 4);

f) The noninfected HCC arm Dose Escalation Phase and Expansion Phase will include subjects with prior HCV or HBV infection provided there is no active viral replication (negative for HBV DNA and/or HBV surface antigen and HCV RNA). HBV exposed subjects with resolved HBV infection who have seroconverted must have detectable HBsAb and HBcAb titers and have undetectable HBsAg and HBV DNA.

g) In the Dose Escalation Phase and Expansion Phase, the HCV infected arm must have evidence of HCV RNA. Subjects may have evidence of prior HBV infection but must have detectable HBsAb and HBcAb titers and have undetectable HBsAg and HBV DNA.

h) In the Dose Escalation Phase and Expansion Phase, subjects with chronic HBV infection must have evidence of ongoing viral replication (detectable HBsAg, HBeAg, or HBV DNA). Subjects with chronic HBV infection must have HBV DNA viral load < 100 IU/mL at screening. In addition, they must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy. If not on antiviral therapy at screening, then the subject must initiate treatment per regional standard of care guidelines at the time of consent. All subjects enrolled in the HBV cohort must continue antiviral therapy through follow-up visit 2. Both HBeAg positive and negative subjects will be included.

i) All subjects must have at least one measurable lesion.

j) For subjects in the Dose Escalation Phase and Expansion Phase, the lesion can be accurately measured by CT-scan (≥ 10 mm) according to RECIST1.1 (malignant lymph nodes must be > 15 mm on short axis) (additional details are included in Appendix 2)
   i) Previously treated lesions can be considered target lesions if there is clear evidence of progression.
   ii) Bone metastases are not considered measurable lesions, unless there is a measurable soft tissue component per RECIST1.1.
   iii) The measurable lesion cannot be biopsied during treatment (if there is only one lesion).

k) A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.6.
   i) Subjects must consent to allow the acquisition of existing formalin-fixed paraffin-embedded (FFPE) material (block or a minimum of 15 unstained slides) for performance of correlative studies; attempts should be made to collect at least 20 unstained slides.
   ii) If archived samples are not available, the subject must provide a fresh biopsy sample at screening - for this biopsy, subjects must have a soft tissue tumor lesion that can be biopsied at acceptable clinical risk (as judged by the investigator) at baseline.

Subjects must consent to the pre-treatment fresh biopsy (if no archived samples are available) as a condition of protocol participation. In this setting, if adequate tissue is not obtained during the first procedure then a repeat biopsy should be considered based on the investigator's assessment of clinical risk. However, a repeat biopsy is not required to meet eligibility. Optional post treatment biopsy may or may not be obtained, depending on procedures specific at each study site.

iii) Lesions selected for biopsy should be large enough to allow for the collection of tumor tissue using a minimum 18 gauge or larger needle with an expected core sample length of 5 mm. A minimum of 2 passages of the needle core should be obtained. If adequate tissue is not obtained following initial passages of the needles, repeat passages of the needle should be performed if clinically feasible. Smaller lesions may be biopsied or smaller gauge needles may be used provided adequate tissue can be collected (similar quantity to amount collected using 18 gauge thickness and 5 mm core length).

iv) The immediate confirmation (eg, touch imprint cytopathology) for presence of viable tumor cells from collected tissue samples is strongly recommended.

l) Adequate organ and marrow function as evidenced by:

i) WBC ≥ 2000/μL (stable, off any growth factor within 4 weeks of study drug administration)

ii) Neutrophils ≥ 1000/μL (stable, off any growth factor within 4 weeks of study drug administration)

iii) Platelets ≥ 60 x 10^3/μL (transfusion to achieve this level is not permitted)

iv) Hemoglobin ≥ 9.0 g/dL (may be transfused to meet this requirement)

v) Creatinine CrCl >40 mL/min (Cockcroft-Gault formula)

vi) AST ≤ 5 X ULN

vii) ALT ≤ 5 X ULN

viii) Bilirubin ≤ 3 mg/dL

ix) INR ≤ 2.3 or Prothrombin time (PT) ≤ 6 seconds above control

x) Albumin ≥ 2.8 g/dL

m) Ability to comply with treatment, PK and immune-monitoring sample collection (when indicated) and required study follow-up.

3. Age and Reproductive Status

a) Males and Females, age 18 or older

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) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.}.

e) 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.

f) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.}.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.3.1.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with suspected brain metastasis are excluded, unless a brain MRI/CT is negative for metastasis

2. Medical History and Concurrent Diseases

a) Any history of hepatic encephalopathy

b) Any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control

c) Active coinfection with both hepatitis B and C

d) Hepatitis D infection in subjects with hepatitis B

e) 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, prostate cancer without evidence of PSA progression or carcinoma in situ such as the following: gastric, prostate, cervix, colon, melanoma, or breast for example.

f) Subjects with any active autoimmune disease or history of known or suspected autoimmune disease except for subjects with vitiligo, resolved childhood asthma/atopy, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

g) Uncontrolled or clinically significant cardiac disease

h) Positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

i) Known active drug or alcohol abuse

j) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways)

k) Prior organ allograft or allogeneic bone marrow transplantation

l) All toxicities attributed to prior anti-cancer therapy other than neuropathy, alopecia and fatigue must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug. Subjects with toxicities attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae are permitted to enroll. Neuropathy must have resolved to Grade 2 (NCI CTCAE version 4).

m) Active bacterial or fungal infections requiring systemic treatment within 7 days

n) Use of other investigational drugs (drugs not marketed for any indication) within 28 days or at least 5 half-lives (whichever is longer) before study drug administration

o) Known or underlying medical condition that, in the Investigator's opinion, would make the administration of study drug hazardous to the subjects or obscure the interpretation of toxicity determination or adverse events.

p) Any history of clinically meaningful variceal bleeding within the last three months

q) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3. Physical and Laboratory Test Findings

a) Laboratory evidence of any underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.

4. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

b) History of allergy to study drug components.

5. 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

6. 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

c) Inability to comply with restrictions and prohibited activities/treatments as listed in Section 3.4.

3.3.2 1L Nivolumab vs Sorafenib Cohort

3.3.2.1 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 and inclusion/exclusion criteria reassessed.

2. Target Population

a) Subjects with advanced hepatocellular carcinoma

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

ii) progressive disease after surgical and /or locoregional therapies

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) Evaluable 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 prior to randomizing a study subject. 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 2)

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 [TAI], etc.)

e) Locoregional therapy for HCC must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment 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 3)

g) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 4)

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

i) Chronic HBV infection as evidenced by detectable HBV surface antigen or HBV DNA. Subjects with chronic HBV infection must be on antiviral therapy and have HBV DNA < 100 IU/mL.

ii) 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

(3) AST and 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, age 18 or older

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) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.} or 100 days post-treatment completion for subject receiving sorafenib.

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

f) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.} or 40 days post-treatment completion if receiving sorafenib.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on

the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.3.2.2 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) Any prior 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 the first dose of study drug administration. (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

(1) HBV DNA positive or HBV surface antigen positive subjects with detectable HCV ab, 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.

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 screening.

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 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 6)

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 (Target disease exception 1.e.)

f) History of non-healing wounds or ulcers, or bone fractures within 3 months of study entry

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 or fine needle aspiration) 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.

   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 autoimmune disease.

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) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways)

b) Prior participation in a BMS nivolumab study.

c) Prior use of systemic investigational agents for HCC.

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

e) Current therapeutic anticoagulation therapy.

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

g) 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.

3.3.3 Nivolumab plus Ipilimumab Combination Cohort

3.3.3.1 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 and inclusion/exclusion criteria reassessed.

2. Target Population

a) Subjects with advanced hepatocellular carcinoma

i) Disease not eligible for surgical and/or locoregional therapies

ii) Documented radiographic progression during or after sorafenib therapy or sorafenib intolerance as defined in Section 1.4.9.

b) 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) Evaluable 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 prior to randomizing a study subject. 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).

c) 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).

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 [TAI], etc.)

d) Locoregional therapy for HCC must be completed at least 4 weeks prior to the baseline scan. All acute toxic effects of any prior local treatment must have resolved to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Grade ≤ 1.

e) Cirrhotic status of Child-Pugh Class A (A5 or A6) (Appendix 3)

f) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1 (Appendix 4)

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

i) Chronic HBV infection as evidenced by detectable HBV surface antigen or HBV DNA. Subjects with chronic HBV infection must be on antiviral therapy and have HBV DNA < 100 IU/mL.

ii) Active or resolved HCV infection as evidenced by detectable HCV RNA or antibody.

h) 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 with serum albumin ≥ 2.8 g/dL, total bilirubin < 3 mg/dL, and AST and ALT ≤ 5 times the institutional upper limits of normal Adequate renal function with a creatinine clearance > 40 mL/min (Cockcroft-Gault formula)

3. Age and Reproductive Status

a) Males and Females, age 18 or older

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) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment {i.e., 90 days (duration of sperm turnover) plus the time required for the investigational drug to undergo approximately five half-lives.}

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

f) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception for the duration of study treatment with study drug and 5 months after the last dose of study treatment {i.e., 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half-lives.}.

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy

Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of one highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner.
- Nonhormonal IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy.
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

3.3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Known fibrolamellar HCC, sarcomatoid HCC, or mixed cholangiocarcinoma and HCC
b) Prior liver transplant
c) No history of hepatic encephalopathy
d) Any prior (within 1 year) or current clinically significant ascites as measured by physical examination and that requires active paracentesis for control
e) Evidence of portal hypertension with bleeding esophageal or gastric varices within the past 3 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 the first dose of study drug administration. (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) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

iii) Active bacterial or fungal infections requiring systemic treatment within 7 days prior to study entry.

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

c) Prior organ allograft or allogeneic bone marrow transplantation

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

e) Subjects with any active, known, or suspected autoimmune disease.

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.

f) 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.

g) 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.

h) 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) Prior treatment with an anti-PD1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
   b) Prior participation in a BMS nivolumab or ipilimumab study.
   c) Radiotherapy within 2 weeks prior to study drug administration and no additional radiotherapy for the same lesion is planned.
   d) Treatment with any chemotherapy, biologics for cancer, or investigational therapy within 28 days of first administration of study treatment, with the exception of sorafenib which requires a 14 day washout period.
4. **Physical and Laboratory Test Findings**
   a) Positive pregnancy test
5. **Allergies and Adverse Drug Reaction**
   a) Known or suspected allergy to nivolumab or ipilimumab 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 in 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.

3.3.4 Women of Childbearing Potential

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

*Women 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 periods below are suggested guidelines and the investigators should use their judgment in checking serum FSH levels. If the serum FSH level is > 40mIU/ml at any time during the washout period, the woman can be considered post menopausal.

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

Other parenteral products may require washout periods as long as 6 months.

3.4 Concomitant Treatments

3.4.1 Prohibited Treatments

- Locoregional therapy for HCC
- 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 local therapy described in Section 3.4.1
- Investigational agents for the treatment of cancer
- For subjects receiving nivolumab, systemic steroids > 10 mg within 14 days of dosing (with a few exceptions eg, steroids for adrenal insufficiency, steroids if taken as part of prophylaxis for CT prep [Section 3.4.2])
- Concurrent immunosuppressive agents (except to treat a drug-related adverse event).
- Medications contraindicated with sorafenib treatment (refer to the package insert, summary of product characteristics (SmPC) or similar document).[103]

3.4.2 Other Restrictions and Precautions

- Subjects are permitted the use of topical, ocular, intranasal, intra-articular, and inhalational corticosteroids (with minimal systemic absorption). Immunosuppressive doses (eg, prednisone > 10 mg/day or equivalent) and/or physiologic replacement doses of systemic corticosteroids (eg, prednisone 10 mg/day) are permitted in the context of treating adverse events. A brief 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) is permitted.
- Hormone replacement therapy - subjects may continue to receive hormonal replacement therapy if initiated prior to randomization.
- Bisphosphonates and RANK-L inhibitors
  - For subjects receiving nivolumab or nivolumab plus ipilimumab, these are allowed for bone metastases
  - For subjects randomized to sorafenib in the 1L Nivolumab vs Sorafenib Cohort , the US-FDA advises caution when combining bisphosphonates and RANK-L inhibitors with anti-angiogenesis agents, including sorafenib.[104,105]

- For subjects in the 1L Nivolumab vs Sorafenib Cohort receiving sorafenib:
  - Avoid concomitant use of strong CYP3A4 inducers such as carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, rifabutin, or St. John's wort because these drugs can decrease the systemic exposure to sorafenib.
  - Therapeutic anticoagulation (eg, coumadin, warfarin, or heparin) is not permitted. Low dose, non-therapeutic anticoagulation for catheter prophylaxis only will be permitted (eg, low dose warfarin).
  - Concomitant use of QT/QTc-prolonging drugs should be avoided to the extent possible.
  - Concurrent use of drugs that can disrupt electrolyte levels is discouraged, including, but not limited to, the following: loop, thiazide, and related diuretics; laxatives and enemas; amphotericin B; high dose corticosteroids.
- 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/1.73 m^2) 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.

3.4.3 Palliative Local Therapy

Palliative local therapy for clinically symptomatic tumor sites (eg bone pain) including palliative (limited-field) radiation 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 therapy and meets criteria to continue with treatment beyond progression (Section 3.1.8).
- The lesion for palliative local therapy is a non-target lesion
- The case is discussed with the BMS medical monitor. Palliative therapy must be clearly documented as such in the study record.
- Tumor lesions requiring palliative local therapy should be evaluated for objective evidence of disease progression prior to the initiation of such therapy. In addition, sites must request an Independent Review of Progression from the third party radiology vendor prior to the initiation of palliative local therapy. However, the initiation of palliative local therapy need not be delayed to await the assessment by the Independent Review of Progression.
- 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.

3.4.4 Treatment of HBV Virological Breakthrough and Ongoing HCV

Subjects will have ongoing assessments of HBV DNA throughout the course of the study. If a subject has an increase in HBV DNA, then virologic breakthrough should be considered. 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 (defined as a > 1 log IU/mL increase in HBV DNA), then this should be managed based on standardized regional guidelines and treatment with nivolumab monotherapy or nivolumab plus ipilimumab temporarily held. In the absence of a dose-limiting toxicity, or hepatic decompensation, the subject may resume treatment with nivolumab monotherapy or nivolumab plus ipilimumab once virologic control is re-established (HBV DNA < 100 IU/mL), provided both the PI and BMS medical monitor assess the benefit-risk ratio to be in the best interest of the subject. If the subject meets the protocol defined criteria for hepatic dose limiting toxicity in the setting of HBV virologic breakthrough, then resumption of nivolumab monotherapy or nivolumab plus ipilimumab can be reconsidered on a case-by-case basis once the hepatic AE has reversed and virologic control is re-established, if the subject has evidence of a clinical response and both the PI and BMS medical monitor assess the benefit-risk ratio to be in the best interest of the subject.

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.

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event (AE), abnormal laboratory test results 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
- Pregnancy, except as described below
- Termination of the study by BMS
- Specific criteria for discontinuation of study drugs outlined for nivolumab in Section 4.1.18, ipilimumab in Section 4.2, or for sorafenib in Section 4.1.12.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Protocol defined disease progression unless subject is eligible for treatment beyond progression (Section 3.1.8 for nivolumab or ipilimumab and Section 4.1.13 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 should comply with protocol specified follow-up procedures as outlined in Table 5.1-8 and Table 5.1-9. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

3.6 Re-Initiation of Study Therapy For Subjects from the Dose Escalation Phase in the Follow-up Period (Not Applicable Post-Amendment 8)

Prior to activation of amendment 8, subjects entering the follow-up period with confirmed CR may be permitted to reinitiate study therapy upon disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy until toxicity or disease progression per RECIST 1.1. Re-initiation of study therapy will only be permitted once for any given subject. Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy. Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

3.7 Post Study Drug Study Follow-up

In this study, overall survival is a key endpoint of the study. 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.

Follow-Up Visit 1 to occur 35 days from the last dose (± 7 days) or coinciding with the date of discontinuation of study drug (± 7 days) if the date of discontinuation is greater than 42 days from the last dose. Follow-Up Visit 2 to occur 80 days from Follow-Up Visit 1 (± 7 days). Survival Follow-Up Visits to occur approximately every 3 months from Follow-Up Visit 2. Survival Follow-up visits may be performed by phone contact or office visit.

BMS may request that survival data be collected on all *randomized* subjects outside of the protocol defined window (Table 5.1-8 and Table 5.1-9). At the time of this request, each subject

will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.8 Withdrawal of Consent

Subjects who request to discontinue study treatment 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.

3.9 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 BMS-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. 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 TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg backbone therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection.

4.1 Study Treatments

Nivolumab 100 mg (10 mg/mL) will be packaged in an open-label fashion. Five or ten nivolumab 10 mL vials will be packaged within a carton. The vials are not subject or treatment group specific.

Prior to activation of Amendment 8, subjects in the Dose Escalation Phase were treated until either a confirmed CR, completion of 2 years of therapy, toxicity, or disease progression. However, upon activation of amendment 8 and to align with the nivolumab program standard for the new cohorts, all subjects are to be treated until RECIST 1.1 defined progression (Appendix 2), unacceptable toxicity, or study discontinuation for any other reason (Section 3.5). In the Dose Escalation Phase, nivolumab will be administered as an IV infusion on treatment every two weeks until either RECIST 1.1 progression (with provisions for treatment beyond progression as outlined in Section 3.1.8) or toxicity. The period for determination of DLTs will be 2 weeks following the 3rd administration of nivolumab in the dose escalation phase. The following dose levels will be explored. Therapy will begin as dose level 1 for the uninfected and HCV-infected HCC subjects and dose level 0 for the HBV-infected HCC cohort in the dose escalation phase.

Table 4.1-1: Study Treatment During Dose Escalation Phase

Dose levels	Dose of Nivolumab, Intravenous, q2 wks
0	0.1 mg/kg
1	0.3 mg/kg
2	1 mg/kg
3	3 mg/kg
4	10 mg/kg

In the Dose Escalation Phase, the maximum dose level is 10 mg/kg in uninfected HCC subjects and 3 mg/kg in HCV and HBV infected HCC subjects, respectively.

In the Expansion Phase, uninfected HCC, HCV-infected subjects, and HBV-infected subjects will receive a dose of 3 mg/kg.

In the 1L Nivolumab vs Sorafenib Cohort, subjects will receive either open-label 240 mg nivolumab IV q2 weeks over 30 minutes (Arm A) or sorafenib 400 mg po BID (Arm B).

In the Nivolumab + Ipilimumab Combination Cohort, subjects will be randomized 1:1:1 to receive:

- Arm A--nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression

- Arm B--nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV q3week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm C--nivolumab 3 mg/kg IV q2week plus ipilimumab 1 mg/kg IV q6week until toxicity or disease progression

Table 4.1-2: Product Description: Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial/ Open-Label	5 or 10 vials per carton/ Open-Label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2° - 8°C. Protect from light and freezing.
Sorafenib Tablets[b]	200 mg	Wallet/blister card containing 28 film-coated tablets/ Open-Label	N/A	Red and round with the Bayer cross on one side and "200" on the other side.	Store at 15° - 25°C.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial/Open-Label	4 vials per carton/Open-Label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2° - 8°C. Protect from light and freezing.

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection.

[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)

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as 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: nivolumab, sorafenib, and ipilimumab.

4.1.2 Noninvestigational 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 noninvestigational products.

In this protocol, noninvestigational product(s) is/are: medications used to treat nivolumab or ipilimumab infusion reactions (please see Section 4.4.1). These medications will not be provided by BMS.

4.1.3 Handling 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.

Investigational product documentation 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).

The sites are responsible for procuring IV bags, diluent, and in-line filters.

For details on prepared drug storage and administration of nivolumab and ipilimumab, please refer to the current Investigator Brochures. Details regarding mixing and concentrations of the doses will be detailed in the pharmacy binder.

The unblinded pharmacist will obtain treatment assignment by IVRS and prepare unblinded drug□

Nivolumab is to be administered as an approximately 30 to 60-minute IV infusion for weight based dosing and a 30-minute IV infusion in the arms utilizing the 240 mg flat dose. At the end of the infusion, flush the line with a sufficient quantity of normal saline or dextrose solution.

In the Nivolumab plus Ipilimumab Combination Cohort, ipilimumab is to be administered as an approximately 30-minute IV infusion. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution. When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the infusion. The second infusion will always be ipilimumab, and will start at least 30 minutes after completion of the nivolumab infusion.

4.1.4 Sorafenib Dose and Schedule

Subjects randomized to Arm B in the 1L Nivolumab vs Sorafenib Cohort will receive treatment with sorafenib. Sorafenib (Nexavar®) will be self-administered orally at 400 mg (2 x 200 mg tablets) taken twice a day (equivalent to a total daily dose of 800 mg) without food (at least 1 hour before or 2 hours after a meal). Sorafenib is to be swallowed with a glass of water. Treatment will continue until progression, unacceptable toxicity, withdrawal of consent, or study end, whichever occurs first.

Trained personnel will dispense study medication to subjects. 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. If the number of capsules 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 patient remembers. However, if it is almost time for the next dose, the missed dose should be skipped and the patient should take his/her next dose as scheduled. A double dose should not be administered to make up for forgotten individual doses.

Subjects will 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 4.1.12). 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.

4.1.5 Nivolumab or Ipilimumab Dose Modifications

In the Dose Escalation and Expansion Phase, there will be no nivolumab dose adjustments allowed except for weight changes. Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

In the 1L Nivolumab vs Sorafenib Cohort, all subjects will receive either a flat dose of nivolumab 240 mg IV q2 week or sorafenib 400 mg po BID, and no dose adjustments regardless of weight change are required for nivolumab.

In the Nivolumab plus Ipilimumab Combination Cohort, nivolumab weight based dosing calculations should be based on the body weight assessed at baseline. It is not necessary to

re-calculate subsequent doses if the participant weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded up or to the nearest milligram per institutional standard.

4.1.6 Nivolumab or Ipilimumab Intrasubject Dose Escalation

No intrasubject nivolumab or ipilimumab dose escalation will be allowed.

4.1.7 Nivolumab or Ipilimumab Dose Reductions

Nivolumab or ipilimumab dose reductions are not permitted in this study.

4.1.8 Sorafenib Dose Reductions

For subjects receiving sorafenib in the 1L Nivolumab vs Sorafenib Cohort, if sorafenib dose reduction is required for the management of an adverse event, the sorafenib dose should be reduced to 400 mg daily. Further dose reductions may be done in accordance with the package insert.

4.1.9 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agent in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic (see protocol specific updates in Section 4.1.15)
- Endocrinopathies
- Skin
- Neurological

The above algorithms are found in Appendix 1 of this protocol.

4.1.10 Dose Delay for Nivolumab Monotherapy

Dose delay criteria apply for all drug-related adverse events. Treatment delay up to 6 weeks (42 days) from the last dose is allowable.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 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 for asymptomatic amylase or lipase, AST, or ALT:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
  - If a subject has a baseline AST or ALT that is within normal limits, delay dosing for drug-related Grade ≥ 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 ≥ 3 toxicity (2-grade shift).
  - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for drug-related increase in AST or ALT at 2x baseline value or when AST or ALT is 8x ULN (whichever is lower).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants interrupting 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.

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

4.1.11 Dose Delay for Nivolumab plus Ipilimumab Combination Cohort

Dose delay criteria apply for all drug-related adverse events. Treatment delay up to 6 weeks (42 days) from the last dose of nivolumab and ipilimumab are allowable in Arms A and B vs 12 weeks (84 days) from the last dose of nivolumab and ipilimumab in Arm C.

Study drug administration should be delayed for the following:

- Any Grade ≥ 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 for lymphopenia, asymptomatic amylase or lipase, AST, or ALT:
  - Grade 3 lymphopenia does not require dose delay.
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
  - If a subject has a baseline AST or ALT that is within normal limits, delay dosing for drug-related Grade ≥ 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 ≥ 3 toxicity (2-grade shift).
  - If a subject has baseline AST or ALT within the Grade 2 toxicity range, delay dosing for drug-related increase in AST or ALT at 2x baseline value or when AST or ALT is 8x ULN (whichever is lower).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants interrupting the dose of study medication.

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

Subjects receiving ipilimumab in combination with nivolumab that have drug-related toxicities that meet the criteria for dose delay, should have both drugs (ipilimumab and nivolumab) delayed until retreatment criteria are met. Refer to Section 4.1.17 Criteria to Resume Ipilimumab Dosing for further details.

In subjects in Arm C receiving ipilimumab 1 mg/kg q6week:

- Nivolumab may be delayed until the next planned ipilimumab dose if the next ipilimumab dose is scheduled within the next 12 days. This will permit periodic ipilimumab dosing to be synchronized with nivolumab dosing.
- Ipilimumab should be dosed at the specified interval regardless of any delays in intervening nivolumab doses. However, in order to maintain periodic synchronized dosing of ipilimumab and nivolumab, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 7-day window, as long as consecutive nivolumab doses are given at least 12 days apart. Ipilimumab may be delayed beyond the 7-day window if needed to synchronize with the next nivolumab dose.
- If an ipilimumab dose is delayed beyond 6 weeks from the prior ipilimumab dose, then subsequent ipilimumab doses should rescheduled to maintain the 6 week interval between consecutive ipilimumab doses.
- A dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.2 (Ipilimumab Dose Discontinuation).

4.1.12 Treatment Interruption or Discontinuation 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.[103]

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.

4.1.13 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 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 in Table 5.1-6.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden (SPD: sum of product of diameters) from time of initial progression (including all target lesions and new measurable lesions). New lesions are considered measurable at the time of initial progression 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 at the time of initial progression 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.

4.1.14 Management of Sorafenib Adverse Events

Toxicities attributable to sorafenib should be managed according to the locally approved product label or applicable Summary of Product Characteristics.[103]

4.1.15 Protocol-Specific Recommendation for Management of Hepatic Events in Nivolumab or Nivolumab plus Ipilimumab Subjects

The nivolumab program has developed a standardized algorithm for the management of hepatic events based on cumulative data across the program in subjects with normal hepatic function. Across most nivolumab studies, the eligibility criteria for inclusion are based on a maximum AST or ALT < 3x ULN; therefore, only subjects with normal to grade 1 LFTs have been enrolled.

Subjects with advanced HCC generally have underlying cirrhosis with decreased hepatic function. They may also have a concomitant chronic viral infection. For CA209040, the upper limits for inclusion were therefore adjusted to account for baseline liver dysfunction. Subjects with AST or ALT elevations within the CTCAE Grade 2 range. This requires a protocol-specific approach for the management of hepatic events, outlined as follows:

- Dose delay criteria for hepatic events are outlined in Sections 4.1.10 and 4.1.11. If AST or ALT levels do not improve with a dose delay of 3 - 5 days or if the levels worsen, initiate steroid therapy at 0.5 - 2 mg/kg/day methylprednisolone or oral equivalent.
- For ALT or AST levels > 8x ULN, initiate steroid therapy promptly at 1 - 2 mg/kg/day methylprednisolone or oral equivalent.
- For all subjects initiating steroids, consult the BMS Medical Monitor within 24 hours after initiation of steroids. Gastroenterology consult is recommended.
- If AST or ALT levels do not improve within 3 - 5 days or the levels worsen after the start of steroid therapy, discuss with the BMS Medical Monitor the possibility of adding mycophenolate mofetil at 1 g BID.
- Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade. Taper steroids slowly over no less than 1 month.

As outlined in Sections 4.1.16 and 4.1.17, nivolumab and ipilimumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached (Sections 4.1.18 and 4.2). The BMS Medical Monitor must be consulted prior to resuming nivolumab for all subjects who required steroid intervention.

4.1.16 Criteria to Resume Treatment with Nivolumab

Subjects may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 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 increased AST, ALT, or bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1 and after discussion with BMS MM.
- Subjects with AST, ALT or bilirubin values meeting discontinuation parameters (Section 4.1.18) should have treatment permanently discontinued.
- 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.
- Subjects who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis, and that is assessed by the investigator to be related to ipilimumab and not to nivolumab, may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

Resuming treatment after a delay of up to 6 weeks from the previous dose is permitted 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 from the last dose, the BMS Medical Monitor must be consulted. Tumor imaging assessments should continue as per protocol even if dosing is interrupted.
- Dosing delays > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor.

4.1.17 Criteria to Resume Treatment with Ipilimumab

Subjects may resume treatment with nivolumab and ipilimumab when drug-related AE(s) resolve(s) to Grade 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 increased AST, ALT, or bilirubin may resume treatment when hepatic parameters are at baseline or Grade 1 and after discussion with BMS MM.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.

- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ± 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor.
- Dose delay of ipilimumab which results in no ipilimumab dosing for >12 weeks requires ipilimumab discontinuation, with exceptions as noted in Section 4.2.

In subjects in Arm C receiving ipilimumab q6week:

- Ipilimumab may not be resumed sooner than 6 weeks (± 7 days) after the prior ipilimumab dose.
- In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted ± 7-day window, as long as consecutive nivolumab doses are given at least 12 days apart.
- One exception to note is when ipilimumab and nivolumab doses are delayed due to drug-related Grade ≥ 3 amylase or lipase abnormalities not associated with symptoms or clinical manifestations of pancreatitis. If the investigator assesses the Grade ≥ 3 amylase or lipase abnormality to be related to ipilimumab and not related to nivolumab, nivolumab may be resumed when the amylase or lipase abnormality resolves to Grade < 3 but ipilimumab may only be resumed when the amylase or lipase abnormality resolves to Grade 1 or baseline. Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the subject's medical chart. The BMS Medical Monitor should be consulted prior to resuming nivolumab in such subjects.

4.1.18 Nivolumab Permanent Discontinuation Due to Adverse Event(s)

Nivolumab administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Any ≥ Grade 2 drug-related uveitis, eye pain, or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - 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
- ♦ Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
  - o AST or ALT > 10 x ULN for > 2 weeks,
  - o AST or ALT > 15 x ULN irrespective of duration,
  - o T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T bilirubin at entry,
  - o Concurrent AST or ALT > 3 x ULN and T. bilirubin > 5 x ULN for subjects entering treatment with a normal bilirubin and up to 8 x ULN for subjects with elevated bilirubin

- Any drug-related 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
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - For Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively
- 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. Dose limiting toxicity for Dose Escalation Phase as defined in Section 3.1.3.1.

For subjects in the Nivolumab plus Ipilimumab Combination Cohort:

- Assessment for discontinuation of nivolumab should be made separately from the assessment made for discontinuation of ipilimumab.
- If the investigator assesses the drug-related AE to be related to ipilimumab only and not related to nivolumab, ipilimumab dosing alone may be discontinued while nivolumab dosing is delayed until the subject meets criteria to resume nivolumab treatment (specified in Section 4.1.16).
- The relationship to ipilimumab should be well documented in the source documents.
- BMS medical monitor needs to be contacted prior to resuming nivolumab at 240 mg IV every 2 weeks.
- If a subject in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

4.2 Ipilimumab Permanent Discontinuation Due to Adverse Event(s)

Ipilimumab administration should be discontinued if at least one of the following drug-related adverse event(s) occurs:

- Any ≥ Grade 2 drug-related uveitis, eye pain, or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any Grade ≥ 3 bronchospasm or other hypersensitivity reaction
- Any other Grade 3 non-skin, drug-related adverse events with the following exceptions for laboratory abnormalities, Grade 3 nausea and vomiting, Grade 3 neutropenia and thrombocytopenia, and symptomatic endocrinopathies which resolved (with or without hormone substitution)
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
    - AST or ALT > 10 x ULN for > 2 weeks,
    - AST or ALT > 15 x ULN irrespective of duration,
    - T. bilirubin > 8 x ULN irrespective of duration for subjects with elevated bilirubin at study entry or > 5 x ULN for those with normal T bilirubin at entry,
    - Concurrent AST or ALT > 3 x ULN and T. bilirubin > 5 x ULN for subjects entering treatment with a normal bilirubin and up to 8 x ULN for subjects with elevated bilirubin
- Any drug-related 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

- Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- For Grade 4 endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidosis, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (steroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

- Any treatment delay resulting in no ipilimumab dosing for > 12 weeks with the following exceptions: Dosing delays to manage drug-related adverse events, such as prolonged steroid tapers, are allowed. Prior to re-initiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. **Tumor assessments should continue as per protocol even if dosing is delayed.**
- Dosing delays resulting in no ipilimumab dosing for > 12 weeks that occur for non-drug related reasons may be allowed if approved by the BMS medical monitor. Prior to reinitiating treatment in a subject with a dosing delay lasting > 12 weeks, the BMS medical monitor must be consulted. **Tumor assessments should continue as per protocol even if dosing is delayed.**
- 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. Dose limiting toxicity as defined in Section 3.1.3.1.

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued.

If a subject in any of the nivolumab/ipilimumab combination arms meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

4.3 Method of Assigning Subject Identification

After 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. The exact procedure for using the IVRS will be detailed in a separate document.

4.4 Selection and Timing of Dose for Each Subject

In the Dose Escalation Phase, subjects will be entered sequentially into the dose level (ranging from 0.1 mg/kg to 10 mg/kg q2week) accruing up to a maximum of 6 subjects. Once the determination that the dose level is safe has been made, the next dose level can begin accrual.

In the Expansion Phase, subjects will receive 3 mg/kg IV nivolumab q2 week in the uninfected, HCV-infected, or HBV-infected cohorts until toxicity or RECIST 1.1 progression.

In the 1L Nivolumab vs Sorafenib Cohort, subjects will be randomized to receive either nivolumab flat dosing 240 mg q2 weeks IV over 30 minutes (Arm A) or sorafenib 400 mg po BID (Arm B) until toxicity or RECIST 1.1 progression.

In the Nivolumab plus Ipilimumab Combination Cohort, subjects will be randomized 1:1:1 to receive:

- Arm A--Nivolumab 1 mg/kg IV plus ipilimumab 3 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm B--Nivolumab 3 mg/kg IV plus ipilimumab 1 mg/kg IV q3 week x 4, followed by nivolumab 240 mg IV q2week until toxicity or disease progression
- Arm C--Nivolumab 3 mg/kg IV q2week plus ipilimumab 1 mg/kg IV q6 week until toxicity or disease progression.

4.4.1 Treatment of Nivolumab or Ipilimumab Infusion Reactions

Infusion reactions should be graded according to CTCAE Version 4.0 allergic reaction/hypersensitivity. Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, these reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm or other symptoms. Severe infusion reactions require the immediate interruption of study drug therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. Following an infusion reaction, subjects should be premedicated with acetaminophen and diphenhydramine for future treatments.

All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab or ipilimumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours)

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.4.2 Re-Initiation of Study Therapy For Subjects from the Dose Escalation Phase in the Follow-up Period (Not Applicable Post-Amendment 8)

Prior to activation of amendment 8, subjects entering the follow-up period with confirmed CR may be permitted to reinitiate study therapy upon disease progression after discussion and agreement with the BMS Medical Monitor. Subjects reinitiating study therapy should continue to meet eligibility criteria at the time study drug resumes and should not have experienced a DLT

that would require permanent discontinuation of study therapy. Subjects will receive study therapy at the same dose level that they received prior to entering the follow-up period. Subjects that resume study therapy in this setting may receive study therapy until toxicity or disease progression per RECIST 1.1. Re-initiation of study therapy will only be permitted once for any given subject. Subjects who have completed 1 year of follow-up without evidence of disease progression will not be considered eligible for re-initiation of study therapy. Additional, separate, safety and efficacy summaries will be presented for those subjects who reinitiated study therapy.

4.5 Blinding/Unblinding

Not applicable.

4.6 Treatment Compliance

Study drug will be administered in the clinical facility. After administration of nivolumab, treatment compliance will be assessed by investigator report on the case report forms and Source Data Verification by Site Monitors.

4.7 Destruction and Return of Study Drug

4.7.1 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 BMS 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 BMS 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.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: CA209040 Screening Procedural Outline for Subjects in Dose Escalation and Expansion Phase (Study Days -28 to -1)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	A subject is considered enrolled only when a protocol specific informed consent is signed. Contact IVRS to obtain study subject number.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Disease Status		
Medical History	X	Include any toxicities or allergy related to previous treatments, smoking history, asthma, COPD, Child-Pugh score determination (only Child Pugh scores of 7 points or less are allowed for subjects in the Escalation Phase, and Child Pugh scores of 6 points or less are allowed for subjects in the Expansion Phase), no history of hepatic encephalopathy. Includes detailed medical history of potential risk factors for potential events such as pulmonary related events.
Archived Tumor tissue block or Unstained slides	X	A fresh tumor biopsy is required at baseline if there is no other record of histological diagnosis of tumor. Tumor material (archived tumor paraffin block or fresh biopsy with a minimum of 15 unstained slides) must be available for correlative studies. If archived material is unavailable, then tumor material from a fresh biopsy must be provided. Biopsied lesions must be distinct from index lesions.
Disease Assessments - Tumor Imaging (CT or MRI of Chest/Abdomen/Pelvis [including triphasic CT of abdomen]; Bone scan if clinically indicated. Brain MRI if history of brain metastasis.	X	• CT or MRI of the chest, abdomen and pelvis with IV contrast, including required tri-phasic evaluation of the liver. • MRI is acceptable if CT is contraindicated. • Modality (CT or MRI) used at baseline should be used across all imaging time points. • Bone scan is required if clinically indicated. • Brain MRI within 28 days prior to first dose of study therapy for subjects with a history of brain metastasis.
Disease Assessments - Serum	X	Serum alpha fetoprotein

Table 5.1-1: CA209040 Screening Procedural Outline for Subjects in Dose Escalation and Expansion Phase (Study Days -28 to -1)		
Procedure	**Screening Visit**	**Notes**
Safety Assessments		
Physical Examination (PE)	X	If the screening PE is performed within 96 hours of dosing on Day 1 then a single exam may count as both the screening and pre dose evaluation.
Physical Measurements	X	Includes height and weight.
ECOG Assessment	X	See Appendix 4 for scale
Child-Pugh Score	X	See Appendix 3 for scale
Vital Signs	X	Includes body temperature, respiratory rate, seated blood pressure and heart rate. Blood pressure and heart rate should be measured after the subject has been seated quietly for at least 5 minutes.
Oxygen saturation	X	Collected by pulse oximetry at rest and after mild exertion
Electrocardiogram (ECGs)	X	A Single 12 lead measurement should be recorded after the subject has been supine for at least 5 minutes.
Pre-treatment Concomitant medication	X	30 days prior to treatment
Clinical Complaints	X	Clinical complaints must be collected from the date of subject's written informed consent until the first dose of study drug.
Laboratory Tests (Hematology, Serum chemistry)	X	Include CBC with differential and platelets, Complete Metabolic Panel (Na, K, Cl, HCO3 or equivalent (if locally available), BUN, Cr, eGFR, AST, ALT, Alk Phos, Albumin, Total Bilirubin, Total Protein, Calcium, glucose), direct bilirubin, lipase, amylase, magnesium, phosphorous, LDH and urinalysis (dip). If screening labs are drawn within 4 days of first treatment then these labs will also qualify as Day 1 (pre-dose) labs.
Thyroid Function Panel	X	TSH, free T3 and free T4. Total T3/T4 are acceptable if free T3/T4 are not available. Subjects with suspected autoimmune thyroid disorders will also be tested for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin. If screening labs are drawn within 4 days of first treatment then these labs will also qualify as Day 1 (pre-dose) labs.
Serology (HepB, HepC, HIV)	X	HepB surface antigen, HepB surface antibody, Hep B Core antibody, Hep B e antigen and e antibody, HBV DNA, HDV testing for subjects with HBV, Hep C viral load (PCR) and Hep C Ab, HIV 1/2

Table 5.1-1: CA209040 Screening Procedural Outline for Subjects in Dose Escalation and Expansion Phase (Study Days -28 to -1)		
Procedure	**Screening Visit**	**Notes**
Coagulation Panel	X	Including PT/INR, aPTT and fibrinogen. If screening labs are drawn within 4 days of first treatment then these labs will also qualify as Day 1 (pre-dose) labs.
HLA typing	X	Blood samples will be collected to explore single nucleotide polymorphisms (SNPs) in specific genes, and HLA typing
Serum/Urine Pregnancy Test	X	For WOCBP within 24 hours of Study Drug Administration. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalents of HCG. If the pregnancy test is positive, the subject must not receive study drug.
Adverse Event Reporting		
Monitor for Serious Adverse Events	X	All SAEs must be collected from the date of the subject's written consent.

Table 5.1-2: Screening Procedural Outline for 1L Nivolumab vs Sorafenib Cohort		
Procedure	**Pre-Treatment Visit (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 an enrollment 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	Child Pugh A5 or A6 only
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 for valve and LVEF evaluation is to be done at baseline and as clinically indicated.
Laboratory Tests	X	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
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 Ab, Hep D antibody Testing to be completed at the Central Laboratory. Local laboratory Hep D result can be used to assess subject eligibility if central laboratory

Table 5.1-2: Screening Procedural Outline for 1L Nivolumab vs Sorafenib Cohort		
Procedure	**Pre-Treatment Visit (Baseline)**	**Notes**
		result not available in time.
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/HLA Sample	X	
Urinary analysis	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 or MRI of the chest, abdomen and pelvis with IV contrast, including required tri-phasic evaluation of the liver. • MRI is acceptable if CT is contraindicated. • Modality (CT or MRI) used at baseline should be used across all imaging timepoints, if possible. • Bone scan is required if clinically indicated. • MRI brain within 28 days prior to first dose of study therapy 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 a minimum of 15 unstained slides of tumor tissue (archival or recent) for biomarker evaluation will be obtained prior to subject randomization. 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 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.

Table 5.1-2: Screening Procedural Outline for 1L Nivolumab vs Sorafenib Cohort		
Procedure	**Pre-Treatment Visit (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. Central lab must provide IVRS with confirmation of receipt of evaluable tumor tissue prior to subject randomization

Table 5.1-3: Screening Procedural Outline for Nivolumab plus Ipilimumab Combination Cohort		
Procedure	**Pre-Treatment Visit (Baseline)**	**Notes**
Eligibility Assessments		
Informed Consent	X	Original informed consent in screening for protocol participation. Study allows