UCSF Helen Diller Family Comprehensive Cancer Center

Multicenter Pilot Study of the Safety, Efficacy, and Immune Cell Profiling in Advanced Hepatocellular Carcinoma (HCC) Patients Treated with the Combination of Sorafenib plus Nivolumab as First-Line of Systemic Therapy

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Protocol Signature Page

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1. I agree to follow this protocol version as approved by the UCSF Protocol Review Committee (PRC), Institutional Review Board (IRB), and Data Safety Monitoring Committee (DSMC).
2. I will conduct the study in accordance with applicable IRB requirements, Federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
3. I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
4. I have read and understand the information in the Investigators' Brochure (or Manufacturer's Brochure) regarding the risks and potential benefits. I agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), and with local regulatory requirements. In accordance with the FDA Modernization Act, I will ensure the registration of the trial on the www.clinicaltrials.gov website.
5. I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

UCSF Principal Investigator / Study Chair

_____
Printed Name

_____ _____
Signature Date

Protocol Signature Page – Participating Sites

Protocol No.: CC# 174523 **Version Date**: 03/09/2022

Participating Site(s)

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I have read this protocol and agree to conduct the protocol in accordance with Good Clinical Practices (ICH-GCP), the applicable ethical principles, the Statement of Investigator (Form FDA 1572), Institutional Review Board regulations, and all national, state and local laws and/or requirements of the pertinent regulatory requirements.

Principal Investigator	**Site**
Printed Name	Institution Name
Signature	Date

Abstract

Title	Multicenter Pilot Study of the Safety, Efficacy, and Immune Cell Profiling in Advanced Hepatocellular Carcinoma (HCC) Patients Treated with the Combination of Sorafenib plus Nivolumab as First-Line of Systemic Therapy
Patient population	Unresectable HCC with no prior systemic therapy and Child Pugh A or B liver function
Rationale for Study	The multikinase inhibitor sorafenib, whose principal targets include VEGFR2, VEGFR3, and RAF kinases, is the only approved first-line therapy with established survival benefit in patients with HCC not amenable to curative therapies.[1,2] Though the survival benefit of sorafenib has been consistent across multiple studies, the overall magnitude of benefit is small, and generally fewer than 5% of patients demonstrate response by conventional Response Evaluation Criteria in Solid Tumors (RECIST) across studies.[1-3] Recently, the anti-programmed death-1 receptor (PD-1) inhibitor, nivolumab, demonstrated a preliminary signal of efficacy in the CheckMate 040 Phase I/II trial in advanced HCC patients, including a dose escalation cohort of 48 patients and a dose expansion cohort of 214 additional patients, across etiologic subtypes.[4] In the dose expansion cohort, tumor responses occurred in 20%, median duration of response has not yet been reached but was over 17 months for the dose escalation cohort. Results of CheckMate 040 have led to an ongoing multinational Phase III trial, CheckMate 459 [NCT02576509] comparing the efficacy of sorafenib versus nivolumab as first-line therapy for advanced HCC.
Primary Objective	Part 1: Escalation Cohort: Maximum tolerated dose (MTD) of sorafenib in combination with standard dose nivolumab in patients with Child Pugh A-B7 liver function Part 2: Child Pugh B Expansion Cohort: Safety in patients with Child Pugh B liver function
Secondary Objectives	1. Safety and tolerability of combination overall 2. Rate of irAE for combination overall and in patients with Child Pugh B liver function 3. Objective response rate (ORR) by RECIST 1.1[5] for overall study 4. ORR by RECIST 1.1 in patients with Child Pugh B liver function 5. Duration of response (DOR), progression free survival (PFS), and overall survival (OS) overall and in Child Pugh B Expansion Cohort

Study Design	This is an open-label, dose-escalation and expansion pilot study to examine the safety and efficacy of sorafenib combined with the PD-1 checkpoint inhibitor, nivolumab, in patients with unresectable HCC not amenable to curative therapies, with no prior systemic treatment. The study is divided into two parts: Dose Escalation Cohort (Part 1, in patients with Child Pugh A-B7 liver function) and Child Pugh B Expansion Cohort (Part 2, in patients with Child Pugh B liver function). There are 2 planned study sites: UCSF and a sub-site which was activated after completion of Part 1: Dose Escalation Cohort. Immune profiling of PBMC will be performed in UCSF patients only; PBMCs will not be collected for sub-site participants.
Number of patients	6-24 patients. Part 1: 6-12 patients; Part 2: 12 patients.
Duration of Therapy	Sorafenib will be administered continuously and nivolumab will be administered every 14 days until progression, unacceptable toxicity, withdrawal of consent, criteria for discontinuation are met, or study end, whichever comes first.
Duration of Follow up	Patients will be followed for survival every 3 months after last dose of study drug for up to 2 years.
Duration of study	The study is expected to complete accrual approximately 48 months from the time the study opened to accrual, based upon expected enrollment of approximately 1-2 subjects per month and enrollment holds for protocol amendment. Accrual will be closed after 12 patients are enrolled to Child Pugh B Expansion Cohort or on 30 April 2022, whichever occurs first.
Study Drugs	Sorafenib is a multikinase inhibitor which inhibits specific targets that are imperative for tumor cell proliferation including the serine/threonine kinases c-Raf and B-Raf (IC_{50} 6 and 25 nM respectively) and the receptor tyrosine kinase RET, Flt-3 and c-Kit (IC_{50} 47, 33 and 68 nM respectively).[6] Sorafenib has potent activity against receptor tyrosine kinases important in tumor angiogenesis including the vascular endothelial growth factor receptor family (VEGFR1, -2, -3; IC_{50} 26, 90 and 20 nM respectively) and platelet derived growth factor-beta (PDGFR-í; IC_{50} 57 nM). In cellular mechanistic (on target) assays, sorafenib was found to be a potent inhibitor of VEGFR-2, VEGFR-3, and PDGFR and Flt-3 receptor phosphorylation.[6] The anti-tumor activity of sorafenib in vivo is driven by its direct effects on tumor growth through its inhibition of the Raf/MEK/ERK pathway and on the anti-angiogenic activity of the compound. Sorafenib demonstrates broad anti-tumor activity in human tumor xenograft models of liver, kidney, lung, prostate, breast and leukemia. In human hepatocellular tumor cell lines, sorafenib potently inhibited cellular proliferations, Raf/MEK/ERK signaling and induced apoptosis. Sorafenib has potent activity against human tumor xenograft model of hepatocellular carcinoma with tumor stabilization seen at moderate doses and partial tumor regressions observed at higher doses. For further information about preclinical pharmacology, please refer to the current version of the sorafenib IB. Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule

	expressed by activated T and B lymphocytes.[7] Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies.

Table of Contents

List of Abbreviations

ADL	Activities of daily living
AFP	Alpha fetoprotein
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCLC	Barcelona Clinic Liver Cancer
BID	*bis in die*, twice daily
B-Raf	B isoform of Rapidly Accelerated Fibrosarcoma protein
BUN	Blood Urea Nitrogen
c-KIT	Stem Cell Factor Receptor Tyrosine Kinase
CR	Complete Response
CRC	Clinical Research Coordinator
C-RAF	C isoform of Rapidly Accelerated Fibrosarcoma protein
CTCAE	Common Terminology Criteria for Adverse Events
DHPD	Dihydropyrimidine dehydrogenase
DSMC	Data Safety Monitoring Committee
DSMP	Data Safety Monitoring Plan
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ERK	Extracellular Signal-regulated Kinases
FDA	Food and Drug Administration (US)
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HFSR	Hand foot skin reaction
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate release
IRB	Institutional Review Board
MAPK	Mitogen Activated Protein Kinase
MEK	MAP Kinase / ERK Kinase 1
NM	Nano molar
NYHA	New York Heart Association
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PR	Partial response
PDGFR	Platelet Derived Growth Factor Receptor
PFS	Progression free survival
PTT	Partial thromboplastin time
RCC	Renal cell carcinoma
SAE	Serious adverse event
SUSARs	Suspected unexpected serious adverse reactions
UCSF CIL	UCSF Cancer Immunotherapy Laboratory
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor

1. Introduction

1.1 Background

Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide with an estimated incidence of over 750,000 new cases and almost as many deaths annually.[8] The incidence and mortality of HCC are rising significantly in the United States.[9] Advanced stage of disease at diagnosis precludes curative treatments in the majority of cases, and there are limited treatment options for patients with unresectable HCC after failure of liver-directed therapies. In 2008, publication of the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) phase III trial demonstrated a significant improvement in overall survival (OS) in patients with advanced HCC treated with the biologic agent, sorafenib.[2] The SHARP trial will be discussed in detail below. After progression on sorafenib, another multikinase inhibitor regorafenib showed significant improvement in 2nd line OS along with modest improvement in progression-free survival (PFS).[10] Despite improvements in outcome with sorafenib and regorafenib, however, the median OS for patients starting first line therapy for advanced HCC remains less than a year. Multiple recent randomized phase 3 trials of other anti-angiogenic multikinase inhibitors in HCC have failed to show benefit, underscoring the challenges of toxicity, comorbidity, and chemoresistance in this treatment-refractory disease.[11] Recently, a Phase I/II trial has shown preliminary activity of the immune checkpoint inhibitor, nivolumab in HCC as discussed below.[4] New active drugs and combinations are urgently needed.

1.2 Rationale of the study

The multikinase inhibitor sorafenib, whose principal targets include VEGFR2, VEGFR3, and RAF kinases, is the only approved first-line therapy with established survival benefit in patients with HCC not amenable to curative therapies.[1,2] Though the survival benefit of sorafenib has been consistent across multiple studies, the overall magnitude of benefit is small, and generally fewer than 5% of patients demonstrate response by conventional Response Evaluation Criteria in Solid Tumors (RECIST) across studies.[1-3]

Recently, the anti-programmed death-1 receptor (PD-1) inhibitor, nivolumab, demonstrated a preliminary signal of efficacy in the CheckMate 040 Phase I/II trial in advanced HCC patients, including a dose escalation cohort of 48 patients and a dose expansion cohort of 214 additional patients, across etiologic subtypes.[4] In the dose expansion cohort, tumor responses occurred in 20%, median duration of response has not yet been reached but was over 17 months for the dose escalation cohort. Results of CheckMate 040 have led to an ongoing multinational Phase III trial, CheckMate 459 [NCT02576509] comparing the efficacy of sorafenib versus nivolumab as first-line therapy for advanced HCC.

1.3 Sorafenib

1.3.1 Sorafenib preclinical data

Sorafenib is a multikinase inhibitor which effects specific targets that are imperative for tumor cell proliferation including the serine/threonine kinases c-Raf and B-Raf (IC_{50} 6 and 25 nM respectively) and the receptor tyrosine kinase RET, Flt-3 and c-Kit (IC_{50} 47, 33 and 68 nM respectively).[6] Sorafenib has potent activity against receptor tyrosine kinases important in tumor angiogenesis including the vascular endothelial growth factor receptor family (VEGFR1, -2, -3; IC_{50} 26, 90 and 20 nM respectively) and platelet derived growth factor-beta (PDGFR-í; IC_{50} 57 nM). In cellular mechanistic (on target) assays, sorafenib was found to be a potent inhibitor of VEGFR-2, VEGFR-3, and PDGFR and Flt-3 receptor phosphorylation.[6] The anti-tumor activity of sorafenib in vivo is driven by its direct effects on tumor growth through its inhibition of the Raf/MEK/ERK pathway and on the anti-angiogenic activity of the compound. Sorafenib demonstrates broad anti-tumor activity in human tumor xenograft models of liver, kidney, lung, prostate, breast and leukemia. In human hepatocellular tumor cell lines, sorafenib potently inhibited cellular proliferations, Raf/MEK/ERK signaling and induced apoptosis. Sorafenib has potent activity against human tumor xenograft model of hepatocellular carcinoma with tumor stabilization seen at moderate doses and partial tumor regressions observed at higher doses. For further information about preclinical pharmacology, please refer to the current version of the sorafenib IB.

1.3.2 Sorafenib clinical experience in HCC

Sorafenib as a single agent has been evaluated globally in multiple trials in various malignancies. Three pivotal international multi-institutional, single agent, randomized, placebo-controlled trials led to sorafenib's approval for the treatment of patients with advanced renal cell carcinoma (RCC, 2005), hepatocellular carcinoma (HCC, 2007) and locally advanced or metastatic differentiated thyroid carcinoma refractory to radioactive iodine (DTC2013).

Clinical results in Phase I studies of sorafenib as a single agent were suggestive of a therapeutic effect in HCC and led to the design of a single arm Phase II study, in which 137 subjects with advanced, inoperable HCC Child-Pugh classes A and B were treated.[12] The results of this study (median TTP of 5.5 months by independent assessment and median overall survival of 9.2 months), provided the basis for the randomized, placebo-controlled Phase III study in subjects with advanced HCC Child-Pugh class A (SHARP, **S**orafenib **H**CC **A**ssessment **R**andomized **P**rotocol). This large (602 subjects) Phase III study was the first international, randomized, double-blind, placebo-controlled study to demonstrate a statistically significant and clinically meaningful improvement in OS in advanced HCC subjects treated with sorafenib over placebo.[2] Of the 299 sorafenib subjects valid for ITT analysis, the median OS was 10.7 months in the sorafenib group and 7.9 months in the 303 subjects randomized to the placebo group (hazard ratio (HR) in the sorafenib group, 0.69; 95% confidence interval, 0.55 to 0.87; $p<0.001$. The nominal alpha for this analysis was 0.0077 according to the pre-specified O'Brien-Fleming-type alpha spending function. Therefore, sorafenib had a

statistically significant effect on prolonging overall survival. This significant survival benefit represented a 31% reduction in risk of death (or 44% improvement in OS) in subjects treated with sorafenib versus those treated with placebo.

Similar improvements in OS and TTP were observed in a Phase III trial of sorafenib versus placebo in 271 Asian patients with advanced HCC randomized 2:1 to sorafenib versus placebo.[1] In the Asian study, the median OS for sorafenib was 6.5 months for sorafenib compared to 4.2 months for placebo (HR 0.68), and median TTP was 2.8 months for sorafenib versus 1.4 months for placebo (HR 0.57).

In the SHARP study, treatment-related adverse events occurred in 80% of patients in the sorafenib group by comparison with 52% in the placebo group.[2] Grade 3 toxicities included diarrhea (8%), hand-foot skin reaction (8%), hypertension (2%), and abdominal pain (2%) in the treatment group. Grade 3 or 4 hypophosphatemia (4%) and thrombocytopenia (4%) were also more common in patients treated with sorafenib. In the Asian randomized, placebo-controlled Phase III study, the most common Grade 3 and 4 toxicities were hand-foot skin reaction (10.1%), diarrhea (6%), hyperbilirubinemia (3.4%), and fatigue (3.4%) with the use of sorafenib.[1] The preceding Phase II study of sorafenib in HCC included 28% of patients with Child-Pugh class B cirrhosis; subgroup analysis in this cohort with greater degree of hepatic impairment showed higher rates of hyperbilirubinemia and encephalopathy developing on study by comparison with patients with Child-Pugh class A.[12,13]

As of 31-December 2015 approximately 70,897 patients have been exposed to sorafenib in company-sponsored interventional clinical trials, non-interventional studies and investigator-sponsored studies for which Bayer has provided grants. The cumulative post-marketing exposure, excluding above mentioned clinical studies, since 2005 is estimated to be 440,109 patients.

Please refer to the current version of the sorafenib IB for the complete list of observed adverse events seen in Phase III studies.

1.4 Nivolumab

1.4.1 Nivolumab preclinical data

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[7] Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies.

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family (nivolumab IB). Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro (nivolumab IB).[14] Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1. In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release.[15] In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents (nivolumab IB).

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted (nivolumab IB). Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 µg●h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[16]

Please refer to the current version of the nivolumab IB for additional data from preclinical studies.

1.4.2 Nivolumab clinical experience in HCC

The anti-programmed death-1 receptor (PD-1) inhibitor, nivolumab, has been studied in multiple tumor types, including HCC. Nivolumab has been approved for treatment of multiple malignancies, including unresectable or metastatic melanoma, as monotherapy or in combination with ipilimumab; metastatic non-small cell lung cancer (NSCLC); advanced renal cell carcinoma (RCC); and relapsed or progressive classical Hodgkin's lymphoma.

In HCC, the Phase I/II clinical trial CheckMate 040 reported on 262 patients with advanced HCC treated with nivolumab in a dose escalation cohort (n=48) and a dose expansion cohort (n=214).[4] In the dose escalation phase, a maximum tolerated dose was not reached; the dose of 3 mg/kg IV every 2 weeks was selected for dose expansion. Grade 3-4 treatment-related adverse events (AE) occurred in 25%, including rash (23%), AST and/or ALT elevation in 21% and 15% respectively, elevated amylase and/or lipase in 21% and 19% respectively, and pruritus in 19%. Three of 48 patients experienced serious adverse events (SAE): pemphigoid, adrenal insufficiency, and liver disorder in 1 each. There were no deaths attributed to treatment-related

toxicity. The objective response rate (ORR) in dose escalation phase was 15% with 3 complete responses (CR) and 4 partial responses (PR), with prolonged median duration of response (DOR) approximately 17 months.[4,17] The median OS for the dose escalation cohort was 15.0 months.

In the CheckMate 040 dose expansion cohort, 214 additional patients with advanced HCC were treated with nivolumab at dose of 3 mg/kg IV every 2 weeks. Safety was similar to the dose escalation cohort with Grade 3-4 treatment-related AE occurring in 19%. There were no events of reactivation HBV. The ORR for the dose expansion cohort was 20%, similar across subgroups defined by positive for hepatitis C virus (HCV), positive for hepatitis B virus (HBV), and uninfected without HBV or HCV; the response rates were also similar for patients without prior sorafenib therapy as for those enrolled after progression on sorafenib. The median OS has not been reached for the overall dose expansion cohort, but the median OS for the uninfected, sorafenib progressor cohort (n=57) was 13.2 months.[4] Among patients with evaluable tumor samples in the CheckMate 040 expansion cohort (81%), tumor responses were not significantly associated with tumor PD-L1 expression which was present in 20%.

Results of CheckMate 040 have led to an ongoing multinational Phase III trial, CheckMate 459 [NCT02576509] comparing the efficacy of sorafenib versus nivolumab as first-line therapy for advanced HCC. Please refer to the nivolumab IB for the complete list of observed adverse events seen in Phase III studies.

1.5 Combination of multikinase inhibition and checkpoint inhibition

1.5.1 Combination multikinase inhibition and checkpoint inhibition preclinical rationale

One potential mechanism for primary or secondary resistance to checkpoint inhibition is immunosuppression by factors within the tumor microenvironment, such as by FOXP3+ regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSC).[18]

Several preclinical studies suggest that multikinase inhibitors such as sorafenib may reduce the number of tumor infiltrating Tregs and myeloid derived suppressor cells (MDSC) as well as inhibiting their function, thereby promoting an immune antitumor response.[19-21] In a syngeneic mouse model, the combination of the multikinase inhibitor, lenvatinib, plus anti-mouse PD-1 mAb showed greater growth inhibition in combination than with either agent as monotherapy, with complete tumor regressions in a subset of mice treated on combination.[22] Re-inoculation with tumor cells did not grow any tumors in the mice with complete tumor regression, while all naïve animals grew tumors. The combination was associated with synergistic upregulation of interferon signaling-related genes; lenvatinib was associated with increased memory T cell and TH1 population compared with vehicle treatment.

In a small study of peripheral blood mononuclear cells (PBMC) derived from 20 HCC patients as well as 11 control patients, *ex vivo* incubation with sorafenib elicited dose-dependent Treg inhibition and effector T cell (Teff) activation at low doses, with Teff suppression at higher doses.[23] In PBMC samples from 19 HCC patients, sorafenib

treatment was associated with decreased frequency and absolute number of FOXP3+ Tregs along with significantly increased ratio of Teff to Treg by FACS analysis after 4 weeks of sorafenib therapy compared to baseline.[24] Conflicting data in human renal cell carcinoma blood samples have been reported, and the timing of these effects has not been well characterized.[25,26]

Sorafenib therapy may also be associated with increased PD-L1 expression on tumor-infiltrating immune cells. In a study of 23 HCC patients with pre-treatment baseline tumor samples compared to tumor biopsies after progression on sorafenib, immune cell PD-L1 expression by IHC was significantly increased post sorafenib therapy.[27] These findings suggest PD-L1 expression as a possible mechanism of sorafenib resistance and support investigation of the combination of sorafenib plus PD-1 inhibition.

1.5.2 Combination multikinase inhibition and checkpoint inhibition clinical experience

Other multikinase inhibitors combined with nivolumab indicate preliminary favorable response rates but are notable for Grade 3-4 hepatotoxicity rates of approximately 18-20% (unpublished data, BMS). CA209-016 is an ongoing phase 1 study of nivolumab plus sunitinib, pazopanib, or ipilimumab in patients with advanced renal cell carcinoma (RCC). Interim data from 33 patients enrolled on CA209-016 (n=14 with prior systemic therapy) treated with combination of nivolumab plus sunitinib shows a promising overall response rate of 52%, with median duration of response of 54 weeks. No DLT were identified at full doses of both sunitinib and nivolumab in combination. Toxicity profile was notable for Grade 3-4 ALT elevation and hypertension, each occurring in approximately 18%, with Grade 3-4 AST elevation and diarrhea in approximately 9% each. For the combination of nivolumab and pazopanib on CA209-016, the overall response rate in previously treated patients was 45%, though study expansion was not pursued due to occurrence of 4 DLT among 20 patients. Grade 3-4 toxicity included elevated ALT and AST each in 20% (requiring treatment discontinuation in 3 patients), diarrhea in 20%, hypertension in 10%, and fatigue in 15%.

1.6 Rationale for selected correlative analyses

1.6.1 PD-L1 expression

Tumor PD-L1 expression by IHC predicts an increased likelihood of response to immune checkpoint inhibition with PD-1 inhibitors in some cancer types.[28] A pooled analysis of 20 trials including 1475 patients with melanoma, non-small cell lung cancer (NSCLC), and genitourinary cancer showed a significant interaction between PD-L1 expression and response overall, with overall RR 34.1% vs. 19.9% ($p<0.0001$).[28] Response rates were significantly higher in PD-L1+ melanoma and NSCLC but no significant difference in response rate was observed according to PD-L1 status for genitourinary cancers, and a significant proportion of patients with PD-L1-negative tumors achieved tumor response to PD-1 inhibition across tumor types.

In HCC patients enrolled on CheckMate-040, 81% of patients in dose expansion had evaluable tumor samples for PD-L1 expression.[4] Among these, approximately 20% of cases exhibited tumor staining positive for PD-L1, defined as membrane expression of PD-L1 on at least 1% of tumor cells. In this study, positive tumor PD-L1 expression was not significantly associated with response to nivolumab therapy.

Tumor and immune cell PD-L1 expression will be analyzed by immunohistochemistry (IHC) from pre-treatment baseline archival tumor samples in all patients and any post-treatment samples if obtained as part of standard clinical care. PD-L1 IHC analyses will be performed in the UCSF Cancer Immunotherapy Laboratory (CIL) or other laboratory approved by Study Chair dependent upon funding and sample availability.

1.6.2 Peripheral Blood Mononuclear Cell (PBMC) Immune Cell Subsets and TCR Clonotype Frequency and Diversity

Research blood samples will be collected from all patients enrolled at UCSF at time points listed in Section 7.1. Research blood samples will not be collected from patients enrolled at the sub-site.

Whole blood will be processed into PBMC and cryopreserved at the UCSF Cancer Immunotherapy Laboratory (CIL) for future analyses in batch after completion of study.

PBMC samples will be analyzed for immune cell subsets by flow cytometry and may also be profiled for T cell receptor (TCR) genotype by next generation sequencing technologies. Dr. Fong's laboratory has demonstrated that treatment with the combination of CTLA-4 blockade plus GM-CSF results in expansion of activated effector CD8+ T cells as well as expansion of tumor antigen-specific T cells in patients with advanced prostate cancer.[29,30] Dr. Fong's laboratory and collaborators also have shown that checkpoint blockade by treatment with CTLA-4 inhibition in patients with metastatic prostate cancer and melanoma can increase T cell clonotype repertoire and diversity.[29,31]

Immune cell subsets will be measured using flow cytometry as has been previously described.[29,30] The frequency of individual clonotypes, and the diversity of overall clonotype repertoire, will be measured by next-generation sequencing.[31] Baseline and changes on treatment in PBMC T cell subsets and TCR clonotype frequency and diversity will be explored for relationship to clinical outcomes including ORR, DOR, PFS, OS, and AFP response.

1.6.3 Tumor immune cell infiltration and subsets

Preexisting tumor immune infiltration has shown association with increased likelihood of tumor response to checkpoint inhibition.[32,33] This association between tumor immune infiltration and increased response to immunotherapy may be due to preexisting tumor-specific T cell clones within the tumor which have been primed by tumor antigens but attenuated by checkpoint signaling, which are then activated upon checkpoint inhibition.

To explore the impact of tumor immune infiltration in HCC treated with the combination of sorafenib plus nivolumab, archival pre-treatment tumor core biopsy or resection

samples (primary and/or non-nodal metastatic site depending on availability) will be obtained from all patients. The samples will be examined for immune cell infiltrates and T cell subset composition in batch at study completion in the UCSF CIL as has been previously described.[29,30,34] The presence of tumor immune infiltrates and T cell subset composition will be explored for association with clinical outcomes including ORR, DOR, PFS, OS, and AFP (Alpha fetoprotein) response.

On-treatment or post-treatment tumor samples will also be analyzed in comparison to the baseline/pre-treatment specimen when available, such as in cases for which an on-treatment or post-treatment tumor resection or biopsy is required for clinical care (e.g. palliative metastatectomy/debulking, biopsy of an equivocal lesion, or if fiducial placement is required for palliative radiotherapy).

The immune cell subsets in tumor tissue will be compared descriptively to paired PBMC from the same patient (Section 1.6.2).[29]

1.6.4 Alpha fetoprotein (AFP) tumor marker

The most commonly measured blood tumor marker of HCC is AFP, a glycoprotein highly expressed during hepatocyte development. AFP is secreted by approximately 70% of HCC. Elevated baseline AFP levels have been shown to correlate with worse prognosis after hepatic resection, transplant, and local therapies. A study of patients enrolled in a phase III randomized trial comparing two palliative cytotoxic chemotherapy regimens showed that patients with AFP decline by at least 20% (designated as AFP responders) demonstrated markedly improved survival by comparison with AFP non-responders, with overall survival 13.5 versus 5.6 months, respectively ($p < 0.0001$).[35] AFP changes are also associated with response to sorafenib and may be an early surrogate marker of response.[36,37]

1.7 Rationale for expansion of eligibility to include Child Pugh B hepatic dysfunction

The CheckMate 040 trial enrolled a cohort of 49 advanced HCC patients with Child Pugh B7 or B8 liver dysfunction which showed objective response rate of 10.2%, with median duration of response 9.9 months.[38] The safety of nivolumab appeared similar to Child Pugh A patients, with discontinuation for toxicity in 2 patients (4.1%). Four patients (8.2%) experienced treatment-related hepatic adverse events, similar to proportion in Child Pugh A patients in CheckMate 040. Similar results were demonstrated in a retrospective case series of patients with Child Pugh B7-B9 hepatic function treated with nivolumab at UCSF, with treatment related discontinuation required in 4 of 18 patients (22%) and objective responses occurring in 17%.[39] Sorafenib also has demonstrated acceptable safety in Child Pugh B patients and similar adverse event and pharmacokinetic profiles to Child Pugh A,[13,40] with no dose modifications recommended in the FDA prescribing information, though a phase 1 and pharmacokinetic study of sorafenib in setting of hepatic dysfunction recommended empiric starting dose reduction according to baseline bilirubin and albumin levels.[41] There are few treatment options with prospective data for safety and efficacy in Child Pugh B patients, noting that the

first-line treatment options of bevacizumab plus atezolizumab as well as lenvatinib have only been studied prospectively in Child Pugh A populations to date, without established safety in Child Pugh B populations.[42,43] Thus, inclusion of carefully-selected Child Pugh B patients provides a treatment option for a subgroup of HCC patients without any established first line treatment options beyond sorafenib alone.

1.8 Rationale for protocol amendment to change Expansion Cohort primary objective to study safety and tolerability in patients with Child Pugh B hepatic function

After completion of Part 1: Escalation Cohort, the results of the IMbrave150 trial were reported demonstrating the superiority of the combination of atezolizumab plus bevacizumab over standard sorafenib in patients with advanced HCC and Child Pugh A liver function, becoming a new global standard of care in this population.[42] Atezolizumab plus bevacizumab has not been studied in patients with Child Pugh B liver dysfunction, however, and is contraindicated in patients with esophageal varices at high risk for upper gastrointestinal bleeding or patients with recent history of gastrointestinal bleeding, complications which are associated with Child Pugh B liver dysfunction.

Due to the changing treatment landscape with new first-line treatment options for patients with advanced HCC and Child Pugh A liver function, and the lack of established combination immunotherapy options for patients with Child Pugh B liver function, the previous version Expansion Cohort (Part 2) of this protocol has been amended and renamed as the Child Pugh B Expansion Cohort (Part 2), in order to study the safety and tolerability of the combination of sorafenib plus nivolumab in patients with both Child Pugh B liver dysfunction and advanced HCC, a population with urgent unmet medical need for safe and efficacious therapies.

2. Study objectives

2.1 Primary objectives

1. Part 1: Escalation Cohort: Maximum tolerated dose (MTD) of sorafenib in combination with standard dose nivolumab with Child Pugh A-B7 liver function
2. Part 2: Child Pugh B Expansion Cohort: Safety in patients with Child Pugh B liver function

2.2 Secondary objectives for Parts 1 and 2

1. Safety and tolerability of combination overall
2. Rate of irAE for combination overall and in patients with Child Pugh B liver function
3. Objective response rate (ORR) by RECIST 1.1[5] for overall study
4. ORR by RECIST 1.1 in patients with Child Pugh B liver function
5. Duration of response (DOR), progression free survival (PFS), and overall survival (OS) for Escalation Cohort and Child Pugh B Expansion Cohort and overall

2.3 Exploratory objectives for Parts 1 and 2

1. Relationship between PBMC immune cell subset frequencies, baseline liver function, and clinical outcomes
2. Relationship between PBMC T cell receptor (TCR) clonotype frequency and diversity, baseline liver function, and clinical outcomes
3. Tumor tissue immune cell subsets and TCR clonotype frequency and diversity in pre-treatment archival tumor tissue samples
4.
5. Tumor and immune cell PD-L1 status in pre-treatment archival tumor tissue samples and relationship to clinical outcomes

6. Changes in HBV and/or HCV viral load on treatment
7. AFP changes on treatment and relationship to clinical outcomes
8. Relationship between clinical outcomes and clinicopathologic features including race/ethnicity, etiology of liver disease including HBV/HCV status, baseline liver function, presence of cirrhosis, macrovessel invasion, extrahepatic spread, site(s) of metastatic disease, prior treatment history including prior radiation and arterial therapies

3. Investigators and other study participants

Principal Investigator: Robin K. Kelley, MD
Associate Professor of Clinical Medicine
University of California, San Francisco (UCSF)

A second study site, University of California, Davis (UCD) was activated after completion of Part 1: Dose Escalation Cohort.

4. Study design

This is an open-label, dose-escalation and expansion pilot study to examine the safety and efficacy of sorafenib combined with the PD-1 checkpoint inhibitor, nivolumab, in patients with unresectable HCC not amenable to curative therapies, with no prior systemic treatment. The study is divided into two parts: Dose Escalation Cohort (Part 1) and Child Pugh B Expansion Cohort (Part 2). Immune profiling of PBMC will be performed in all patients enrolled at UCSF. There are 2 planned study sites: UCSF and a sub-site UCD which was activated after completion of Part 1: Dose Escalation Cohort.

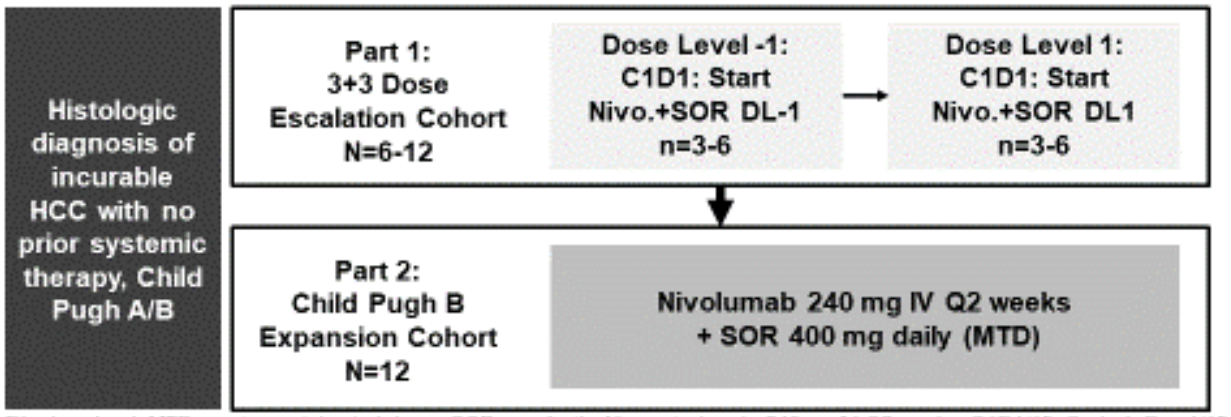
4.2 Duration of Therapy

Sorafenib will be administered continuously and nivolumab will be administered every 14 or 28 days until progression, unacceptable toxicity, withdrawal of consent, criteria for discontinuation are met, or study end, whichever comes first.

4.3 Duration of Follow Up

Patients will be followed for survival every 3 months after completion of treatment or removal from study, or until death, whichever occurs first, for up to 2 years. Patients removed from study for unacceptable treatment related adverse event(s) will be followed until resolution or stabilization of all treatment related adverse events to Grade 2 or lower, or determination of chronic/irreversible by treating investigator and Study Chair.

4.4 Study schema



DL=dose level; MTD=maximum tolerated dose; SOR=sorafenib; Nivo.=nivolumab 240 mg IV Q2 weeks; C1D1/15=Cycle 1, Day 1/15

4.5 Study Timeline

4.5.1 Primary Completion

The study is expected to complete accrual within approximately 48 months after enrolment of first patient, based upon expected accrual rate of 1-2 subjects per month and transition time required for protocol amendment. Accrual is expected to be completed by 30 April 2022; no subsequent patients will be enrolled after 30 April 2022 unless approved by Study Chair and Bayer.

4.5.2 Study Completion

The study is expected to complete primary and secondary endpoint measurements and survival follow up approximately 60 months after enrolment of first patient, based upon expected 48 month accrual period, median time on treatment of 4 months, and 24 months of survival follow up from the last dose for last patient on study.

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

1. Histologic or cytologic diagnosis of unresectable, locally advanced and/or metastatic HCC not amenable to curative surgery, transplantation, or ablative therapies based upon assessment of treating investigator
    a. For patients without prior histologic or cytologic diagnosis, radiographic diagnosis is allowed provided patients meet American Association for the Study of Liver Diseases (AASLD) criteria for radiographic diagnosis 44
2. Radiographically measurable disease by RECIST version 1.1 in at least one site not previously treated with chemoembolization, radioembolization, radiation, or other local/liver-directed procedures (i.e. must have at least one measurable target lesion, either within the liver or in a measurable metastatic site); a new area of tumor progression within or adjacent to a previously-treated lesion, if clearly measurable by a radiologist, is acceptable
3. Untreated/pretreatment archival tumor tissue must be available for correlative analyses
4. Age at least 18 years at enrollment
5. ECOG 0 or 1 at enrollment
6. At least 4 weeks after any prior chemoembolization, radioembolization, local ablative therapies, or hepatic radiation and recovery to ≤ grade 1 treatment-related toxicity
7. At least 6 weeks after any major surgery including prior hepatic resection and recovery to ≤ grade 1 treatment-related toxicity
8. At least 7 days after minor surgery (such as central venous access) or biopsy and recovery to ≤ grade 1 treatment-related toxicity
9. At least 2 weeks after any prior palliative radiation (e.g. to focal metastatic lesion such as bone metastases) and recovery to ≤ grade 1 treatment-related toxicity
10. Blood pressure ≤140/90 mm Hg with or without anti-hypertensive therapy
    a. Patients may be rescreened after initial ineligibility if due to elevated blood pressure, if adequately medically managed within approximately 30 days
11. Adequate baseline organ and marrow function as defined below:
    a. adequate bone marrow function:
        absolute neutrophil count at least 1,200/mcL
        platelets at least 50,000/mcL
        hemoglobin at least 9 g/dL
    b. adequate hepatic function:
        Part 1: total bilirubin less than 2.6 mg/dL or 2 times ULN, whichever is higher, and albumin at least 2.5 g/dL if otherwise meets criteria for Child Pugh A or B7

Part 2: total bilirubin less than 3.9 mg/dL or 3 times ULN[41], whichever is higher, and albumin at least 2.0 g/dL, if otherwise meets criteria for Child Pugh B
Part 1: AST(SGOT) and ALT (SGPT) less than 5 X ULN, INR less than 1.7
Part 2: AST(SGOT) and ALT (SGPT) less than 8 X ULN, INR less than 1.7

c. creatinine less than 1. 5 X ULN and/or creatinine clearance ≥ 60 mL/min

12. Child Pugh A or B7 (Part 1); Child Pugh B7-9 (Part 2) (See Appendix 14.3)
13. If HBV sAg and/or core Ab positive, must be treated with appropriate antiviral therapy according to institutional practice with HBV DNA by PCR less than 500 IU/mL
14. If clinical or histologic diagnosis of cirrhosis and/or clinical or radiographic evidence esophageal or gastric varices, must have had EGD surveillance and adequate endoscopic therapy according to institutional standards
15. Able to swallow and retain oral medications
16. Women of child-bearing potential (WOCBP) must have a negative pregnancy test within 28 days before study enrollment
17. WOCBP and male partners of WOCBP must agree to use two methods of contraception until at least 5 months after last dose of each study drug for WOCBP subjects, and 7 months for male partners of WOCBP
18. Able to understand and willingness to provide informed consent, and the willingness to comply with the requirements of the protocol
    a. Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines and before the performance of any protocol related procedures that are not part of standard of care

5.1.2 Exclusion criteria

1. Any prior systemic therapy for HCC
2. Known fibrolamellar or mixed HCC-cholangiocarcinoma histology
3. Requirement for paracentesis to control ascites within 6 months before enrollment
    a. Ascites which is not clinically detectable or mild on stable doses of diuretics during screening is allowed provided meets criteria for Child Pugh A or B7 (Part 1) or B7-9 (Part 2)
4. Symptomatic hepatic encephalopathy requiring medication (such as lactulose or rifaximin) (Part 1) or any hospitalization for encephalopathy within 6 months before enrollment (Part 1 or 2)
    a. Hepatic encephalopathy that is adequately controlled on stable doses of lactulose and/or rifaximin per assessment of treating investigator is allowed in Part 2, provided no hospitalization for encephalopathy within 6 months before enrollment
    b. Medications such as lactulose used for other indications (e.g. constipation) are allowed in both Part 1 and 2
5. History of upper GI bleeding from esophageal and/or gastric varices within 12 months before enrollment

6. Requirement for systemic corticosteroids unless used for adrenal replacement, acute therapy for asthma or bronchitis exacerbation (≤ 2 weeks), or premedication for contrast allergy
    a. Topical, intranasal, or inhaled steroids are not excluded
7. Active autoimmune condition requiring systemic immunosuppressive medication
8. Known HIV infection
9. Active coinfection with HBV plus HDV or HCV:
    a. Both hepatitis B and C as evidenced by detectable HBV surface antigen or HBV DNA and detectable HCV RNA
    b. Hepatitis D infection (HDV antibody positive) in subjects with detectable hepatitis B surface antigen or HBV DNA
10. Prior allogeneic transplant of any solid organ or bone marrow/stem cells
11. Symptomatic hypothyroidism without replacement
    a. Patients may be rescreened after initiating adequate replacement therapy
12. History of seizure disorder requiring antiepileptic medication or brain metastases with seizures
13. Non-healing wound, ulcer, non-healing traumatic bone fracture, or abscess within 30 days of enrollment
    a. Nondisplaced, uncomplicated pathologic fracture due to tumor may be eligible provided adequately treated with radiation, surgery or other treatments with full recovery based upon investigator assessment
14. Central or necrotic lung metastases
15. Known brain or leptomeningeal metastases
16. Uncontrolled hypertension (systolic pressure >140 mm Hg and/or diastolic pressure > 90 mm Hg [NCI-CTCAE v4.0] on repeated measurement) despite optimal medical management
17. Active or clinically significant cardiac disease including:
    a. Congestive heart failure – New York Heart Association (NYHA) > Class II
    b. Active coronary artery disease including unstable or newly diagnosed angina or myocardial infarction within 6 months prior to study entry
    c. Cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin
    d. QTc (Fridericia) > 450 msec on two consecutive ECGs (baseline ECG should be repeated if QTc is found to be > 450 msec)
18. Subject with any pulmonary hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 2 or higher within 6 months before first dose of study treatment any other hemorrhage/bleeding event of NCI-CTCAE v4.0 Grade 3 or higher within 6 months before first dose of study treatment
19. Subjects with arterial or venous thrombotic or embolic events, such as cerebrovascular accident (including transient ischemic attacks), myocardial infarction, or deep venous thrombosis (DVT) within 6 months of informed consent
    a. Tumor or bland thrombus in hepatic vasculature is not an exclusion provided hepatic function criteria are met
    b. Asymptomatic thromboembolic events such as incidentally-detected subsegmental pulmonary emboli or superficial thromboses are not an

exclusion provided the patient does not require treatment with therapeutic anticoagulation

20. Subjects who have used strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbital, St. John's Wort [Hypericum perforatum], dexamethasone at a dose of greater than 16 mg daily, or rifampin [rifampicin], and/or rifabutin) within 28 days before first dose of study treatment
21. Subjects who require therapeutic anticoagulation or anti-platelet therapy
    a. Low dose aspirin (≤100 mg/day) is allowed
    b. Prophylactic doses of low molecular weight heparin (LMWH) are allowed if approved by Study Chair or designee
22. Subjects with any previously untreated and concurrent cancer that is distinct in primary site or histology from HCC except cervical cancer in-situ, treated non-melanoma skin cancers, localized prostate cancer not requiring systemic therapy undergoing surveillance, or superficial bladder tumor; subjects surviving a cancer that was curatively treated and without evidence of disease for more than 2 years before enrollment are allowed provided that cancer therapy was completed at least 2 years prior to study entry (date of the informed consent form)
23. Any uncontrolled intercurrent illness including, but not limited to: Ongoing or active infection requiring antibiotic therapy, pulmonary disease impairing functional status or requiring oxygen, impairment in gastrointestinal function that may affect or alter absorption of oral medications (such as malabsorption or history of gastrectomy or bowel resection), or uncontrolled diarrhea
24. Known or suspected allergy or hypersensitivity to any of the study drugs, study drug classes, or excipients of the formulations given during the course of this trial
25. Women who are pregnant or breast-feeding at enrollment
26. Inability to comply with the protocol and/or not willing or not available for follow-up assessments
27. Any condition which, in the investigator's opinion, makes the subject unsuitable for trial participation

5.2 Inclusion and Recruitment of Women and Minorities

Individuals of any sex/gender, race, or ethnicity may participate.

5.3 Withdrawal of subjects from study

5.3.1 Screen failures/dropouts

A subject who discontinues study participation prematurely (without meeting a study defined safety or efficacy endpoint) for any reason is defined as a "dropout" if the subject has already received at least one dose of either study drug. A subject who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before receiving dose of either study drug is regarded a "screen failure".

5.3.2 Replacement

Patients enrolled to Part 1 or Part 2 who are determined ineligible after enrollment and/or who are not evaluable for the endpoints of DLT or safety will be replaced. See "Statistical methods and determination of sample size" in Section 8.0.

5.3.3 Withdrawal

Subjects must be withdrawn from the trial (treatment and procedures) for the following reasons:

- Subject withdraws consent from study treatment and study procedures. A subject must be removed from the trial at his/her own request or at the request of his/her legally acceptable representative. At any time during the trial and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Subject is lost to follow-up.
- Death.

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

- The subject is non-compliant with study drug, trial procedures, or both; including the use of anti-cancer therapy not prescribed by the study protocol.
- Pregnancy. Pregnancy will be reported as an SAE. (Note: subjects who have been withdrawn from treatment with study drug because of pregnancy should not undergo CT scans [with contrast]/MRI or bone scans while pregnant.)
- If, in the investigator's opinion, continuation of the trial would be harmful to the subject's well-being.
- Severe allergic reaction or unacceptable toxicity to both study drugs (see Section 6.9).
- The development of a second cancer.
- Development of an intercurrent illness or situation which would, in the judgment of the investigator, significantly affect assessments of clinical status and trial endpoints.
- Deterioration of ECOG performance status to greater than 2 despite best supportive care and attributed as at least possibly related to protocol therapy.
- Use of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise skewing trial result.

- Administrative or safety reasons requiring study closure.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable. In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. Details for the premature termination of the study as a whole are provided in Section 10 (Premature termination of the study).

6. Treatments

6.1 Treatments to be administered

All patients will be treated with the combination of sorafenib plus nivolumab. Patients will be enrolled to one of two sequential cohorts: the Dose Escalation Cohort (Part 1) or the Child Pugh B Expansion Cohort (Part 2). Patients enrolled to the Dose Escalation Cohort (Part 1) will be enrolled starting at Dose Level -1 according to Table 6.2.1-1 below, following standard 3+3 dose escalation rules as outlined in Section 6.2.2 below. Patients enrolled to the Child Pugh B Expansion Cohort (Part 2) will be enrolled to the maximum tolerated dose (MTD) of sorafenib identified in Part 1 along with standard dose nivolumab, as described below in Section 6.2.2.

6.2 Part 1: Dose Escalation Cohort

Between 3-12 patients will be enrolled in Part 1 starting at Dose Level (DL) -1. See Table 6.2.1-1 for dose levels and Table 6.2.2-1 for dose escalation decision rules. Standard dose nivolumab 240 mg IV every 14 days will be used for both dose levels based upon absence of established dose-relationship for toxicities attributed to this agent in advanced HCC patients.[4]

6.2.1 Part 1 dose levels

Table 6.2.1-1. Part 1 Dose Levels

Drug	**Dose Level -2**	**Dose Level -1 (starting dose)**	**Dose Level 1**
	n =3-6 patients	*n* = 3-6 patients	*n* = 0-6 patients
Sorafenib	400 mg PO QOD	400 mg PO daily	400 mg PO BID
Nivolumab	240 mg IV Q2 weeks over 30 minutes		

6.2.2 3+3 dose escalation rules

Table 6.2.2-1. Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Dose escalate to next higher dose level. If already at DL 1, enroll 3 additional patients at DL 1.
≥ 2 out of 3*	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). The next lower cohort will be expanded to 6 patients. If no DLTs are seen consider an intermediate dose level between this dose and the MAD dose.
1 out of 3	Enter 3 more patients at this dose level. If 0 of these 3 patients experience a DLT, proceed to the next dose level. If already at DL 1, then DL 1 is the MTD. If 1 or more of these 3 patients suffer a DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose.
≤ 1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and recommended Expansion Cohort dose.

Note: Dose escalation will stop at Dose Level 1 which is the FDA-labeled dose of sorafenib as monotherapy for HCC. If >1 DLT occur at DL-2 a decision will be made whether to amend or terminate the study.

6.2.3 Dose limiting toxicity (DLT) window and definitions

The DLT window will be 28 days (1 cycle). Subjects must receive 2 doses of nivolumab and at least 75% of sorafenib doses within 28 days (1 cycle), or experience a qualifying DLT event, to be evaluable for DLT. DLT will be defined as clinically-significant toxicities which are at least possibly treatment-related and meet criteria listed in the sections below.

Toxicity will be graded by NCI CTCAE v.4.03 (https://ctep.cancer.gov/). Toxicity grade should be determined after standard, optimal supportive care treatments have been provided when appropriate. Optimal supportive care is defined as standard of care measures (such as electrolyte supplementation, the use of loperamide for diarrhea or antiemetics for nausea, or topical skin care for rash) that the treating physician deems appropriate and sustainable over multiple cycles of therapy. Clinically significant toxicity is defined as requiring therapeutic intervention beyond standard supportive care and/or placing the patient at risk for other toxicity by the judgment of the treating investigator.

After experiencing a DLT, a subject may resume treatment with dose reduction and/or optimal supportive care according to protocol guidance on dose modification and delay, once criteria for retreatment have been met and provided criteria for discontinuation have not been met.

6.2.3.1 **Hematologic DLT**

1. Grade 4 hematologic toxicity (limited to neutrophil, hemoglobin, and platelet counts)
    1. Lymphopenia is excluded
2. Prolonged Grade 3 thrombocytopenia > 7 days, requiring dose modifications during Cycle 1, requiring platelet transfusion, or associated with clinically relevant bleeding (as defined by bleeding requiring hospitalization, transfusion, or an invasive procedure such as endoscopy)

3. Grade 3 neutropenia with fever (ANC < 1000 and T ≥ 38.5°C)

6.2.3.2 **Non-hematologic DLT including immune-related AE (irAE)**

1. Any treatment-related Grade ≥ 3 non-hematologic toxicities with exceptions listed below in Section 6.2.3.3
2. Treatment-related hepatotoxicity as evidenced by any of the following is considered a DLT:
    a. AST and/or ALT > 5 x ULN (Grade 3) for patients with normal or grade 1 AST and/or ALT at baseline, if bilirubin ≤ 2 x ULN
    b. AST and/or ALT > 8 x ULN for patients with grade 2 AST and/or ALT at baseline, if bilirubin ≤ 2 x ULN
    c. T. bilirubin > 5 x ULN irrespective of baseline
    d. AST and/or ALT > 3 x ULN with concurrent increase in bilirubin > 2 x ULN without evidence for other cause (e.g. cholangitis, obstruction, viral hepatitis, tumor progression, etc.) (Hy's Law)
    e. Clinical deterioration manifested by drug-related hepatic decompensation not identified above (e.g., new onset Grade >2 ascites or encephalopathy attributed to treatment)
3. Any Grade ≥ 3 irAE during DLT window that does not downgrade to ≤ Grade 2 within 7 days after onset of the event despite optimal medical management including systemic corticosteroids and/or hormone replacement and/or does not downgrade to ≤ Grade 1 or baseline within 14 days, with exceptions of pneumonitis and eye toxicity as below:
    a. Any Grade ≥ 2 pneumonitis irAE that does not improve to ≤ Grade 1 within 7 days of initiation of maximal supportive care
    b. Any Grade ≥ 2 ophthalmologic irAE such as uveitis causing eye pain or reduction of visual acuity that does not improve to Grade ≤ 1 severity within 14 days of starting topical therapy or requires systemic treatment
4. Any Grade ≥ 2 toxicity despite optimal supportive care that requires sorafenib dose reduction during the DLT window (with exceptions for hand-foot skin reaction (HFSR) and hypertension as detailed below) or results in a treatment delay or discontinuation of either drug for > 7 days
5. Removal from study due to toxicity attributable to treatment during DLT window

6.2.3.3 **DLT exceptions**

The following AE will not be considered DLT:

1. Asymptomatic Grade 3 non-hepatic laboratory values, with the following specifications:
    a. Asymptomatic Grade 3 laboratory values are only considered DLT if determined treatment-related and clinically significant (e.g. requiring therapeutic intervention)
    b. Liver function test abnormalities will be determined DLT according to DLT definitions in Section 6.2.3.

2. Grade 3 hypertension that resolves to ≤140/90 within 7 days of adjustment or addition of oral blood pressure medication(s)
3. Grade 3 HFSR attributed to sorafenib
4. Grade 3 infusion reactions which resolve within 6 hours of supportive therapy are not considered DLT but require nivolumab discontinuation (see Section 6.9)
5. Grade 3 fatigue
6. Toxicity attributed to hepatocellular carcinoma (e.g. AE due to mass effect, obstruction, or pain caused by tumor growth or new lesions)

6.3 Part 2: Child Pugh B Expansion Cohort

After identification of MTD for sorafenib in combination with standard dose nivolumab in Part 1, approximately 12 additional patients with liver function will be enrolled to the Child Pugh B Expansion Cohort on combination therapy with sorafenib at MTD from Part 1 (400 mg PO daily) and nivolumab 240 mg IV every 14 days both starting on C1D1.

6.3.1 Dose Levels for Part 2 Child Pugh B Expansion Cohort

Drug	Dose	Part 2 (*n* =12 patients)
Sorafenib	400 mg PO daily	Start on C1D1
Nivolumab	240 mg IV Q14 days*	Start on C1D1

*Option to switch nivolumab dosing to 480 mg IV Q28 days on or after C4D1 (see Section 6.5.1) with Study Chair approval in eligible patients.

6.4 Sorafenib

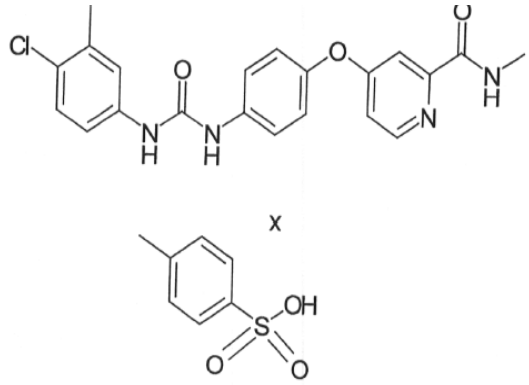
Sorafenib (BAY 43-9006) is an oral multi-kinase inhibitor targeting both tumor cells and the tumor vasculature. The chemical name for sorafenib tosylate is 4

Chloro-3-trifluoromethyl-phenyl)-ureido] -phenoxy}-pyridine-2

carboxylic acid methylamide-4-methylbenzene-sulfonate, and its molecular weight is 637 daltons. The structure of sorafenib is depicted in Figure 6.4-1.

Sorafenib (as Nexavar™) is approved for use in multiple countries including the United States (US), the European Union (EU), and many other countries for multiple oncology indications including renal cell carcinoma, HCC, and differentiated thyroid cancer.

Figure 6.4-1: Structure of sorafenib (BAY 43-9006)



Structure of BAY 43-9006 tosylate (BAY 54-9085)

6.4.1 Sorafenib dosage and administration

Subjects will be instructed on the proper administration of sorafenib. Sorafenib tablets should be taken approximately 12 hours apart if assigned to BID dose level or approximately 24 hours apart if assigned to QD dose level, at approximately the same time(s) each day. Sorafenib tablets should be taken without food, at least 1 hour before or at least 2 hours after a meal, and with up to 240 mL (approximately 1 cup or 8 oz.) of water. Consumption of grapefruit and grapefruit juice should be avoided while receiving study drug.

6.4.1.1 Sorafenib missed doses

Missed doses of sorafenib should be taken as soon as the subject remembers. However, if it < 12 hours before next dose due, the missed dose should be skipped and the subject should take his/her next dose as scheduled. A double dose should not be administered to make up for missed individual doses.

6.4.2 Sorafenib drug supply and handling

For Part 1 of study, sorafenib tablets were obtained locally from commercial supplies with prescription from treating investigator, as a standard therapy for HCC. For Part 2 of study after amendment to restrict to Child Pugh B7-9 liver dysfunction, sorafenib tablets will be supplied by Bayer HealthCare. The 200-mg tablet formulation contains sorafenib tosylate and the excipients croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, and magnesium stearate. The tablets have a film coating comprised of hypromellose, polyethylene glycol, titanium dioxide, and red ferric oxide, which has no effect on the release rate of the active ingredient, sorafenib tosylate. The tablets are un-debossed, salmon colored, weigh approximately 350 mg each, and are 10 mm (millimeter) round in shape. Sorafenib tablets do not need to be protected from light. They are sufficiently stable with regard to light, oxidation, thermal stress, and hydrolytic degradation. The formulation is presented as an immediate release (IR) dosage form, i.e., the active ingredient is completely dissolved under in

vitro test conditions within a short period of time. Additional information on prepared drug storage and administration are available in the sorafenib Investigator Brochure.

6.5 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab (as OPDIVO™) is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014) for multiple oncology indications. OPDIVO™ is not approved for use in HCC as of 1 June 2017.

6.5.1 Nivolumab dosage and administration

Nivolumab 240 mg flat dose will be administered as an IV infusion over 30 minutes through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles. At the end of the infusion, the line should be flushed with a sufficient quantity of dextrose or normal saline.

For patients enrolled to Part 2, nivolumab may be switched to monthly infusion of 480 mg Q28 days on or after C4D1 with Study Chair approval in patients with investigator-assessed clinical benefit and without any uncontrolled or grade >2 immune-related toxicity, based upon established safety and efficacy of the monthly dosing regimen across tumor types.[44] A note to file will be placed in the subject's study chart to document Study Chair or designee approval.

6.5.1.1 Nivolumab schedule modifications and definition of delay

Subjects may be dosed no less than 12 days between nivolumab doses at 240 mg dose Q14 days, and no less than 24 days between nivolumab doses at 480 mg monthly dose. Subjects may be dosed up to 3 days (for Q14 day dosing) or 6 days (for Q28 day dosing) after the scheduled date if necessary. A dose given more than 3 or 6 days after the intended dose date will be considered a delay for each respective dosing interval. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

6.5.1.2 Nivolumab premedication

Premedication for nivolumab is not required unless a subject has experienced prior infusion reaction. See Section 6.8.2.2. In subjects who have experienced a prior infusion reaction (< Grade 3) and who are determined eligible for retreatment, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

6.5.2 Nivolumab drug supply and handling

Nivolumab was supplied by Bristol-Myers Squibb to each study site for Part 1 and beginning of Part 2 patient enrollment. Starting after protocol amendment (version 4.0) requiring Child Pugh B7-9 liver dysfunction for eligibility to Part 2, nivolumab will be prescribed as a standard therapy option for patients with Child Pugh B liver dysfunction from commercial supplies and administered according to package insert instructions. Additional information on prepared drug storage and administration are available in the nivolumab Investigator Brochure and package insert.

6.6 Blinding

This is an open-label study. No blinding will be performed.

6.7 Dose modifications and delays

Toxicity will be assessed according to NCI CTCAE v.4.03 (https://ctep.cancer.gov/). Dose modifications, interruptions, and treatment discontinuation for one or both study drugs will be determined according to the system showing the greatest degree of toxicity and according to the treating investigator's assessment of cause of toxicity. Toxicity will be formally assessed at protocol-defined safety assessment time points well as by investigator review of weekly laboratory testing and, in the interim, by any unscheduled patient contact with the study team.

General principles of dose modification and delay are listed below:

- Optimal supportive care should be provided for all clinically relevant toxicities.

- See Section 6.8 for guidance on supportive care/rescue medications for specific toxicities.
- For any toxicity (regardless of grade), despite optimal supportive care, that is felt by the treating investigator to represent a risk to the patient's safety, additional dose reduction, treatment delay, and/or treatment discontinuation (beyond per protocol dose modifications) are permitted at the discretion of the treating investigator.
- Scheduled safety and tumor assessments for all subjects should continue as per protocol even if dosing is delayed.
    - Safety assessments may be required more often if treatment delay for toxicity.
- No dose re-escalation is permitted after dose reduction for toxicity.
- If a treatment-related toxicity requiring treatment delay has not recovered to ≤ Grade 1 after treatment delay ≥ 6 weeks (42 days) for toxicity, treatment will be discontinued.
    - Exceptions allowing longer treatment delay up to approximately 12 weeks for recovery of treatment-related toxicity in subjects who have demonstrated previous treatment benefit (e.g. radiographic regression and/or clinical improvement such as reduced pain or tumor marker) are permitted with documented approval from Study Chair or designee.

6.7.1 Sorafenib dose modifications and delays for toxicity

Sorafenib doses will be delayed or reduced for clinically significant hematologic and non-hematologic toxicities that are determined to be related to sorafenib therapy according to the guidelines in the sections below, according to types of toxicity.

Sorafenib dose reduction will follow predefined dose levels in Table 6.2.1-1 in Section 6.2.1. Subjects requiring dose reduction at current dose should be treated at next lower dose level until Dose Level -2. If additional toxicity attributed to sorafenib occurs despite reduction to Dose Level -2, sorafenib will be discontinued.

Table 6.7.1-1 Sorafenib dose modifications and delays for hematologic toxicity

Toxicity	ANC (x 10^9/L)	Hemoglobin (g/dL)	Platelets (x 10^9/L)	Sorafenib
Grade 1	≥ 1.5	< LLN – 10.0	≥75	Treat on time No change
Grade 2	≥ 1.0 to < 1.5	< 10.0 – 8.0	≥ 50 to < 75	Treat on time No change
Grade 3	≥ 0.5 to < 1.0	< 8.0 – 6.5	≥ 25 to < 50	Treat on time Reduce by one dose level
Grade 4	< 0.5	Life-threatening consequence; urgent intervention indicated	<25	Discontinue from study

Febrile Neutropenia				Delay sorafenib until toxicity has resolved to Grade 2 or less; when sorafenib is restarted, reduce by one dose level

Table 6.7.1-2: Sorafenib dose modifications and delays for non-hematologic toxicity

Grade	Dose interruption	Dose modification
Grade 0-2* (except for HFSR or diarrhea)	Treat on time	No change
Grade 2 HFSR* or diarrhea	1st occurrence: Continue treatment with augmented HFSR skin care and/or antidiarrheal regimen If no improvement within 7 days or ≥ 2nd occurrence: Interrupt until < Grade 2	Decrease one dose level
Grade 3	Interrupt until ≤ Grade 2	Decrease one dose level
Grade 4	Discontinue from study	Discontinue from study

*See Table 6.8.1-1 and Sections 6.8.1.1 through 6.8.1.3 for HFSR, diarrhea, and HTN supportive care guidance.

6.7.2 Nivolumab dose modifications and delays

No dose reductions for nivolumab are permitted under this protocol. Nivolumab administration will be delayed for the following:

1. Any Grade ≥ 2 non-skin drug-related adverse event, with the following exceptions:
    a. Grade 2 drug-related fatigue or asymptomatic laboratory abnormalities do not require a treatment delay.
2. Any Grade ≥ 3 skin drug-related adverse event.
3. Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions:
    a. Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay.
4. Dose delay for changes in AST or ALT as follows:
    a. 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).
    b. If a subject has baseline AST or ALT within the Grade 1 toxicity range, delay dosing for drug-related increase to ≥ 8x ULN.
    c. If a subject has baseline AST or ALT within the Grade 2-3 toxicity range, delay dosing for two-fold drug-related increase in AST or ALT or for AST or ALT values 10x ULN (whichever is lower).
5. Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

See Section 6.8.2 and Appendix 14.5 for guidance on management of toxicity attributed to nivolumab including initiation of immunosuppression for possible immune-related toxicity. 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 at least weekly until levels peak or begin to decline. Nivolumab dosing can be resumed when the following re-treatment criteria are met.

6.7.2.1 **Criteria to resume nivolumab dosing after delay for toxicity**

Subjects may resume treatment with a study drug after treatment hold for toxicity if the drug-related AE(s) resolve to Grade ≤ 1 or baseline within 6 weeks (42 days), with the following exceptions:

1. Subjects may resume treatment in the presence of Grade 2 fatigue.
2. Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
3. 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.
4. Subjects who require dose delays for drug-related elevations in AST, ALT, or total bilirubin may resume treatment when these values have returned to their baseline CTCAE Grade or normal, provided the criteria for unacceptable toxicity requiring permanent discontinuation are not met (Section 6.9).
5. Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
6. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement are acceptable for resuming treatment.
7. A longer treatment delay up to approximately 12 weeks for recovery of treatment-related toxicity in subjects may be permitted in subjects who have demonstrated previous treatment benefit (e.g. radiographic regression and/or clinical improvement such as reduced pain or tumor marker), with approval from Study Chair or designee.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol.

6.7.3 Dose delays for reasons other than treatment-related toxicity

Dosing interruptions in either or both drugs are permitted in the case of unrelated medical or surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, administrative reasons, patient vacation or personal reasons, and/or holidays). Subjects should be placed back on study therapy within approximately 4 weeks (28 days, 1 cycle) of the scheduled interruption if within the first 6 months (6 cycles) of protocol therapy, or within approximately 8 weeks (56 days, 2 cycles) if the delay occurs after the first 6 months (6 cycles) of protocol therapy. Scheduled safety and tumor assessments for all subjects should continue per protocol

even if dosing is delayed.

Longer delays may be permitted on a case-by-case basis if approved in writing by Study Chair.

The reason for interruption should be documented in the patient's study record. Before resuming treatment, patients must demonstrate adequate clinical and laboratory parameters to resume treatment without indication for dose modification or delay according to Section 6.8.

6.8 Supportive care for toxicity

6.8.1 Sorafenib supportive care

Standard supportive care should be provided to all patients according to institutional practice for sorafenib therapy. The following tables provide guidance on supportive care to prevent and/or mitigate toxicity related to sorafenib, to be employed at discretion of treating investigator. The treating investigator may employ different or additional interventions according to institutional practice and clinical judgment.

6.8.1.1 Hand-foot skin reaction (HFSR)

Table 6.8.1.1-1 Guidance on prevention and supportive care for HFSR on sorafenib

Toxicity Grade	Practical Prevention / Management Strategies for HFSR

Grade 0 (Preventive strategies)	• Maintain frequent contact with trial physician to ensure early diagnosis of HFSR.
	• Practical prevention strategies
	  ○ Subjects should avoid hot water, tight clothing, or activities that can cause friction on the skin.
	  ○ Moisturizing cream should be applied frequently.
	• Padded gloves and open shoes with padded soles should be worn to relieve pressure points.

Grade 1
Any occurrence
	• Continue preventive strategies and in addition:
	  ○ Soak hands and feet in cool water.
	  ○ Apply petroleum jelly to moist skin.

Grade 2 Any occurrence or **Grade 3** Any occurrence	• Continue supportive/management measures and add analgesic(s) for pain.

6.8.1.2 Diarrhea

Diarrhea is a common side effect of sorafenib. The preventive and supportive care strategies for diarrhea should be consistent with local standard of care on sorafenib (e.g., anti-diarrheals, optimized hydration status for diarrhea, dietary modifications).

6.8.1.3 Treatment-emergent hypertension

Hypertension is a known and potentially serious AE associated with sorafenib treatment. Subjects will undergo brief physical examinations, including blood pressure monitoring, approximately every other week per Section 7.1. Blood pressure measurements that are out of the normal range must be reported to the treating

physician. Blood pressure measurements considered out of the normal range are diastolic pressure > 90 mm Hg and/or systolic pressure > 140 mm Hg.

The choice of anti-hypertensive medication to be used in cases of treatment-emergent hypertension will be at the investigator's discretion and based on site-specific treatment guidelines as applicable. All anti-hypertensive medications used for the management of treatment-emergent hypertension should be recorded in the subject's records.

6.8.2 Nivolumab supportive care

6.8.2.1 Immune-related adverse events (irAE) on nivolumab

For potential immune-related adverse events (irAE) attributed to nivolumab, immunosuppressive therapy should be promptly initiated at discretion of treating investigator. General guidelines for immunosuppressive therapy are provided below. Specific guidance for common irAE are provided in Appendix 14.6.

Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. These treatment guidelines are intended to be applied when the investigator determines the events to be related to nivolumab.

Suggested steroid regimens include:

1. Systemic steroids equivalent to prednisone 1-2 mg/kg/day for severe immune-related toxicity requiring immunosuppressive therapy.
2. Oral prednisone 0.5 mg/kg/day or other equivalent steroid regimen for mild-moderate immune-related toxicity requiring immunosuppressive therapy.
3. Topical corticosteroids for mild-moderate dermatitis.
4. Corticosteroid eye drops for ocular immune-related toxicity.

Supportive care on prolonged steroid therapy including blood pressure and blood glucose monitoring, gastroprotection with proton pump inhibition, and antibacterial prophylaxis (e.g. trimethoprim-sulfamethoxazole prophylactic doses) should be employed at discretion of treating investigator according to institutional standards.

Once symptoms resolve or return to Grade 1/baseline, initiate slow steroid taper over at least 4 weeks, with close monitoring. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

6.8.2.2 Infusion reactions during nivolumab infusion

Since nivolumab contains 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, it might manifest with fever, chills, rigors, headache, rash,

pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. Infusion reactions should be graded according to NCI CTCAE (version 4.03) guidelines.

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

1. For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)
    - Remain at bedside and monitor subject until recovery from symptoms.
    - For future infusions, the following prophylactic premedications are recommended: Diphenhydramine 50 mg (or equivalent) PO and acetaminophen 325 to 1000 mg PO at least 30 minutes before additional nivolumab administrations.
2. 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, bronchodilators, IV fluids]; prophylactic medications indicated for $\leq$ 24 hours).
    - Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and acetaminophen 325 to 1000 mg PO; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator 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. The amount of study drug infused must be recorded on the electronic case report form (eCRF). Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
    - For future infusions, the following prophylactic premedications are recommended: Diphenhydramine 50 mg PO (or equivalent) and acetaminophen 325 to 1000 mg PO should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
3. For Grade 3 or Grade 4 symptoms: (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; presser or ventilator support indicated).
    - Immediately discontinue infusion of nivolumab. 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 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.

4. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

6.9 Unacceptable toxicity requiring treatment discontinuation

If one study drug is discontinued for unacceptable toxicity, treatment with the other agent will also be discontinued.

6.9.1 Unacceptable toxicity from sorafenib

The decision to discontinue sorafenib for toxicity should follow local standards of care as guided by the FDA label for sorafenib in HCC. Grade ≥ 4 AE attributed to sorafenib require discontinuation of sorafenib.

6.9.2 Unacceptable toxicity related to nivolumab

Treatment with nivolumab should be permanently discontinued for the following toxicities attributed to nivolumab therapy:

1. Any Grade ≥ 2 ophthalmologic irAE such as uveitis causing eye pain or reduction of visual acuity that does not improve to Grade ≤ 1 severity within 14 days of starting topical therapy or requires systemic treatment
2. Any Grade ≥ 3 non-skin, drug-related adverse event that does not downgrade to Grade ≤ 2 within 7 days with optimal medical management including systemic corticosteroids and/or hormone replacement and/or does not downgrade to ≤ Grade 1 or baseline within 14 days, with the following exceptions:
    a. Any Grade ≥ 2 pneumonitis irAE that does not improve to ≤ Grade 1 within 7 days of initiation of maximal supportive care requires discontinuation
    b. Any event of Grade ≥ 3 drug-related uveitis, bronchospasm, pneumonia or pneumonitis, hypersensitivity reaction, or infusion reaction regardless of duration requires discontinuation
    c. Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
    d. Asymptomatic/uncomplicated Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation
3. Hepatotoxicity as evidenced by the following lab values requires discontinuation:

a. AST or ALT > 8 x ULN for > 2 weeks, irrespective of baseline
b. AST or ALT > 15 x ULN irrespective of baseline or duration
c. Total bilirubin > 5 x ULN, irrespective of baseline or duration

4. Any Grade 4 drug-related adverse event or laboratory abnormality requires discontinuation, except for the following events which do not require discontinuation:
    a. Grade 4 neutropenia < 7 days
    b. Grade 4 lymphopenia or leukopenia
    c. Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis including no evidence of pancreatitis on CT or MRI imaging
    d. Isolated Grade 4 electrolyte imbalances or abnormalities that are not associated with clinical sequelae and are corrected with supplementation and appropriate management within 7 days of their onset
    e. Grade 4 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
5. Any dosing delay for treatment-related toxicity lasting > 6 weeks (42 days) with the following exceptions:
    a. Dosing delays up to 12 weeks to allow for prolonged steroid tapers to manage drug-related irAE are allowed with approval from Study Chair.

6.10 Discontinuation of therapy

Protocol treatment will be discontinued if criteria for withdrawal are met (Section 5.2) or for the following reasons:

1. Unacceptable toxicity attributed to either study drug (see Section 6.9)
2. Radiographic disease progression by RECIST 1.1
    - Subjects meeting criteria for treatment beyond progression may continue treatment until progression confirmed on one follow up imaging study, according to Section 6.11 below
3. Complete response after 24 months of protocol treatment

Follow up for protocol endpoints including safety and survival will continue per Section 7.1 after discontinuation.

6.11 Treatment beyond progression

A subject may be granted an exception by Study Chair to continue on treatment with both sorafenib plus nivolumab until the next scheduled scan time point (approximately 8 more weeks, or earlier if clinically indicated by signs or symptoms of progression) if scans within first 6 months of treatment demonstrate radiographic progression by

RECIST 1.1, in order to account for possible delayed responses on immunotherapy, provided the patient meets criteria below:

1. No significant symptoms of progression
2. No evidence of impending complication due to tumor progression (such as radiographic evidence of impending obstruction or mass effect, bleeding, or liver failure) by treating investigator and Study Chair assessment
3. No other criteria for drug discontinuation are met (Section 6.10)

Subjects meeting criteria for treatment beyond progression will have note to file documenting appropriate to continue treatment post progression signed by Study Chair or designee and treating investigator signed in study chart. Subjects will be informed by the treating Investigator and in the main consent form for the study, of the risks and benefits of continuing treatment beyond progression. Subjects will be informed the choice of continuing treatment is ultimately their decision. Treatment with both study drugs will continue according to schedule of procedures for originally assigned study cohort (Section 7.1). If progression is confirmed at a follow up imaging time point, the subject will be discontinued from protocol therapy.

6.12 Drug logistics and accountability

Nivolumab will be stored at the investigational sites in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practices (GMP) requirements and the instructions given by the clinical supplies department of the Institution and will be inaccessible to unauthorized personnel. Sorafenib will be prescribed and provided by local Pharmacy to patients according to standard practice.

6.12.1 Drug accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocolDevelopment for the “Policy and Guidelines for Accountability and Storage of Investigational Agents” or to obtain a copy of the drug accountability form.)

6.12.2 Destruction and return of unused study drug

At the end of the study, unused supplies of nivolumab should be destroyed according to institutional policies. Destruction will be documented in the site Investigational Pharmacy drug accountability records according to institutional Standard Operating Procedures (SOP). The certificates of destruction should be sent to Bayer and BMS for sorafenib and nivolumab, respectively.

6.13 Treatment compliance

An adequate record of receipt, distribution, and return of all study drugs (if applicable) must be kept in the form of a Drug Accountability Form according to site Investigational Pharmacy SOP.

Subject compliance with protocol therapy includes willingness to comply with all aspects of the protocol, including safety and efficacy evaluations. At the discretion of the principal investigator, a subject may be discontinued from the trial for non-compliance with follow-up visits, procedures, or study drug administration.

6.14 Concomitant therapy

All concomitant medications starting within 28 days of first dose and last dose of protocol therapy (including start/stop dates and indication) must be recorded in the subject's source documentation.

6.14.1 Permitted concomitant therapies and medications

1. For patients with active HBV infection or prior HBV exposure, antiviral therapy and monitoring viral load should be administered per institutional standards.
2. Subjects may receive standard of care treatment for any underlying illness or infection.
3. Bisphosphonates or denosumab are permitted as supportive care for bone metastases and/or hypercalcemia at discretion of treating investigator.
4. Steroid and other immunosuppressive therapy is permitted for treatment of treatment-related irAE per Section 6.9.
5. Supportive care on steroid or immunosuppressive therapy such as proton pump inhibitor for gastroprotection or prophylactic antibacterial agents such as trimethoprim-sulfamethoxazole are permitted according to institutional practice.
6. Treatment with non-conventional therapies (e.g., herbs [with the exception of St. John's Wart], acupuncture) and vitamin/mineral supplements is acceptable provided that, in the opinion of the investigator, such treatment will not interfere with the trial endpoints.
7. If AE of neutropenia, anemia, or thrombocytopenia, subjects may receive appropriate supportive care (e.g., transfusion, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). This supportive care should not substitute a recommended dose modification.
8. Caution is recommended when administering substrates of CYP2B6 and CYP2C8 with sorafenib. Systemic exposure to substrates of CYP2B6 and CYP2C8 is expected to increase when these are co-administered with sorafenib.

6.14.2 Prohibited concomitant therapies and medications

1. Concurrent anti-cancer therapy (chemotherapy, radiation therapy, surgery, immunotherapy, biologic therapy, or tumor embolization) other than sorafenib and nivolumab
2. Patients who require palliative radiation for worsening symptoms related to underlying malignancy must be removed from study
    a. Requirement for radiation may be considered a clinical progression event depending on judgment of treating investigator and clinical context
3. Concurrent use of another investigational drug or device therapy (i.e., outside of study treatment) during, or within 4 weeks of trial entry (signing of the informed consent form)
4. Antiviral therapy for active HCV is not allowed during protocol therapy unless approved by the Study Chair due to potential for overlapping toxicity
5. Therapeutic anticoagulation with Vitamin-K antagonists (e.g., warfarin) or with heparins and heparinoids are prohibited
    a. Low dose aspirin (≤ 100 mg daily) is allowed
    b. Prophylactic doses of heparin are allowed with written approval from Study Chair
    c. Requirement for therapeutic anticoagulation requires removal from study

7. Procedures and variables

7.1 Schedule of procedures

The schedule of procedures including allowed time windows are provided in Tables 7.1-1 and 7.1-2 for Part 1: Dose Escalation Cohort and Part 2: Child Pugh B Expansion Cohort.

7.1.1 Schedule for Part 1: Dose Escalation Cohort

Study Event	**Screening**	**Treatment Cycle**						**Safety Follow Up**		**Survival Follow Up**
Time point (Cycle (C) & Day (D) or days after last dose)		**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3+D1**	**C3+D15**	**30 days after last dose (SFUV1)**	**100 days after last dose (SFVU2)**	**Every 3 months after last dose**
Window (days)	**-28 to 1**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**±14**	**±28**	**±28**
Administrative Procedures										
Informed consent & registration on OnCore®	X									
Eligibility determination	X									
Prior & concomitant medication review	X	X	X	X	X	X	X	X	X	
Demographics & medical history	X									
HCC staging & liver disease history	X									
Confirmation of appropriate antiviral therapy if HBV+	X									
Enrollment	X									
Subsequent Therapy								X	X	
Survival status										X
Treatment										
Sorafenib[1]		X	X	X	X	X	X			
Nivolumab[2]		X	X	X	X	X	X			
Clinical procedures and assessments										
AE monitoring	X	X	X	X	X	X	X	X	X	
Compliance with oral study drug		X	X	X	X	X		X		
Vital signs	X	X	X	X	X	X	X	X	X	
ECG	X									

Study Event	**Screening**	**Treatment Cycle**						**Safety Follow Up**		**Survival Follow Up**
Time point (Cycle (C) & Day (D) or days after last dose)		**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3+D1**	**C3+D15**	**30 days after last dose (SFUV1)**	**100 days after last dose (SFVU2)**	**Every 3 months after last dose**
Window (days)	**-28 to 1**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**±14**	**±28**	**±28**
Complete physical examination	X	X	X	X	X	X		X	X	
ECOG	X	X	X	X	X	X		X	X	
Liver function assessment (by Child Pugh Score)	X	X	X	X	X	X		X	X	
Tumor imaging[3]	X[3]					X[3] (every 8 weeks ±14 days)		X[3] (±28 days)		
Laboratory procedures performed at local laboratory										
CBCD, CMP, PT/INR[4]	X	X[5]	X	X	X	X	X	X	X	
T3, fT4, TSH	X	X[5]		X		X		X	X	
Urinalysis	X	X[5]		X		X		X	X	
Pregnancy test in WOCBP only[6]	X	X	X	X	X	X	X	X	X	
Viral hepatitis viral load & serologic testing[7]	X[7]									
AFP[10]	X	X[5]		X		X		X	X	
Archival tumor sample[8]	X							X[8]	X[8]	
PBMC sample[9]	X	X	X	X	X	X (C3D1 & C7D1 only)		X		

Footnotes:

1. Sorafenib dose and schedule (QD or BID) will be determined according to Section 6.2.1 and administered continuously.
2. Nivolumab will be administered at flat dose of 240 mg IV over 30 minutes every 14 days (-2 to +3 days) on D1 and D15 each cycle.
3. Cross-sectional imaging with CT or MRI abdomen plus pelvis (including triphasic/multiphase liver) and CT chest with or without contrast is required at screening and every 8 weeks ±14 days until end of treatment; at SFFUV1, imaging does not need to be repeated if performed within 28 days prior (±28 day window). Imaging may be performed more frequently if clinically indicated to evaluate for progression or toxicity. RECIST 1.1 measurements should be performed by a radiologist or qualified investigator at each time point.
4. Complete blood count and differential (CBCD), metabolic panel including liver and kidney function and electrolytes (see Section 7.3.6 for individual tests required), and PT/INR should be obtained as standard of care safety monitoring before every nivolumab infusion.
5. C1D1 blood tests and urinalysis do not need to be repeated if performed within 3 days before C1D1 during screening.
6. Perform on women of childbearing potential only at screening within 28 days, 24 hours prior to each nivolumab infusion (including C1D1), and at safety follow up visits. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
7. Baseline hepatitis screening should be performed in all patients including HCV Ab, HBcAb total, HBsAg, and in patients positive for HBcAb, HDV Ab. Prior serologic values collected within approximately 2 years may be used for screening if available. If HBcAb and/or HBsAg is positive, HBV DNA level by PCR should be monitored on treatment according to institutional standards (recommended is every 4 weeks according to treating investigator discretion) and patient should be treated with antiviral prophylaxis according

to institutional practice. HCV RNA PCR should be monitored on treatment according to institutional practice. HBV DNA and HCV RNA should be checked and monitored in all cases of hepatotoxicity on treatment according to institutional standard practices.

8. Archival tumor samples (FFPE block when available and/or at least 10 unstained slides of approximately 10 µm thickness plus at least 10 unstained slides of approximately 5 µm thickness plus a paired H&E slide) should be obtained from prior tumor sampling/diagnostic procedure(s) such as prior resection, core biopsy, or cytology/cell button when available. FFPE block or slides should also be obtained from any subsequent tumor sampling which occurs during or after protocol therapy (such as repeat biopsy to confirm progression or palliative metastatectomy surgery). See Appendix 14.8.
9. Blood samples will be obtained in all patients enrolled at UCSF for PBMC immune profiling at Screening, on Day 1 and 15 of Cycles 1 and 2, Day 1 of Cycles 3 and 7, then at SFUV1. See Appendix 14.8.
10. AFP will be performed at screening, all cycles D1, at disease progression, SFUV1, and SFUV2.

7.1.2 Schedule for Part 2: Child Pugh B Expansion Cohort

Study Event	**Screening**	**Treatment Cycle**						**Safety Follow Up**		**Survival Follow Up**
Time point (Cycle (C) & Day (D) or days after last dose)		**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3+D1**	**C3+D15**	**30 days after last dose (SFUV1)**	**100 days after last dose (SFVU2)**	**Every 3 months after last dose**
Window (days)	**-28 to 1**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**±14**	**±28**	**±28**
Administrative Procedures										
Informed consent & registration on OnCore®	X									
Eligibility determination	X									
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	
Demographics & medical history	X									
HCC staging & liver disease history	X									
Confirmation of appropriate antiviral therapy if HBV+	X									
Enrollment	X									
Subsequent Therapy								X	X	
Survival status										X
Treatment										
Sorafenib[1]		X	X	X	X	X	X			
Nivolumab[2]		X	X	X	X	X	X[2]			
Clinical procedures and assessments										
AE monitoring	X	X	X	X	X	X	X	X	X	
Compliance with oral study drug		X	X	X	X	X		X		
ECG	X									
Vital signs	X	X	X	X	X	X	X	X	X	
Complete physical examination	X	X	X	X	X	X		X	X	
ECOG	X	X	X	X	X	X		X	X	
Liver function assessment (by Child Pugh Score)	X	X	X	X	X	X		X	X	

Study Event	Screening	Treatment Cycle						Safety Follow Up		Survival Follow Up
Time point (Cycle (C) & Day (D) or days after last dose)		**C1D1**	**C1D15**	**C2D1**	**C2D15**	**C3+D1**	**C3+D15**	**30 days after last dose (SFUV1)**	**100 days after last dose (SFVU2)**	**Every 3 months after last dose**
Window (days)	**-28 to 1**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**-2 to +3**	**±14**	**±28**	**±28**
Tumor imaging[3]	**X[3]**					**X[3] (every 8 weeks ±14 days)**		**X[3] (±28 days)**		
Laboratory procedures performed at local laboratory										
CBCD, CMP, PT/INR[4]	**X**	**X[5]**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
T3, fT4, TSH	**X**	**X[5]**		**X**		**X**		**X**	**X**	
Urinalysis	**X**	**X[5]**		**X**		**X**		**X**	**X**	
Pregnancy test in WOCBP only[6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Viral hepatitis viral load & serologic testing[7]	**X[7]**									
AFP[11]	**X**	**X[5]**		**X**		**X**		**X**	**X**	
Archival tumor sample[8]	**X**							**X[8]**	**X[9]**	
PBMC sample[9]	**X**	**X[5]**	**X**	**X**	**X**	**X (C3D1 and C7D1 only)**		**X**		

Footnotes:

1. Sorafenib dose and schedule will be MTD from Part 1: Dose Escalation cohort and will be administered continuously. For patients enrolled to Part 2: Arm 1, sorafenib will start on C1D15. For patients enrolled to Part 2: Arm 2, sorafenib will start on C1D1.
2. Nivolumab will be administered at flat dose of 240 mg IV over 30 minutes every 14 days (-2 to +3 days) on D1 and D15 each cycle starting on C1D1. In Part 2 and with Study Chair approval, patients meeting criteria in Section 6.5 may switch to monthly dosing of nivolumab starting on or after C4D1 (-4 to +6 days) provided no uncontrolled or grade >2 immune related toxicity. A note to file must be included in study chart documenting Study Chair or designee approval. For patients who switch to monthly dosing on or after C4D1, the D15 visit and other assessments may be omitted if not clinically-indicated.
3. Cross-sectional imaging with CT or MRI abdomen plus pelvis (including triphasic/multiphase liver) and CT chest with or without contrast is required at screening and every 8 weeks ±14 days until end of treatment; ; at SFFUV1, imaging does not need to be repeated if performed within 28 days prior (±28 day window). Imaging may be performed more frequently if clinically indicated to evaluate for progression or toxicity. RECIST 1.1 measurements should be performed by a radiologist or qualified investigator at each time point.
4. Complete blood count and differential (CBCD), metabolic panel including liver and kidney function and electrolytes (see Section 7.3.6 for individual tests required), and PT/INR should be obtained as standard of care safety monitoring before every nivolumab infusion.
5. C1D1 blood tests and urinalysis do not need to be repeated if performed within 3 days before C1D1 during screening.
6. Perform on women of childbearing potential only at screening within 28 days, 24 hours prior to each nivolumab infusion (including C1D1), and at safety follow up visits. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
7. Baseline hepatitis screening should be performed in all patients including HCV Ab, HBcAb total, HBsAg, and, in patients positive for HBcAb, HDV Ab. Prior serologic values collected within approximately 2 years may be used for screening if available. If HBcAb and/or HBsAg is positive, HBV DNA level by PCR should be monitored on treatment according to institutional standards (recommended is every 4 weeks according to treating investigator discretion) and patient should be treated with antiviral prophylaxis according to institutional practice. HCV RNA PCR should be monitored on treatment according to institutional practice. HBV DNA and HCV RNA should be checked and monitored in all cases of hepatotoxicity on treatment according to institutional standard practices.
8. Archival tumor samples (FFPE block when available and/or at least 10 unstained slides of approximately 10 µm thickness and at least 10 unstained slides of approximately 5 µm thickness plus a paired H&E slide) should be obtained from prior tumor sampling/diagnostic procedure(s) such as prior resection, core biopsy, or cytology/cell button when

available. FFPE block or slides should also be obtained from any subsequent tumor sampling which occurs during or after protocol therapy (such as repeat biopsy to confirm progression or palliative metastatectomy surgery). See Appendix 14.8.

9. Blood samples will be obtained in UCSF patients only for PBMC immune profiling at Screening, on Day 1 and 15 of Cycles 1 and 2, Day 1 of Cycles 3 and 7, then at SFUV1. See Appendix 14.8.
10. Removed.
11. AFP will be performed at screening, all cycles D1, at disease progression, SFVU1, and SFVU2.

7.2 Administrative procedures and data collection

7.2.1 Informed consent

The treating investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.2.1 Registration

All patients who consent will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS).

7.2.1.1 Sub-site registration

The sub-site must notify the UCSF Clinical Research Coordinator (CRC) and Study Chair of patient consent(s) at sub-site within 3 business days of consent. A study ID will be provided as confirmation of receipt which will enable registration on OnCore®.

7.2.2 Eligibility determination

All inclusion and exclusion criteria (see Section 5.1) will be reviewed and signed off on by the investigator or qualified designee at study site, and site study coordinator to ensure that the subject qualifies for the trial. For patients in screening at sub-site, the UCSF Study Chair or designee must review and confirm eligibility to prior to enrollment (see Section 7.2.6.1).

7.2.3 Prior and concomitant medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Prior treatments for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

The investigator or qualified designee will record medication, if any, taken by the subject during the trial treatment until approximately 100 days after last dose of study drug at the Safety Follow Up Visits (SFUV1 and SFUV2). All medications related to reportable SAEs should be recorded.

7.2.4 Demographics and medical history

Standard demographic information (e.g. age, gender, race/ethnicity) will be collected from medical records. Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication

- Start before signing of the informed consent
- Considered relevant to the study.

Detailed instructions on the differentiation between medical history and adverse events can be found in Section 7.4.1.

7.2.5 HCC staging and disease history

The investigator or qualified designee will obtain prior and current details regarding disease status, including HCC stage at enrollment, stage at diagnosis, diagnostic test(s), and site(s) of disease. Staging will be captured by both American Joint Committee on Cancer (AJCC) TNM staging (Appendix 14.4) and Barcelona Clinic Liver Cancer (BCLC) staging (Appendix 14.5).

7.2.5.1 **Prior treatments for HCC**

The investigator or qualified designee will review all prior cancer treatments including surgery, ablative treatments, arterial therapies (such as transarterial chemoembolization (TACE) or transarterial radioembolization (TARE)), or radiation. No prior systemic therapy for HCC is permitted by this protocol.

7.2.5.2 **Liver disease history**

The investigator or qualified designee will review liver disease history including risk factors for HCC (including viral hepatitis, alcohol use, non-alcoholic steatohepatitis or fatty liver disease diagnosis or risk factors, cirrhosis/fibrosis, autoimmune disease, any other prior liver injury). History of and any new episodes of esophageal varices, ascites, or encephalopathy will be documented at baseline, during treatment, and until the SFUV.

7.2.5.3 **Subsequent therapy**

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment until approximately 100 days after last dose of protocol therapy at the SFUV1 and SFVU2. Once new anti-cancer therapy has been initiated or if transition to palliative/end of life care such as Hospice enrollment occurs, the subject will transition to the Survival Follow-Up Phase.

7.2.6 Enrollment

Once screening is completed, eligibility documents and checklist for all patients will be reviewed by and confirmed by investigator and/or Study Chair, CRC, and lead or senior CRC following UCSF HDFCCC SOP. Once eligibility is confirmed, approval to treat documentation indicating Cohort and dose level assignment as applicable will be provided to treating investigator and placed in study chart as confirmation of enrollment to proceed with protocol therapy.

7.2.6.1 **Sub-site enrollment**

The sub-site coordinator will send by secure e-mail or fax de-identified HIPAA-compliant copies of all consent and screening source documents to UCSF study team for eligibility confirmation. Once eligibility is confirmed by the Study Chair or designee, a document of approval to treat indicating Cohort and dose level assignment as applicable will be provided by secure e-mail by the UCSF CRC to the sub-site coordinator and treating investigator as confirmation of enrollment to proceed with protocol therapy.

7.3 Clinical procedures and assessments

7.3.1 Adverse event (AE) monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Schedule of Procedures (Section 7.1) and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study according to NCI CTCAE Version 4.03. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. Please refer to Section 7.4 for further information on AE assessment and reporting.

7.3.2 Compliance with oral study drug

Patients will be provided a sorafenib drug diary to record time and dose of sorafenib administration each cycle (Appendix 14.7).

7.3.3 Vital signs

The investigator or qualified designee will obtain vital signs at the time points specified in the Schedule of Procedures (Section 7.1). Vital signs should include temperature, pulse, respiratory rate, oxygen saturation (pulse oximetry), weight and blood pressure. Height will be measured at screening only.

7.3.4 Complete physical examination

The investigator or qualified designee will perform a complete physical examination according to institutional practice for the management and monitoring of patients with liver cancers. Complete physical exams are required at screening, C1D1, C1D15, C2D1, C2D15, C3D1, and every D1 after Cycle 3. They are also required at Safety Follow-up 30 days and 100 days after lase dose (SFUV1 and SFVU2). Clinically significant abnormal findings during Screening should be recorded as medical history.

7.3.5 Eastern Cooperative Oncology Group (ECOG) performance scale

The investigator or qualified designee will assess ECOG status (see Appendix 14.2) at the time points specified in the Schedule of Procedures (Section 7.1).

7.3.6 Liver function assessment

The investigator or qualified designee will assess liver function by Child Pugh score (see Appendix 14.3) at the time points specified in the Schedule of Procedures (Section 7.1).

7.3.7 Tumor imaging and response assessment

Cross-sectional imaging with CT (preferred) or MRI abdomen plus pelvis and CT chest with/without or without contrast is required at screening then every 8 weeks (±14 days) until end of treatment. Multiphase/triphasic liver imaging should be included as appropriate. Additional baseline imaging such as PET scan, bone scan, or MRI brain are only required if clinically indicated by symptoms and/or to assess known bone metastases or other sites of known metastatic disease. All baseline evaluations will be performed as close as possible to the beginning of treatment and ≤ approximately 28 days before C1D1. The same imaging modality/modalities should be used if possible throughout study unless there is a clinical indication to use a different modality (i.e. based upon Radiology recommendation to better assess a target lesion, an event of new contrast allergy, etc.). RECIST 1.1 measurements will be performed by a radiologist or qualified investigator.

7.3.8 Laboratory procedures/assessments

The specific laboratory procedures/assessments to be performed in this trial are provided in Table 7.3.6-1 below, at time points listed in Schedule of Procedures (Section 7.1). Scheduled laboratory procedures and assessments should be performed at the study site of treatment.

Table 7.3.6-1 Laboratory procedures and assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	Urine β-human chorionic gonadotropin†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Thyroid stimulating hormone (TSH)
Red Blood Cell Count	Creatinine	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon dioxide (C02 or bicarbonate)	Urine pregnancy test †	Free thyroxine (T4)
	Calcium		AFP tumor marker
	Chloride		Hepatitis B or C viral load and serology (including Hepatitis D) as clinically indicated (see Tables 7.1-1 and 7.1-2 footnote 7)
	Glucose		
	Phosphorus		**Blood samples for correlative studies***

Table 7.3.6-1 Laboratory procedures and assessments

Hematology	Chemistry	Urinalysis	Other
	Potassium		**Archival tumor sample accessioning***
	Sodium		
	Magnesium		
	Total bilirubin		
	Direct bilirubin		
	Blood urea nitrogen (BUN)		
† Perform urine pregnancy test on WOCBP only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test is required. *See Section 7.3.7 and Appendix 14.8 for further information on research sample collection.			

7.3.9 Tumor and blood sample collection and banking for correlative analyses

Archival tumor samples for all patients and peripheral blood samples for patients enrolled at UCSF will be obtained and stored for planned future exploratory and correlative analyses (see Sections 1.6 and 2.3) which will be performed in batch after completion of study and pending funding.

7.3.9.1 Archival tumor sample collection

In all patients, left-over diagnostic tumor block and/or slides from any tumor sampling procedure(s) (e.g. biopsy, fine needle aspiration, and/or resection specimens) performed prior to enrollment, during study treatment, and/or after treatment discontinuation due to progression will be obtained to determine tumor PD-L1 expression status, to characterize tumor immune infiltrates/T cell subsets, and (optional for UCSF patients only) to bank for future correlative analyses as part of the UCSF Hepatobiliary Tissue Bank and Registry (CC#124512) as a companion protocol to this study.

Formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks will be accessioned whenever available. In addition to blocks or if a block is not available, at least 10 unstained slides (prefer 10 µm) plus 1 H&E slide from a tumor tissue block may be accessioned. Corresponding pathology reports from initial diagnosis and/or subsequent tumor sampling will be obtained. Specimens will be obtained from the Pathology Department for banking as soon as possible after consent and/or occurrence of post-enrollment tumor sampling and stored in the UCSF Biorepository. Correlative analyses using archival tissue samples will be performed in batch at completion of study and pending funding. See Appendix 14.8 for correlative specimen procurement and handling instructions.

7.3.9.2 Peripheral blood mononuclear cell (PBMC) collection

In all patients enrolled at UCSF, approximately 60 mL of whole blood will be collected into green top tubes (e.g. six 10 cc tubes filled approximately to 10 mL) at the time

points listed in the Schedule of Procedures (Section 7.1). The tubes will be delivered directly to the UCSF Cancer Immunotherapy Lab for PBMC isolation then freezing for future analysis in batch at end of study and pending funding. See Appendix 14.8 for correlative specimen procurement and handling instructions.

7.3.9.3 **Optional specimen banking**

For patients enrolled at UCSF who consent to optional specimen banking as part of companion protocol CC#124512, all left-over blood and/or tumor samples will be banked under the UCSF Hepatobiliary Tissue Bank and Registry protocol. See Appendix 14.8 for correlative specimen procurement and handling instructions.

7.3.10 Electrocardiogram

A baseline electrocardiogram (ECG) should be obtained during screening at the study site per Section 7.1 in all patients.

7.4 Assessing and reporting adverse events (AE)

All subjects who receive at least one dose of study treatment will be evaluable for safety from the time of informed consent until 100 days after last dose of protocol therapy or the start of a new anti-cancer therapy after study discontinuation, whichever is earlier. Any serious adverse events (SAE) occurring later than 100 days after the last dose of protocol therapy or after start of new anti-cancer therapy also should be recorded and reported if assessed as at least possibly related to study drug or a protocol-specified procedure. All observations pertinent to the safety of the study treatment will be recorded and included in the final report.

Safety variables include the following: AEs, laboratory changes (complete blood counts, electrolytes, chemistry, and coagulation) if determined clinically significant by treating investigator and/or Study Chair, changes in vital signs (blood pressure, heart rate, respiratory rate, and temperature), and in some instances, changes in imaging findings if indicative of a safety event.

All AEs whether considered drug-related or not, will be recorded in case report forms in the OnCore® CTMS including Grade, attribution to one or both study drugs, other attribution(s), start/stop dates, and whether serious and/or unexpected. For all events, the relationship to treatment and the intensity of the event will be determined by the investigator. This trial will use the NCI CTCAE v.4.03 (https://ctep.cancer.gov/) for assessment of toxicity and SAE reporting with regard to toxicity grade. Investigators should refer to the Safety Information section of the current IB for sorafenib and nivolumab, including the DCSI (development core safety information), for the expected side effects of the study drugs.

7.4.1 AE and SAE definitions

7.4.1.1 Definition of adverse event (AE)

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding determined to be of clinical significance by the treating investigator or Study Chair), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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

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

Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints). Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic rhinitis). Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

7.4.1.2 Definition of serious adverse event (SAE)

An SAE is classified as any AE that, at any dose, meets any of the following criteria:

1. Results in death.
2. Is life-threatening.
    a. The term ‘life-threatening’ in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
    a. A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
    b. The admission results in a hospital stay of less than 12 hours.
    c. The admission is pre-planned. (i.e., elective or scheduled surgery

arranged prior to the start of the study)

d. The admission is not associated with an AE. (e.g., social hospitalization for purposes of respite care).

e. However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

4. Results in persistent or significant disability or incapacity.
    a. Disability means a substantial disruption of a person's ability to conduct normal life's functions.

5. Is a congenital anomaly or birth defect.

6. Grade 3 or 4 hypersensitivity or infusion reaction to nivolumab.

7. Is another medically important serious event as judged by the investigator (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)

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

9. Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

10. Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

7.4.2 Reporting of SAE to Bayer

All SAEs occurring from date of informed consent until 100 days after last dose of protocol therapy regardless of attribution should be reported to Bayer within 24 business hours/1 business day using a MedWatch Form 3500A (which can be accessed at http://www.accessdata.fda.gov/scripts/medwatch/ and in Appendix 14.9), using one of the mechanisms below. Any serious adverse events (SAE) occurring later than 100

days after the last dose of protocol therapy also should be recorded and reported if assessed as at least possibly related to study drug or a protocol-specified procedure.

Bayer SAE Electronic Mailbox: [redacted]@bayer.com

Bayer SAE Facsimile: [redacted]

Bayer USPS Address: Global Pharmacovigilance - USA
Bayer Corporation
[redacted]

Reports for all Bayer products can also be phoned in via the Clinical Communications Dept.:

Bayer SAE Phone: [redacted] (Medical Communications)

7.4.3 Reporting of SAE to BMS for protocol versions 1.0-3.0

For patients enrolled to Part 1 and Part 2 under protocol versions 1.0-3.0, all SAEs occurring from date of informed consent until 100 days after last dose of protocol therapy regardless of attribution should be reported to BMS within 24 business hours/1 business day using a MedWatch Form 3500A (which can be accessed at http://www.accessdata.fda.gov/scripts/medwatch/ and in Appendix 14.9), using one of the mechanisms below. Any serious adverse events (SAE) occurring later than 100 days after the last dose of protocol therapy also should be recorded and reported if assessed as at least possibly related to study drug or a protocol-specified procedure.

BMS SAE Email Address: [redacted]@BMS.com

BMS SAE Facsimile Number: [redacted]

Starting with protocol version 4.0 for patients enrolled to Part 2, nivolumab will be sourced as a standard of care therapy for advanced HCC in setting of Child Pugh B liver dysfunction and will not be provided by BMS. SAE reporting to BMS is not required for patients receiving treatment under protocol version 4.0 or later versions.

7.4.3.1 SAE Reconciliation Reports

The Study Chair or designee at UCSF will reconcile the clinical database SAE cases at all study sites (case level only) transmitted to BMS Global Pharmacovigilance [redacted]) using the reporting form in Appendix 14.10. Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary, or until activation of protocol version 4.0. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to [redacted] The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

7.4.4 SAE follow up reports

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 business hours/1 business day to both Bayer (for patients enrolled to both Part 1 and 2) and BMS (for patients enrolled prior to protocol version 4.0 and not required after activation of protocol version 4.0) using the same procedures used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

7.4.5 IND safety reporting

UCSF will report to the FDA all IND reportable events occurring in patients enrolled on this study (at UCSF or sub-site) using FDA Medwatch Form 3500A (which can be accessed at http://www.accessdata.fda.gov/scripts/medwatch/ and in Appendix 14.9). Reportable events must meet the definition in Federal Regulations (21 CFR §312.32):

1. Suspected adverse reaction (defined as a reasonable possibility that the investigational agent caused the adverse event)
2. Unexpected (not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed)
3. Serious (as defined in Section 7.4.1.2)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report. The timeline for submitting an IND safety report to FDA is no later than 15 calendar days after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)). Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than 7 calendar days after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

A copy of all 15 Day Reports and Annual Progress Reports will be submitted as required by FDA.

The Study Chair or designee will cross reference this submission according to local regulations to the Bayer and/or BMS Investigational Compound Number (IND) at the time of submission, based upon investigator attribution of causality. Additionally, Study Chair or designee will submit a copy of these reports to Bayer and BMS at the time of submission to FDA.

7.4.6 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) for each drug. Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IBs. If relevant new

safety information is identified, the information will be integrated into an update of the corresponding IB and distributed to any participating site(s).

The expectedness of AEs and SAEs will be determined locally by the treating investigator and Study Chair or designee. For reportable SAE, expectedness will also be assessed by Bayer and BMS according to the applicable reference document and according to all local regulations.

7.4.7 Pregnancies

The investigator must report to Bayer and BMS any pregnancy occurring in a study subject, or in his partner, during the subject's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study subject, the outcome of the pregnancy should be followed up carefully, and any abnormal outcome of the mother or the child should be reported.

For the pregnancy of a study subject's partner, all efforts should be made to obtain similar information on course and outcome, subject to the partner's consent.

For any reports of pregnancy occurring in study subject or WOCBP partner, a Medwatch form (Appendix 14.9) should be used for reporting as an SAE.

8. Statistical methods and determination of sample size

8.1 Analysis sets

8.1.1 DLT population (Part 1)

Subjects must receive 2 doses of nivolumab and at least 75% of sorafenib doses within 28 days (1 cycle), or experience a qualifying DLT event (Section 6.2.3), to be evaluable for DLT. Patients enrolled to Part 1 who are determined ineligible after enrollment and/or who are not evaluable for the endpoint of DLT will be replaced (see Section 5.2.2).

8.1.2 Safety population (Parts 1 and 2)

The safety population will include all enrolled patients who receive at least one dose each of sorafenib and nivolumab and have the potential to complete 1 cycle (28 days) of safety assessments. All patients will be evaluable for toxicity and safety assessment from the time of their first treatment with the investigational combination. Patients who are determined ineligible after enrollment or who are not evaluable for safety (e.g. due to withdrawal of consent or discontinuation due to complications of HCC or underlying liver disease assessed as not related to tumor progression and not treatment-related

toxicity before completing 1 cycle) will not be included in safety analyses (see Section 5.2.2).

8.1.3 Efficacy population (Parts 1 and 2)

The evaluable population for the secondary efficacy endpoint of ORR will include all patients have received at least one complete cycle of therapy (4 weeks) and have had restaging imaging for response assessment (Section 7.3.5) or been removed for clinical progression. Imaging to confirm progression should be obtained if possible. Patients who are determined ineligible after enrollment or who do not complete at least 1 cycle of therapy (4 weeks) and who do not have a qualifying progression event (radiographic or clinical) (e.g. due to withdrawal of consent or discontinuation due to complications of HCC or underlying liver disease assessed as not related to tumor progression and not treatment-related toxicity) will not be included in efficacy analyses (see Section 5.2.2).

8.2 Statistical and analytical plans

8.2.1 Primary endpoints

Primary and secondary endpoints will be measured in evaluable patients as defined in Section 8.1.

8.2.1.1 Part 1: Dose Escalation Cohort primary endpoint

For Part 1, the primary endpoint of MTD will be determined according to Section 6.2.3.

8.2.1.2 Part 2: Child Pugh B Expansion Cohort primary endpoint

For Part 2: Child Pugh B Expansion Cohort, the primary endpoint is safety of the combination in patients with Child Pugh B liver function as measured by rate of grade ≥3 AE (CTCAE v. 4.03) assessed as at least possibly related to sorafenib, nivolumab, or the combination of therapies. Adverse events will be graded using NCI CTCAE v.4.03 (https://ctep.cancer.gov/). Relationship to sorafenib, nivolumab, or combination will be adjudicated by the treating investigator and/or Study Chair.

This is a pilot study. For Part 2, an acceptable rate of grade ≥3 treatment-related AE would be ≤ 50% based upon rate of treatment-related grade ≥3 AE of 24.5% of Child Pugh B7-8 HCC patients treated with nivolumab in the CheckMate 040 Child Pugh B cohort,[38] and 28% of Child Pugh B7-9 HCC patients treated with nivolumab in a retrospective institutional cohort,[39] along with rates of grade 3-4 treatment-related AE of 30-36% in Child Pugh B7-9 HCC in the GIDEON registry.[40]

With an expected sample size of 12 patients with Child Pugh B7-9 HCC treated in Part 2, the 95% confidence interval (CI) for determining the rate of grade ≥3 treatment-related AE if the actual rate is 50% will be (0.22, 0.78). If the actual rates are 30%, 40% or 60%, the 95% CI will be (0.07, 0.60), (0.14, 0.70) and (0.30, 0.86) respectively.

If the Child Pugh B Expansion Cohort end of enrollment date of 30 April 2022 is reached before completion of enrollment of n=12, rates of grade ≥3 treatment-related AE will be described along with 95% CI according to the sample size accrued at time of discontinuation (Table 8.2.1-1).

Table 8.2.1-1. Sample Size of Child Pugh B Expansion Cohort for Estimating Rate of Grade ≥3 TRAE.

Sample size in Child Pugh B Expansion Cohort	Actual rate of Grade ≥3 TRAE	95% CI
6	30%	0.0, 0.71
	40%	0.0, 0.71
	50%	0.10, 0.90
	60%	0.30, 1.0
8	30%	0.0, 0.55
	40%	0.0, 0.71
	50%	0.15, 0.85
	60%	0.29, 0.96
10	30%	0.02, 0.58
	40%	0.10, 0.71
	50%	0.19, 0.81
	60%	0.30, 0.90
12	30%	0.07, 0.60
	40%	0.14, 0.70
	50%	0.22, 0.78
	60%	0.30, 0.86

8.2.2 Secondary endpoints

For secondary endpoints, due to the small sample size in this pilot study, descriptive statistics with mean and 95% confidence intervals will be used. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, min and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. For comparison between subgroups, ANOVA and t-tests will be used when appropriate to determine the association of the efficacy endpoints and specific biomarkers.

8.2.2.1 **Safety and tolerability**

Safety events will be classified using NCI CTCAE v.4.03 (https://ctep.cancer.gov/).

Overall rates of AE and SAE will be summarized based on frequency and proportion of total subjects, by system organ class, preferred term, Grade, and investigator-assessed relationship to sorafenib, nivolumab, or the combination. Dose reductions, dose delays, and discontinuations for toxicity will be summarized.

8.2.2.2 **Rate of irAE for combination overall and in Child Pugh B patients**

Safety events assessed by treating investigator and/or Study Chair as being at least possibly Immune-related on nivolumab (irAE) will be summarized based on frequency and proportion of total subjects, by system organ class and preferred term as for overall safety. Rate of irAE in Child Pugh B patients in Part 2 will also be summarized.

8.2.2.3 **ORR by RECIST 1.1 for overall study and in Parts 1 and 2 individually**

ORR is a key secondary endpoint and will be based on RECIST 1.1[5] as assessed by local radiographic review. ORR will be analyzed for all efficacy-evaluable patients (Parts 1 and 2 combined) as well as for Part 1 and Part 2 individually. ORR defined as the proportion of subjects with RECIST 1.1-measurable disease at study entry (which is required for eligibility) who have a CR or partial response (PR) using RECIST 1.1 at any time during the main study. Subjects with measurable disease at study entry who have unknown or missing response information will be treated as non-responders.

The ORR of sorafenib was approximately 2% in SHARP trial,[2] and the ORR of nivolumab as monotherapy was 10.2% in Child Pugh B7-8 patients treated with nivolumab in the Child Pugh B cohort of CheckMate 040.[38] The ORR of nivolumab in Child Pugh A patients treated with nivolumab as 1st line therapy in CheckMate 459 was 15%.[45] Thus, an ORR of at least 15% for the combination of sorafenib plus nivolumab in this study would be an encouraging signal of efficacy, if accompanied by acceptable safety in Child Pugh B patients in Part 2 as defined above, and would warrant consideration of a larger study.

For the overall study population, a sample size of 24 evaluable patients from Parts 1 and 2 combined T will have 83% power with 1-sided alpha of 5% to determine true ORR >15%, using Chi-square tests with 1-sided alpha of 5%.

8.2.2.4 **Duration of response (DOR), PFS, and OS for Child Pugh B Expansion Cohort and overall study population**

In subjects who achieve PR or CR, DOR is defined as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death. For all patients, PFS will be calculated in months from date of first dose of protocol therapy to date of first documented radiographic and/or clinical disease progression or

death from any cause. For patients discontinued from study for other reasons than progression or death (see Section 5.2), PFS will be censored at the date last known to be progression-free. OS is defined as the time from the date of first dose of protocol therapy to the date of death due to any cause. Censoring will be performed using the date of last known contact for those who are alive at the time of analysis.

Median DOR, median PFS and OS will be summarized overall and according to treatment group. Kaplan-Meier medians and quartiles may be provided if data warrant. If data warrant, Kaplan-Meier quartile estimates along with the 95% CI will be calculated. Descriptive summaries including swim lane plots may also be generated depending on results.

8.2.3 Exploratory endpoints

For exploratory endpoints, due to the small sample size in the study, descriptive statistics with mean and 95% confidence intervals will be used. Depending on funding availability, we plan to explore immunologic and genomic biomarkers (including PBMC T cell subsets and TCR frequency and diversity, tumor immune subset composition and immune infiltrates) for relationships to clinical features including etiology of liver disease, baseline liver function, and to the primary and secondary efficacy endpoints. No type I error will be adjusted for multiple endpoints. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, min and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. For comparison between subgroups, ANOVA and t-tests will be used when appropriate to determine the association of the efficacy endpoints and the specific biomarkers. For association between biomarkers, Spearman correlations will be calculated to determine the significance of the association between the biomarkers of interest. A selection of planned analyses is described further below.

8.2.3.1 PBMC immune cell subset frequencies and relationship to treatment and clinical outcomes

Serial blood samples for PBMC analyses will be collected at time points in Section 7.1, Schedule of procedures. Immune cell subsets will be measured using flow cytometry as has been previously described, or similar updated methods.[29,30] PBMC analyses for all patients will be performed in the UCSF CIL.

Baseline levels of individual PBMC T cell and other immune cell subset components as well as change in levels on combination treatment will be explored for relationship with ORR, baseline liver function, as well as secondary efficacy endpoints (including PFS, DOR, OS) to determine if there is an association using Fisher's Exact tests.

8.2.3.2 **PBMC T cell receptor (TCR) clonotype frequency and diversity and relationship to treatment and clinical outcomes**

If funds are available, the frequency of individual TCR clonotypes and the diversity of overall TCR clonotype repertoire from PBMC samples will be measured by next-generation sequencing as has been previously described or by a similar, updated methodology.[31] PBMC analyses for patients enrolled at UCSF will be performed in UCSF CIL.

The frequency of TCR clonotypes with identical sequences[31] will be calculated by dividing the number of identical sequence reads by the total number of sequencing reads for that sample. TCR repertoire diversity will be calculated as the number of unique clonotypes comprising the top 25% of cumulative reads sorted by abundance.[31] Baseline frequency and diversity as well as changes on combination treatment will be explored for relationship with ORR, baseline liver function, as well as secondary efficacy endpoints using Fisher's Exact tests.

PBMC TCR clonotype diversity/frequency will also be described at baseline and after starting combination therapy in Part 2 to characterize the time course of these effects and to better understand the relative impact of each study drug.

8.2.3.3 **Tumor immune infiltrates, T cell subsets, and TCR profiling**

The presence and composition of tumor immune infiltrates including T cell subsets in pretreatment archival tumor sample will be explored for relationship with ORR, baseline liver function, as well as secondary efficacy endpoints (including PFS, DOR, OS, AFP response) and with tumor PD-L1 status by IHC to determine if there is a relationship using Fisher's Exact tests. Descriptive comparisons between primary and metastatic site samples and according to tumor location (e.g. liver vs. non-liver) or etiology (e.g. viral vs. nonviral), will be performed between subsets in the overall study depending on sample availability. TCR frequency and diversity may be analyzed depending on sample adequacy.

Any leftover archival material from any other tumor samples obtained on treatment or post-treatment for diagnostic purposes (e.g. if patient is determined to require palliative resection or need a biopsy to confirm progression) may be accessioned and analyzed for immune infiltration, T cell subsets, and TCR profile depending on quantity of evaluable tumor tissue available.

Tumor tissue immune cell profiling and TCR analyses will be performed in UCSF CIL depending on funding adequacy.

8.2.3.4 **Tumor and immune cell PD-L1 expression**

Tumor and immune cell PD-L1 expression will be tested in batch after completion of enrollment. The proportion of subjects with archival tumor samples positive for PD-L1 or

PD-L1 and CD-45 expression by IHC will be reported along with 95% CI. For subjects with more than one tumor sample available for testing, designation as positive for PD-L1 expression will be based upon ≥1 positive sample. Concordance and rates of positivity between primary and metastatic site, tumor location (e.g. liver vs. non-liver), etiology (e.g. viral vs. nonviral), and pre-treatment, , and post-treatment samples (if available) will be described individually due to expectation of small subset/paired sample sizes. PD-L1 expression status in tumor and immune cells will be explored for association with ORR, PFS, and OS.

Tumor and IC PD-L1/CD45 analyses will be performed in UCSF CIL or other laboratory approved by Study Chair dependent upon funding and sample availability.

8.2.3.5 **AFP response**

Among patients with baseline AFP ≥ 20 ng/mL, baseline AFP levels (using various cut points from literature) will be explored for association with ORR, PFS, and OS using Fisher's Exact tests or by Wilcoxon Rank-Sum test. Changes in levels on therapy will be measured as an increase by ≥ 20% and ≥ 50% from baseline, stable value within 20% and 50% of baseline, or decrease by ≥ 20% and ≥ 50% from baseline. The changes in level will be used to evaluate the predictive value for ORR, PFS, or OS.

8.3 Planned interim analyses

8.3.1 Part 1: Dose Escalation Cohort DLT analyses

In Part 1, a standard 3+3 design for dose escalation and expansion decisions will be used as described above.

8.4 Determination of sample size

The total sample size will be 6-24 patients for Parts 1 and 2 combined.

8.4.1 Part 1: Dose Escalation Cohort sample size

It is estimated that 6-12 patients will be enrolled to Part 1 following 3+3 dose escalation rules in Section 6.2.2.

8.4.2 Part 2: Child Pugh B Expansion Cohort sample size

The Part 2 expected evaluable sample size is n=12 patients.

9. Data handling and quality assurance

9.1 Pre-study documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigator will have written and dated approval from the Institutional Review Board for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

9.2 Institutional Review Board approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (UCSF Institutional Review Board). Prior to obtaining IRB approval, the protocol must be approved by the Helen Diller Family Comprehensive Cancer Center Gastrointestinal Oncology Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

9.3 Informed consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4 Changes in the protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB within writing within five (5) working days after implementation. The Study Chair and the UCSF study team will be responsible for updating any participating sites.

9.5 Handling and documentation of clinical supplies

The UCSF Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The Principal Investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Principal Investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

9.6 Case report forms (CRFs)

The Principal Investigator and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the study calendar, using single data entry with a secure access account. The CRC will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and OnCore data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the treating investigator.

9.7 Oversight and monitoring plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP) for multi-center trials (Appendix 14.11). The DSMC will routinely review all adverse events and suspected adverse reactions considered “serious”. The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 14.11, Data and Safety Monitoring Plan for additional information.

9.8 Multicenter communication

The UCSF Coordinating Center provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate, at weekly conference calls with the participating sites for Phase I dose escalation studies prior to each cohort escalation and at the completion of each cohort or more frequently as needed to discuss risk assessment. The following issues will be discussed as appropriate:

- Enrollment information
- Cohort updates (i.e. DLTs) and enrollment status
- Adverse events (i.e. new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

9.9 Record keeping and record retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends. The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and

regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

9.10 Coordinating Center documentation of distribution

It is the responsibility of the Study Chair to maintain adequate files documenting the distribution of study documents as well as their receipt (when possible). The HDFCCC recommends that the Study Chair maintain a correspondence file and log for each segment of distribution (e.g., FDA, drug manufacturer, participating sites, etc.).

Correspondence file: should contain copies (paper or electronic) of all protocol versions, cover letters, amendment outlines (summary of changes), etc., along with distribution documentation and (when available) documentation of receipt.

Correspondence log: should be a brief list of all documents distributed including the date sent, recipient(s), and (if available) a tracking number and date received.

At a minimum, the Study Chair must keep documentation of when and to whom the protocol, its updates and safety information are distributed.

9.11 Regulatory documentation

Prior to implementing this protocol at UCSF or any participating site, the protocol, informed consent form, and any other information pertaining to participants must be approved by the UCSF IRB. Prior to implementing this protocol at the participating sites, approval of the UCSF IRB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to UCSF HDFCCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, informed consent form, and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals.

Upon receipt of the required documents, UCSF HDFCCC will formally contact the site and grant permission to proceed with enrollment.

9.12 Audit and inspection

Inspections by regulatory health authority representatives i.e. FDA and IEC(s)/IRB(s) are possible. The investigator should notify Bayer and BMS immediately of any such inspection.

10. Protection of Human Subjects

10.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all participants involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the participant's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

10.2 Protection of Privacy

Participants will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the participant's medical records, and each participant will receive a copy of the signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

11. Premature termination of the study

The investigator has the right to close his/her center at any time for reasons such as listed below.

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of any interim analysis
  - Results of parallel clinical studies

- Results of parallel animal studies
  (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- In case of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 5.3.

12. Ethical and legal aspects

12.1 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the investigator abide by Good Clinical Practice (GCP) guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the EC/IRB approval must be obtained and also forwarded to Bayer.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by the investigator without discussion and agreement by Bayer. However, the investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/Bayer approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution. Any deviations from the protocol must be explained and documented by the investigator.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and properly documented.

12.2 Subject information and consent

Each subject or legal representative or proxy consenter will have ample time and opportunity to ask questions and will be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.

Only if the subject or legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The subject or legal representative or proxy consenter will receive a copy of the signed and dated form. The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

The informed consent form and any other written information provided to subjects or legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject or legal representative or proxy consenter of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IRB's approval in advance of use.

12.3 Publication policy

The Principal Investigator will ensure that the information regarding the study be publicly available on the internet at www.clinicaltrials.gov.

12.4 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

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HEPATOCELLULAR CARCINOMA (AHCC), European Society of Medical Oncology. Barcelona, Spain, 2019

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APPENDIX 1: RECIST 1.1

Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

APPENDIX 2: ECOG performance status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

APPENDIX 3: Child Pugh score

The Child Pugh score will be calculated using the modified Child Pugh scoring system[46] at time points specified in Section 7.1, Schedule of procedures. Ascites should be assessed by clinical examination (rather than radiographic findings). Encephalopathy and ascites are considered as present (i.e. at least 2 points) in any patient taking medications for these conditions (e.g., lactulose, diuretics) even if well-controlled at the time of Child Pugh score assessment.

	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	none	mild/moderate (diuretic-responsive)	tense (diuretic-refractory)
Total bilirubin, mg/dL	< 2	2-3	> 3
Albumin, g/dL	> 3.5	2.8-3.5	< 2.8
Prothrombin time			
Seconds over control	1–3	4–6	> 6
or			
INR	< 1.7	1.7-2.3	> 2.3
Encephalopathy	none	Grade 1-2 (or precipitant-induced)	Grade 3-4 (chronic)

Child-Pugh score (A, B, or C) based on total score from the above point assignments:

Grade	**Points**	**1-year survival**	**2-year survival**
A: well-compensated disease	5–6	100%	85%
B: significant functional compromise	7–9	80%	60%
C: decompensated disease	10–15	45%	35%

APPENDIX 4: AJCC staging for HCC

AJCC stage (8th Ed.) will be determined based upon review of imaging and other clinical data from date of radiographic (by diagnostic imaging) or histologic diagnosis, whichever is earliest. AJCC stage will also be determined at date of enrollment. AJCC stage will be recorded in CRFs on OnCore.

American Joint Committee on Cancer (AJCC)
TNM Staging for Perihilar Bile Duct Tumors (8th ed., 2017)

***Table 7.* Definitions for T, N, M**

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*/high-grade dysplasia
T1	Tumor confined to the bile duct, with extension up to the muscle layer or fibrous tissue
T2	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue, or tumor invades adjacent hepatic parenchyma
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally, or the common hepatic artery; or unilateral second-order biliary radicals bilaterally with contralateral portal vein or hepatic artery involvement

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1

M	**Distant Metastasis**
M0	No distant metastasis
M1	Distant metastasis

***Table 8.* AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a-b	N0	M0
Stage IIIA	T3	N0	M0
Stage IIIB	T4	N0	M0
Stage IIIC	Any T	N1	M0
Stage IVA	Any T	N2	M0
Stage IVB	Any T	Any N	M1

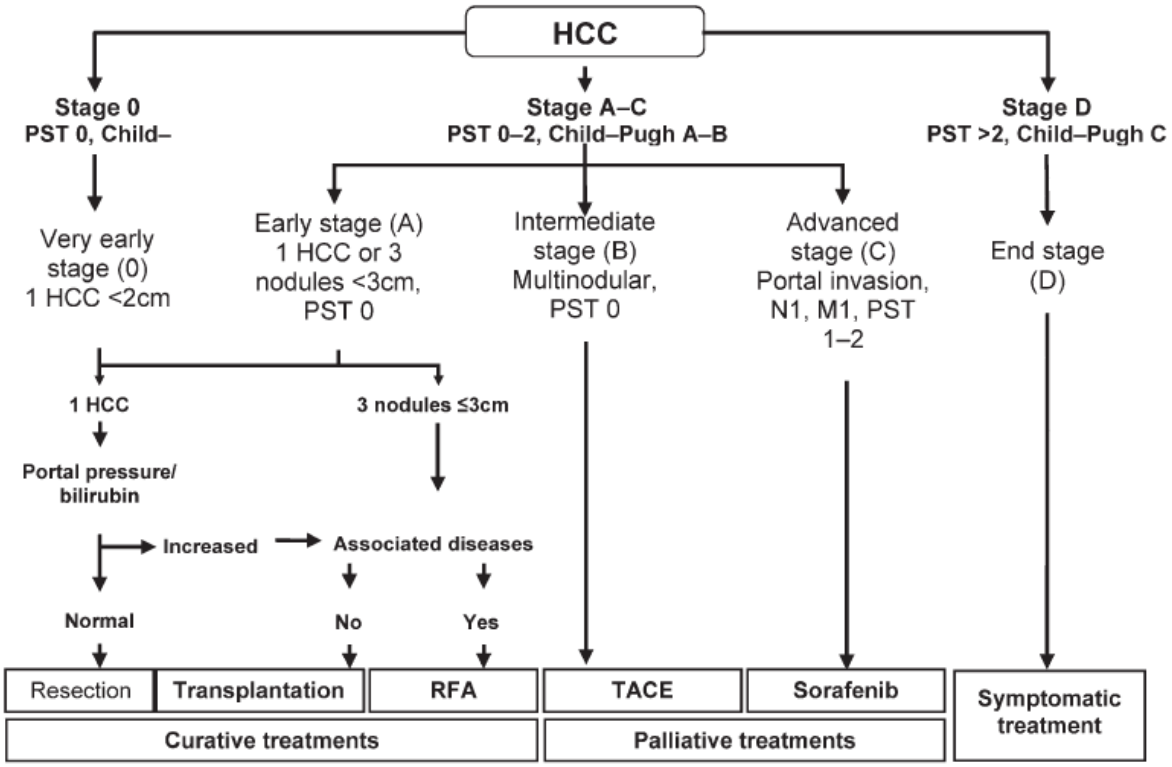
Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated

AJCC Staging for HCC, adapted from www.nccn.org

APPENDIX 5: BCLC staging for HCC

BCLC stage will be determined based upon review of imaging and other clinical data from date of radiographic (by diagnostic imaging) or histologic diagnosis, whichever is earliest. BCLC stage will also be determined at date of enrollment. BCLC stage will be recorded in CRFs on OnCore.

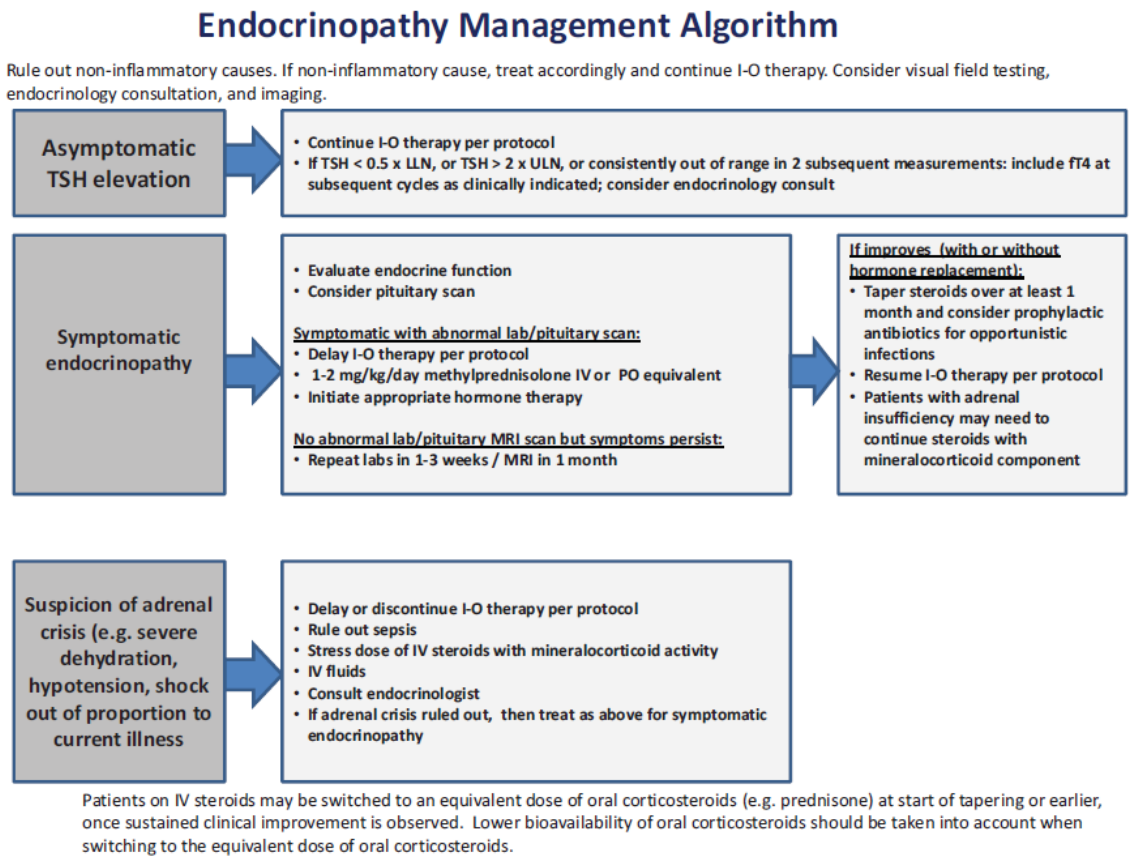


Bruix and Sherman Hepatology 53(3) 2011

APPENDIX 6: irAE management

The following algorithms from Nivolumab IB (v.15.0) represent clinical guidance to the treating investigator for management of selected irAE which have been associated with nivolumab. Additional management including optimal supportive care should be employed in all cases as clinically appropriate, according to clinical judgment of treating investigator. Subspecialty consultation for additional management recommendations should be obtained whenever needed, e.g. for severe or refractory cases, at discretion of treating investigator.

Endocrine irAE*



*For cases with new onset diabetes mellitus, the role for steroid therapy is unknown and consultation with Endocrinologist is strongly recommended. For symptomatic diabetes, nivolumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Nivolumab must be permanently discontinued for life-threatening diabetes.

GI irAE

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

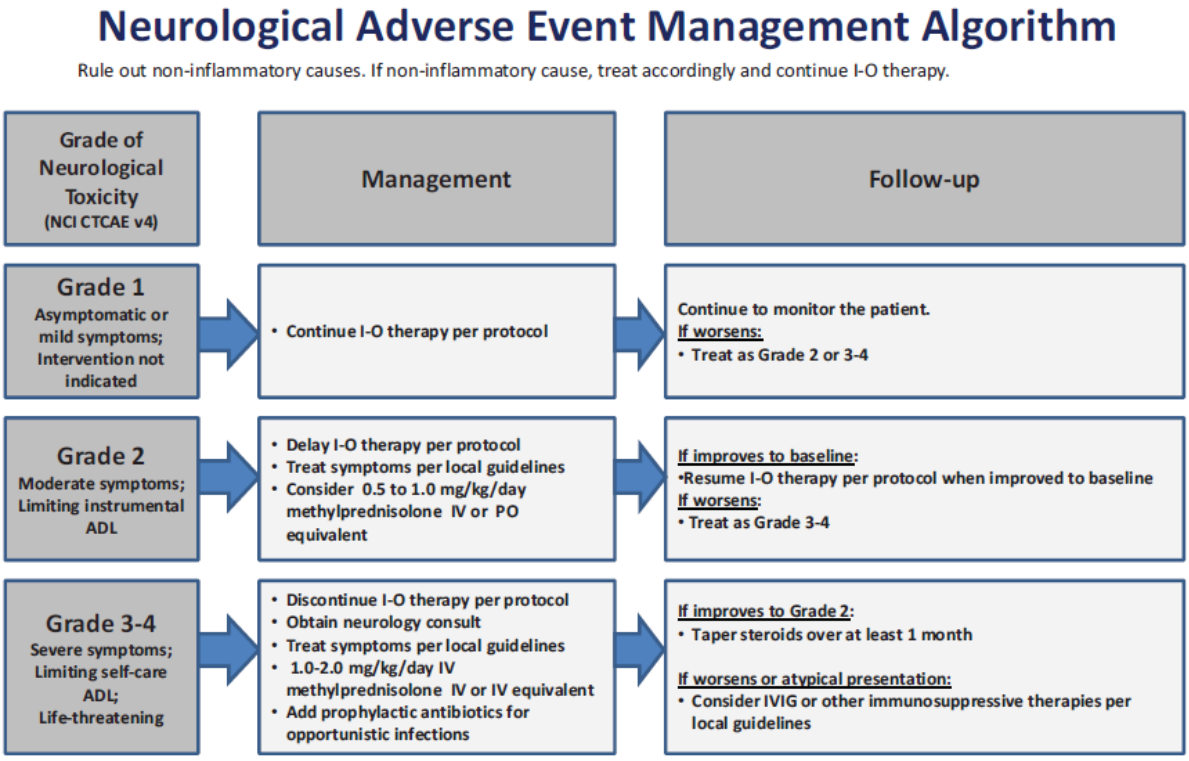
Hepatic irAE

Subjects with advanced HCC generally have underlying cirrhosis with decreased hepatic function, thus this protocol allows inclusion of patients with AST or ALT elevations within the CTCAE Grade 2 range. The protocol-specific approach for the management of hepatic events in this population with baseline hepatic dysfunction is as follows:

1. 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.
2. Check for alternate causes of elevated AST or ALT including test HBV or HCV viral load as applicable, discontinue any new medications or supplements, and consider imaging for tumor progression and/or vascular involvement.
3. For ALT or AST levels > 8x ULN, initiate steroid therapy promptly at 1-2 mg/kg/day methylprednisolone or oral equivalent.
4. For all subjects initiating steroids, Hepatology/Gastroenterology consult is recommended if any evidence associated hepatic decompensation (e.g. new ascites, encephalopathy, or elevated INR).
5. If AST or ALT levels do not improve within 3-5 days or the levels worsen after the start of steroid therapy, it is recommended to contact Study Chair and consider adding mycophenolate mofetil at 1 g BID.
6. Tapering of steroids can start once AST or ALT levels have declined by 1 CTCAE grade.
7. Taper steroids slowly over no less than 1 month.

As outlined in Section 6.7.2.1, nivolumab therapy may resume when AST or ALT have returned to near baseline unless the criteria for permanent discontinuation are reached.

Neurologic irAE



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary irAE

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal irAE

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

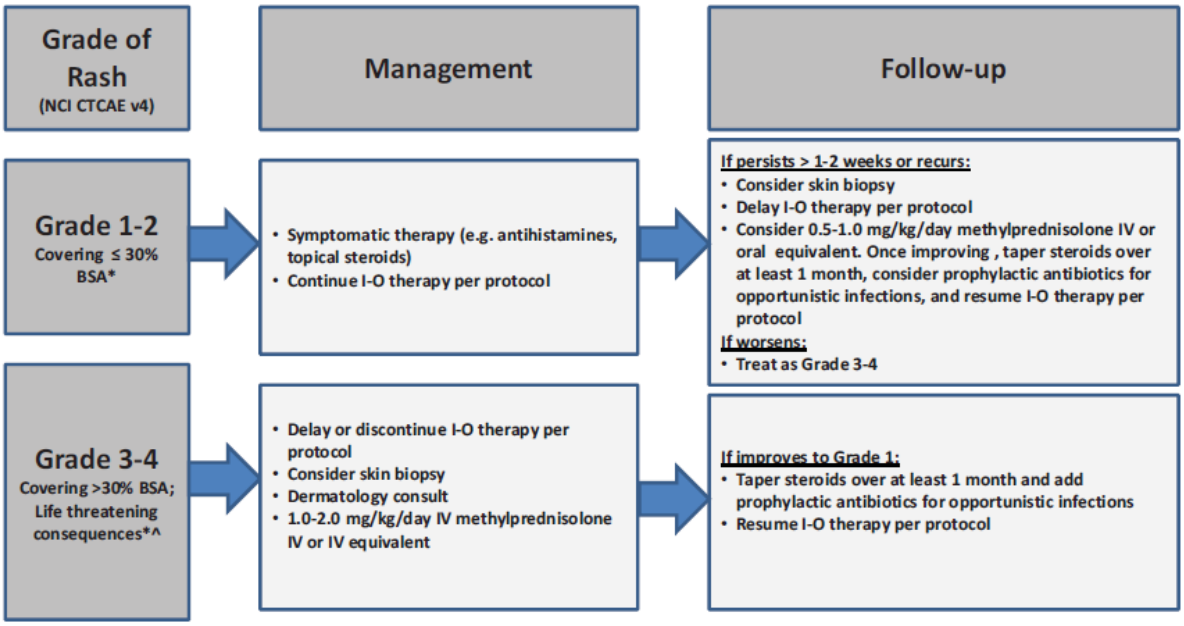
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1: Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin irAE

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

APPENDIX 7: Sorafenib drug diary

PATIENT ID #:_____ CYCLE #: _____

INSTRUCTIONS: PLEASE FILL OUT AND BRING THIS SHEET TO YOUR NEXT VISIT.

DOSE LEVEL:
- ☐ 400 mg (2 x 200 mg tablets) orally twice a day
- ☐ 400 mg (2 x 200 mg tablets) orally once a day
- ☐ 400 mg (2 x 200 mg tablets) orally every other day

SORAFENIB 200 MG TABLETS: TAKE ORALLY WITHOUT FOOD WITH A GLASS OF WATER.

Day	Date	Morning time of dose # of caps taken	Evening time of dose # of tablets taken	Missed Dose Time/date missed
EXAMPLE	**1/1/2017**	**___:___AM # ___ tabs**	**___:___PM # ____ tabs**	**# ____tabs:**
Day 1				
Day 2				
Day 3				
Day 4				
Day 5				
Day 6				
Day 7				
Day 8				
Day 9				
Day 10				
Day 11				
Day 12				
Day 13				
Day 14				
Day 15				
Day 16				
Day 17				
Day 18				
Day 19				
Day 20				
Day 21				
Day 22				
Day 23				
Day 24				
Day 25				
Day 26				

Day 27				
Day 28				
Day 29				
Day 30				
Day 31				

Please complete this section at the end of cycle when returning any leftover pills and pill bottle:

Number of pills returned: _____ Date:

Patient Signature: _____ Date: _____

Health Care Provider Signature: _____ Date: _____

APPENDIX 8: Biospecimen acquisition and handling

Archival FFPE tumor blocks and/or sections

Samples of all available archival specimens (preferentially at least 1 representative FFPE block(s) plus H&E slide(s) from prior diagnostic core biopsy or biopsies and/or resection specimen(s), or if block not available, at least 10*5 µm and 10*10 µm unstained slides plus H&E slide will be requested, or maximum available in cases of limited sample) will be accessioned from UCSF and/or outside institution clinical laboratories as soon as possible after consent is obtained for study participation. Any leftover material (after all planned tissue extraction for study correlative analyses has been completed) will be returned to outside institution Pathology department (for non-UCSF patients) or logged and stored according to UCSF Biorepository SOP or returned at end of study for UCSF subjects if consented for banking in companion banking and registry study, CC#124512 (see below). If multiple tumors and/or satellite nodules are present, at least 1 block and/or corresponding unstained slides plus matching H&E slide should be requested for each discrete lesion whenever available.

Block/slides should be delivered or shipped to:

Attn: CC#174523

UCSF-Biospecimen Repository and Tissue Biomarker Technology Lab
UCSF Helen Diller Family Comprehensive Cancer Center
[redacted]

For patients who consent to the companion study CC#124512, left-over specimens will be collected, processed, and banked and clinical data will be collected according to separate CC#124512 protocol.

Whole blood for PBMC isolation (UCSF site only)

In all patients enrolled at UCSF, approximately 60 mL of whole blood will be collected into green top (sodium heparin) tubes (e.g. six 10 cc tubes filled approximately to 10 mL) at the time points listed in the study Schedule of procedures (Section 7.1) and according to instructions below. The tubes will be delivered by study coordinator or approved courier directly to the UCSF Immune Monitoring Core for PBMC isolation then freezing for future analysis in batch after study completion.

Whole blood for PBMC Sample Collection and Delivery Instructions:

- Draw 60 mL into the appropriate number of green top tubes (e.g. six 10cc tubes) by phlebotomist or other trained health care provider.
- Invert the tube gently several times to avoid clotting.
- Label samples with study ID (CC#174523), subject ID, cycle/day, date, time of blood draw.
- For each delivery, an inventory of the samples should accompany the delivery. This inventory should include the study ID (CC#174523) subject ID, cycle/day, date, and time of blood draw.
- All samples should be delivered on a Monday through Thursday between approximately 9am-5pm PST or on a Friday between approximately 9am-1pm PST by a coordinator or approved courier service:
- Samples should not be sent after approximately 1pm Friday through Sunday or on University holidays, to prevent arrival over the weekend or on holidays, unless by special arrangement with the UCSF CIL staff.
- Samples have to be packed according to the ICAO/IATA-Packing-Instructions in a room temperature shipper or specimen bag.

Deliver samples at room temperature within approximately 12 hours or less after time of blood collection to:

Attn: CC#174523

UCSF Cancer Immunotherapy Laboratory (CIL)

[redacted]

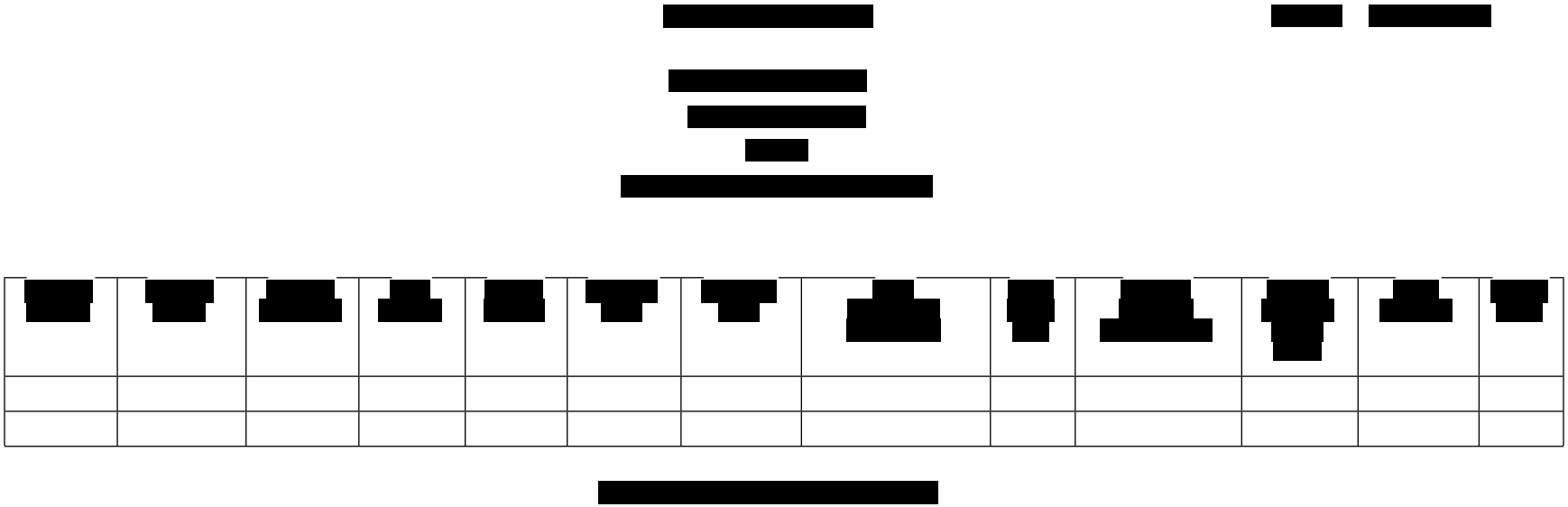
APPENDIX 9: MedWatch 3500A form

This form will be used for submission of SAE events to Bayer, BMS, and FDA as appropriate.

- For SAE occurring at UCSF: Reports will be sent to Bayer, BMS, and FDA as applicable depending upon criteria in Section 7.4.
- For SAE occurring at sub-site: Reports will be sent to Bayer, BMS, and UCSF. IND safety reporting will be submitted by study team at UCSF.

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

APPENDIX 10: BMS SAE Reconciliation Reports



APPENDIX 11: UCSF Data and Safety Monitoring Plan (DSMP) for Multicenter Institutional Study

Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and participant safety for all HDFCCC institutional clinical trials and cancer-specific trials at UCSF. A summary of DSMC activities for this trial includes:

- Participant monitoring prior to dose escalation.
- Review of participant data in each cohort
- Approval of dose escalation by DSMC Chair or Vice Chair
- Review of serious adverse events
- Minimum of biennial regulatory auditing

2. Monitoring and Reporting Guidelines

The Principal Investigator at the UCSF Coordinating Center will hold the role of Study Chair. The Study Chair is responsible for the overall conduct of the trial and for monitoring its safety and progress at all participating sites. The Study Chair will conduct continuous review of data and participant safety at weekly UCSF Site Committee meetings. The discussions are documented in the UCSF Site Committee meeting minutes.

The UCSF HDFCCC Data and Safety Monitoring Committee (DSMC) is responsible for participant safety for all domestic sites for HDFCCC Multicenter and Consortium institutional clinical trials. The International sites must be monitored by a Clinical Research Organization (CRO) that is formally approved by the HDFCCC Cancer Center Clinical Research Oncology Committee (CCCROC) and the HDFCCC DSMC via the HDFCCC Policy of Minimum Standards for Partnership with International CROs.

All multicenter phase I dose escalation trials are monitored prior to the requested dose escalation of the dosing cohort. All participants are monitored through the Dose Limiting Cohort until the Maximum Tolerated Dose (MTD) is determined. Once the MTD is determined, then the trial is audited on an annual basis with twenty percent of the participants enrolled in this expansion cohort that are audited through their first five cycles of treatment. Scheduled auditing of participant source documents is complete after all files have been reviewed for five cycles of treatment (20% of participants). For Phase I high risk therapeutic trials that are not dose finding, all participants are monitored on a quarterly basis (depending on accrual) through the first cycle of therapy.

DSMC Monitor/Auditors will send a follow-up report to the study team within 20 business days after the monitoring visit is complete for the PI and the study team to resolve all action items from this report within 20 business days. An abbreviated regulatory review (i.e., reviewing protocol and consent versions, SAEs, PVs, DOA logs, 1572 forms, etc.) will occur at each participant monitoring review; however, a full regulatory review will occur on a biennially basis by the DSMC for regulatory compliance.

Monitoring of enrolled participants in the dose expansion portion of the trial will be complete after 20% of enrolled participants have been monitored through two cycles of treatment. However, regulatory reviews of the trial, safety reviews (i.e., Serious Adverse Event (SAE) reviews and Protocol Violation (PV) reviews), as well as audit/inspection preparation (as applicable) will continue until the trial is closed by the IRB.

Multicenter communication

The UCSF Coordinating Center includes the UCSF PI (Study Chair) and the UCSF study team. The UCSF Coordinating Center and provides administration, data management, and organizational support for the participating sites in the conduct of a multicenter clinical trial. The UCSF Coordinating Center will also coordinate monthly conference calls with the participating sites. The following issues will be discussed as appropriate:

- Enrollment information.
- Cohort updates (i.e., DLTs).
- Adverse events (i.e., new adverse events and updates on unresolved adverse events and new safety information).
- Protocol violations.
- Other issues affecting the conduct of the study.

Dose Level Considerations

The PI/Study Chair, participating investigators, and research coordinators from each site will review enrollment for each dose level cohort during the regularly scheduled conference calls. The dose level for ongoing enrollment will be confirmed for each participant scheduled to be enrolled at a site. Dose level assignments for any participant scheduled to begin treatment must be confirmed by the UCSF Coordinating Center via email.

If a participant experiences a Dose Limiting Toxicity (DLT), the UCSF Coordinating Center will notify all sites within one business day of awareness. If the DLT occurs at a participating site, the local investigator must report the DLT to the UCSF Coordinating Center within one business day. The Study Chair has one business day (after first becoming aware of the event at either the UCSF Coordinating Center or the participating site) in which to report the DLT information to all participating sites.

Adverse events reporting to the DSMC will include reports from both the UCSF Coordinating Center, as well as the participating sites. The DSMC will be responsible for monitoring all data entered in OnCore® at the UCSF Coordinating Center and the participating sites as per the study-specific guidelines. The data (i.e., redacted copies of source documents) from the participating sites will be downloaded into the PC console of OnCore prior to the monitoring visits or the DSMC will be provided with access to the participating site's electronic medical record (EMR) access in order for the DSMC to perform remote monitoring of the participating site's compliance with the protocol and applicable FDA regulations

Dose Escalations

At the time of dose escalation, a written and signed Dose Escalation Report will be submitted to the DSMC Chair (or Vice Chair) and DSMC Director describing the cohorts, dose levels, adverse events, safety reports, and any Dose Limiting Toxicities (DLTs) observed, in accordance with the protocol. The report will be reviewed by the DSMC Chair or Vice Chair and written authorization to proceed or a request for more information will be issued within two business days of the request. The report is then reviewed at the subsequent DSMC Committee meeting. In the event that the committee does not concur with the DSMC Chair's (or Vice Chair's decision, study accrual is held while further investigation takes place.

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All clinically significant adverse events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of study drug, will be entered into OnCore, UCSF's Clinical Trial Management System.

Adverse events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to investigational agent or study procedure. Attribution categories are:

- **Definite** – clearly related to the investigational agent(s) or study procedure.
- **Probable** – likely related to the investigational agent(s) or study procedure.
- **Possible** – may be related to the investigational agent(s) or study procedure.
- **Unrelated** – clearly not related to the investigational agent(s) or study procedure.

All adverse events entered into OnCore will be reviewed on a weekly basis at the UCSF Coordinating Center's Site Committee meetings. The UCSF Site Committee will review and discuss the selected toxicity, grade, and the attribution assignment for the adverse events that occurred at both the UCSF Coordinating Center and the participating sites.

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

- Death,
- Life-threatening adverse experience*,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,

Congenital anomaly/birth defect, or cancer, or

- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above,
- Event that changes the risk/benefit ratio of the study.

* A life-threatening adverse experience is any AE that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event reporting will be in accordance with all IRB regulations. For trials conducted under an investigational new drug (IND) application, the SAE will be reported in accordance with Code of Federal Regulation Title 21 Part 312.32 and will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:

https://irb.ucsf.edu/adverse-event

Med Watch forms and information:

www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore, as well as submitted to the IRB (per IRB guidelines). All SAEs, whether expected or unexpected, must be reported to the UCSF Coordinating Center within 10 business days of becoming aware of the event or during the next scheduled conference all, whichever is sooner. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE was sent to all required reporting agencies will be documented in OnCore.

If a death occurs during the treatment phase of the study or within 30 days after the last administration of the study drug(s) and is determined to be possibly, probably, or definitely related either to the investigational drug or any research related procedure, the Study Chair at the UCSF Coordinating Center or the assigned designee must be notified within 1 business day from the participating site(s) and the Study Chair must then notify the DSMC Chair (or Vice Chair) and the DSMC Director within one business day of this notification.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Study Chair at the UCSF Coordinating Center is responsible for notifying the DSMC at the time the increased rate is identified via a report. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator's Brochure or package insert.

If at any time the Study Chair voluntarily holds enrollment or stops the study due to safety issues, the DSMC Chair (or Vice Chair) and the DSMC Director must be notified within one business day via e-mail and the IRB must be notified their reporting requirements.

3.4 Data and Safety Monitoring Board (DSMB) Reports

Data and Safety Monitoring Board (DSMB) Reports which provide information on trial accrual, participant safety, and data integrity will be provided to all sites, including the domestic and international sites, on an annual basis. The DSMB Report will be signed by the DSMC Chair (or Vice Chair) and provided to the DSMC Committee for formal review at the next scheduled DSMC Committee meeting.

Data and Safety Monitoring Committee Contacts:

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