Official Title:	A PHASE II, RANDOMIZED, CONTROLLED TRIAL OF NIVOLUMAB IN COMBINATION WITH BMS-986253 IN ADVANCED HEPATOCELLULAR CARCINOMA (HCC) PATIENTS
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Clinical Research Protocol
Perlmutter Cancer Center

A PHASE II, RANDOMIZED, CONTROLLED TRIAL OF NIVOLUMAB IN COMBINATION WITH BMS-986253 IN ADVANCED HEPATOCELLULAR CARCINOMA (HCC) PATIENTS

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Study Product:	Nivolumab (Opdivo), BMS-986253
Study Product Provider:	Bristol-Myers Squibb
Coordinating Center:	NYU Langone Health

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Participating sites:	NYU Langone Health and University of Pennsylvania
ClinicalTrials.gov Number	*NCT04050462*

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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the supporter and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A PHASE II, RANDOMIZED, CONTROLLED TRIAL OF NIVOLUMAB IN COMBINATION WITH BMS-986253 IN ADVANCED HEPATOCELLULAR CARCINOMA (HCC) PATIENTS

Protocol Number: s18-01028

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

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Signature

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Date

Table of Contents

List of Abbreviations

AE	Adverse Event/Adverse Experience
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CI	Confidence Interval
CrCl	Creatinine Clearance
CFR	Code of Federal Regulations
CRF	Case Report Form
CSC	Cancer Stem Cell
CTO	Clinical Trials Office
DCR	Disease Control Rate
DHHS	Department of Health and Human Services
DOR	Duration of Response
DSMC	Data Safety Monitoring Committee
ECI	Event of Clinical Interest
EMT	Epithelial Mesenchymal Transition
FACS	Fluorescence Activated Cell Sorting
GCP	Good Clinical Practice
HCC	Hepatocellular Carcinoma
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
LR	Local-regional
MOP	Manual of Procedures

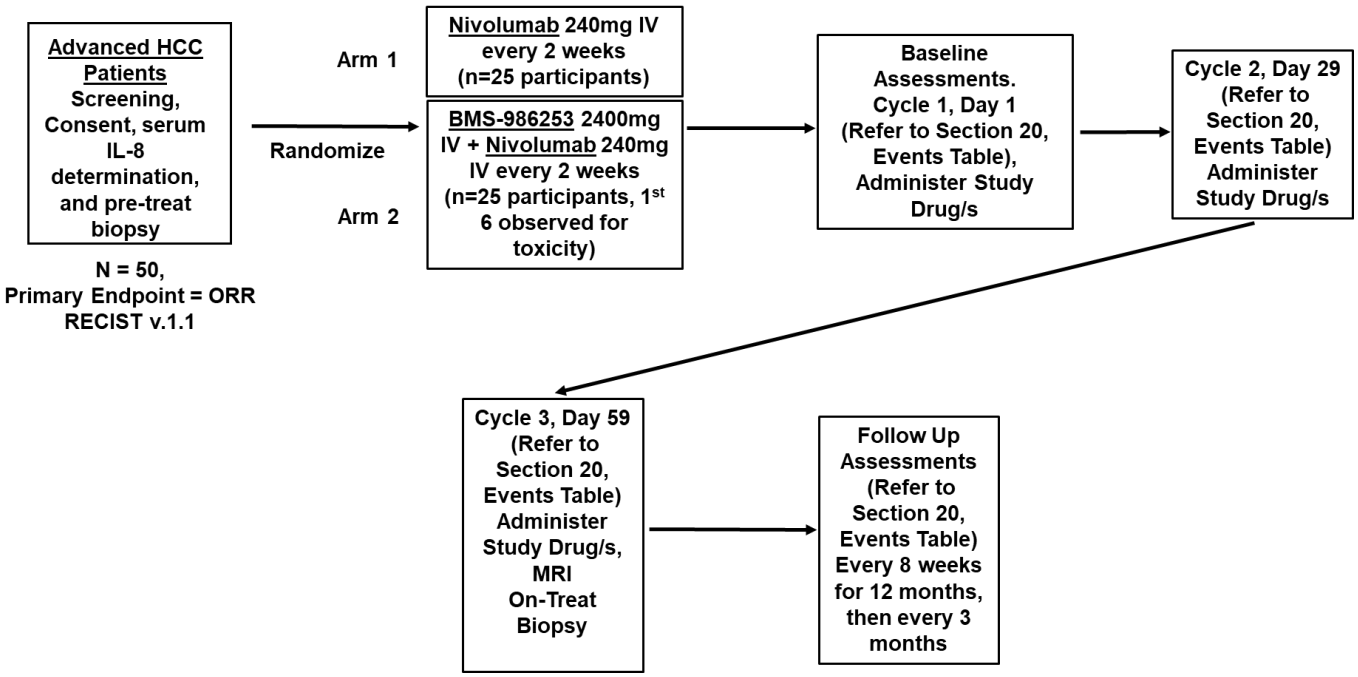
N	Number (typically refers to participants)
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
NIH	National Institutes of Health
NYULH	New York University Langone Health
OHRP	Office for Human Research Protections
ORR	Objective Response Rate
OS	Overall Survival
PCC	Perlmutter Cancer Center
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PR	Partial Response
QA	Quality Assurance
QC	Quality Control
RECIST	Response Evaluation Criteria in Solid Tumors
mRECIST	Modified RECIST
SAE	Serious Adverse Event/Serious Adverse Experience
TAM	Tumor Associated Macrophage
TME	Tumor Microenvironment
TTR	Time to Response
ULN	Upper Limit of Normal
US	United States
WB	Whole Blood
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

Protocol Summary

Title	A Phase II, Randomized, Controlled Trial of Nivolumab in Combination with BMS-986253 in Advanced Hepatocellular Carcinoma (HCC) Patients
Short Title	Nivolumab Combined with BMS-986253 in HCC Patients
Brief Summary	A phase II clinical trial is utilized to examine whether BMS-986253 (25 subjects) when combined with Nivolumab offers improved radiographic objective response rates (ORR) over Nivolumab monotherapy (25 subjects) in advanced HCC patients. Primary endpoint, ORRs, will be assessed at 2 month increments while on treatment. Safety will be verified for the Nivolumab/BMS-986253 combination. Secondary endpoints of time to response (TTR), duration of response (DOR), progression free survival (PFS), and overall survival (OS) will also be assessed. Pre- and on-treatment tumor biopsies will be utilized for translational/correlative research.
Phase	Phase 2
Objectives	1. Determine the ORR of BMS-986253 in combination with Nivolumab. 2. Determine the safety of BMS-986253 in combination with Nivolumab. 3. Determine the TTR, DOR, PFS, and OS for subjects receiving BMS-986253 in combination with Nivo. 4. Exploratory study of the tumor microenvironment (TME) using novel NYU technologies of 30-parameter flow cytometry and single cell RNAseq on pre- and on-treatment fresh core biopsies.
Methodology	Randomized, controlled, single blind trial
Endpoint	Primary Endpoints: ORR of BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy and safety of BMS-986253 in combination with Nivolumab. Secondary Endpoints: TTR, DOR, PFS, OS, and exploratory analysis of the HCC TME in subjects receiving either BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy
Study Duration	The duration of this study from enrollment until completion of data analysis is up to 6 years
Participant Duration	2-5 years
Enrollment Period	2 years
Duration of IP administration	2-5 years
Population	50 total male and female participants: 25 participants Nivolumab monotherapy group, 25 participants Nivolumab/BMS-986253 combination, Age ≥ 18, Two U.S. sites
Study Centers/Sites	Multicenter (Two): NYU Langone Health and Univ. of Pennsylvania
Number of participants	50 participants across 2 sites
Description of Study Agent/Procedure	Nivolumab 240 mg IV every 2 weeks + BMS-986253 2400 mg IV every 2 weeks
Reference Therapy	Nivolumab 240 mg IV every 2 weeks
Key Procedures	Key procedures include pre- and on-treatment biopsies, peripheral blood for IL-8 determination

Statistical Analysis	With the recent results of the CheckMate-040 study in HCC patients, we would expect a primary endpoint, ORR of 15%, for the Nivolumab monotherapy group (n=25 participants). For the combination group (Nivolumab + BMS-986253) with n=25 participants each, a change in ORR of 34% would be able to be detected at 80% power. Thus an absolute ORR for the combination group of 49% would be able to be detected at 80% power, assuming the 15% ORR for the Nivolumab monotherapy group, utilizing the two-sided Z-Test with unpooled variance and significance level of 0.05. Secondary endpoint outcomes (TTR, DOR, PFS, OS) will be analyzed using the Kaplan-Meier method. Exploratory endpoints for translational and correlative research will be assessed using logistic regression analysis.

Schematic of Study Design



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2 Introduction, Background Information and Scientific Rationale

2.1 Background Information and Relevant Literature

HCC has the 2nd highest incidence and mortality rate worldwide among solid organ malignancies and has the highest rate of increasing incidence and mortality among all cancers in the U.S.(1, 2). Despite surveillance of high risk populations, many patients present with advanced disease or progress despite initial therapies such as surgical resection or local-regional (LR) treatments (3, 4). While recently tyrosine kinase inhibitors such as sorafenib and regorafenib have had some efficacy in advanced HCC patients (5, 6), the immune oncology agent, Nivolumab (Nivo) (Opdivo®) has demonstrated safety and efficacy in HCC patients (CheckMate-040) resulting in its recent FDA approval for 2nd line in HCC patients (7). Radiographic objective response rates (ORR) are reported to be 15% with 3% having a CR and 42% having stable disease. Given HCC's known prognostic link to the balance of immunosuppression versus immune activation within the tumor microenvironment (TME), ongoing studies of Nivo as possible 1st line therapy (Checkmate-459) are underway.

In order to maximize the potential response to immunotherapeutics, other targeting strategies in the TME should be investigated. TAMs and myeloid-derived suppressive cells (MDSCs) are the dominant immune suppressive cells within the TME (8). In HCC, TAMs have been directly linked to a worse prognosis (9, 10) and TAMs often reside at the invasive front of malignancies (11). We and others have shown that TAMs and their secreted factors, particularly IL-6 and IL-8, contribute to HCC CSC and EMT phenotype (12, 13) (**Fig. 1-2**). Additionally, IL-6 and M-CSF are both known to contribute to monocyte differentiation

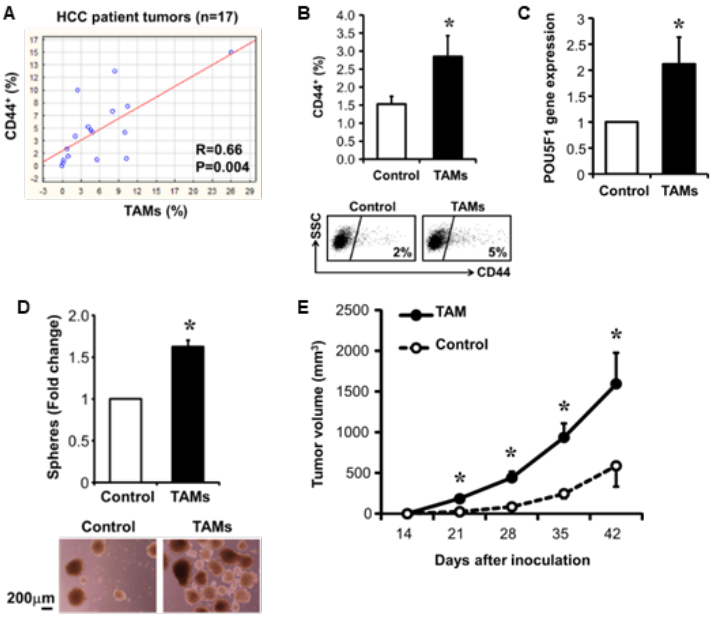

Figure 1. (A) Correlation of HCC TAM infiltration (Lin$^-$ CD11b$^+$CD14$^+$) and CD44$^+$ HCC Cancer Stem cells (CSCs) (Lin$^-$ CD44$^+$) in HCC patients by FACS on fresh tumor cell suspensions (n=17 patients) (B-D) Enrichment of CD44$^+$ HCC cells by TAMs after transwell co-culture followed by FACS of HepG2 cells, *POU5F1* expression, and sphere formation (n=5 HCC patients TAMs). Control is HepG2 cells alone. *p < 0.05 vs. control. Representative FACS and spheres are shown. (E) 1000 HepG2 cells following co-culture without or with TAMs were injected subcutaneously into opposing flanks of NSG mice, respectively, and tumor volume determined, n=5 mice/group, one of four representative experiments is shown.

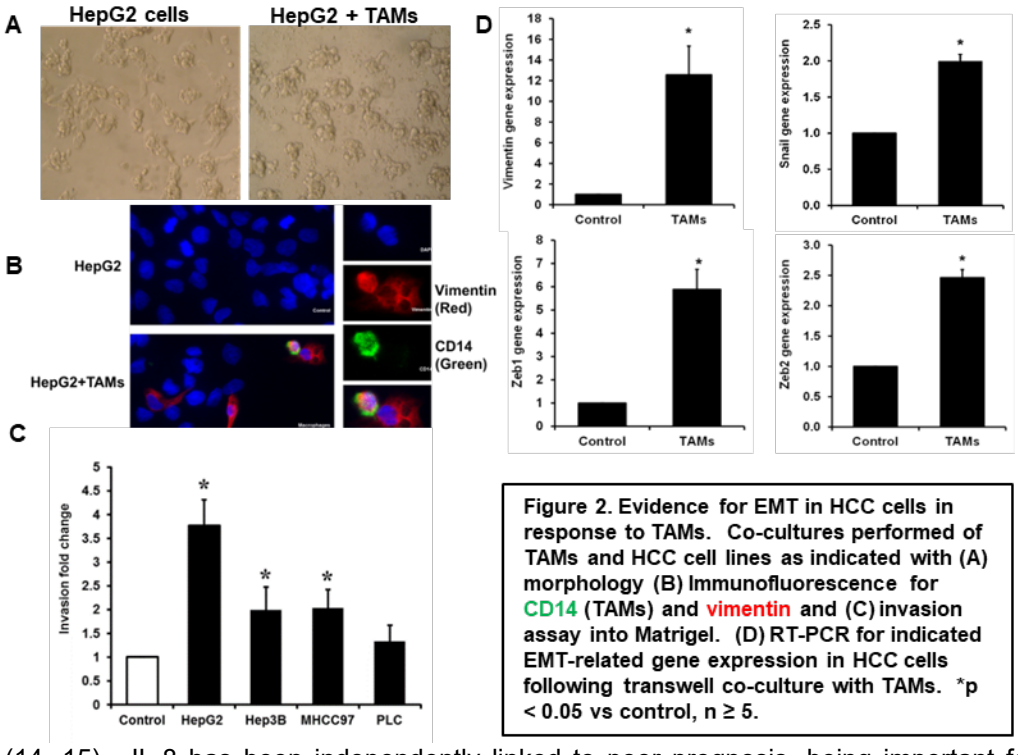

Figure 2. Evidence for EMT in HCC cells in response to TAMs. Co-cultures performed of TAMs and HCC cell lines as indicated with (A) morphology (B) Immunofluorescence for CD14 (TAMs) and vimentin and (C) invasion assay into Matrigel. (D) RT-PCR for indicated EMT-related gene expression in HCC cells following transwell co-culture with TAMs. *p < 0.05 vs control, n ≥ 5.

into TAMs (14, 15). IL-8 has been independently linked to poor prognosis, being important for tumor angiogenesis. Indeed, we have shown that serum levels of IL-8 independently predicted worse survival in

a cohort of HCC patients (16) (**Fig. 3**). Furthermore, we have shown that IL-6 and IL-8 are dominant cytokines released from TAMs in HCC (**Fig. 4**). These cytokines are responsible for stimulating

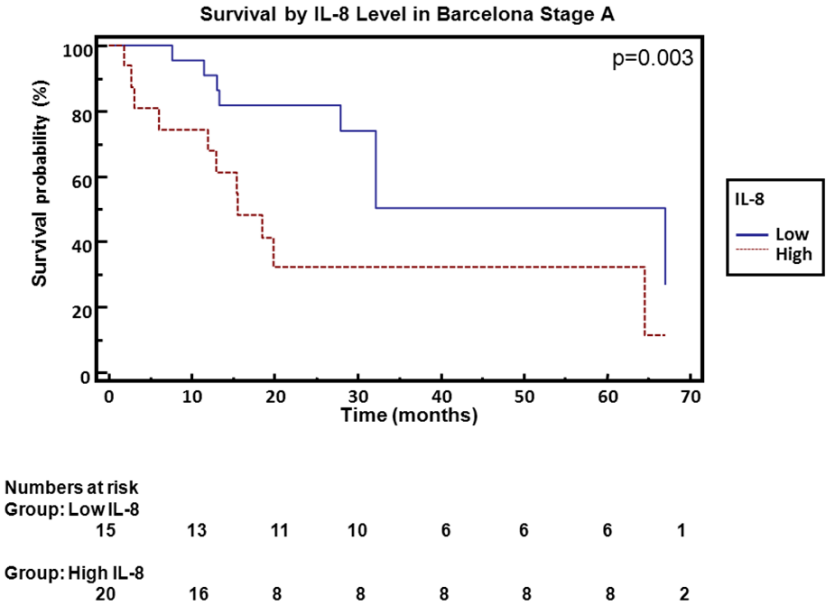

Figure 3. Kaplan-Meier survival analysis of cirrhotic HCC patients stratified by high vs. low serum levels of IL-8 for early stage (BCLC A) HCC patients. Multivariate analysis showed IL-8 independently predicted outcome of all cytokines tested (HR 2.15; 95% CI:1.21-3.74). High vs. Low IL-8 defined based on 50th percentile (37.6 pg/mL) for the HCC cohort of all stages.

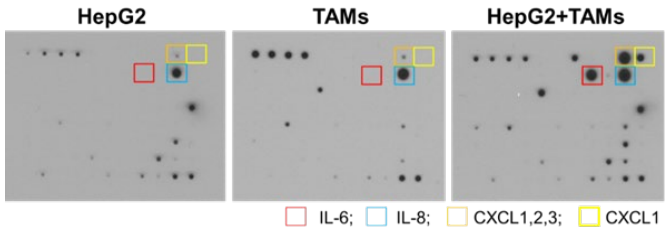

Figure 4. Co-cultures of HepG2 cells and TAMs performed as in Fig. 1 with supernatants collected and subjected to cytokine antibody array (representative one of three experiments).

cancer stem cell (CSC) function as well as epithelial-mesenchymal transition (EMT) behavior (**Fig. 5-6**). *Therefore, our overall hypothesis is that therapeutic agents directed at targeting the function of TAMs may provide additive or synergistic benefits to known checkpoint inhibitor drugs such as Nivolumab.*

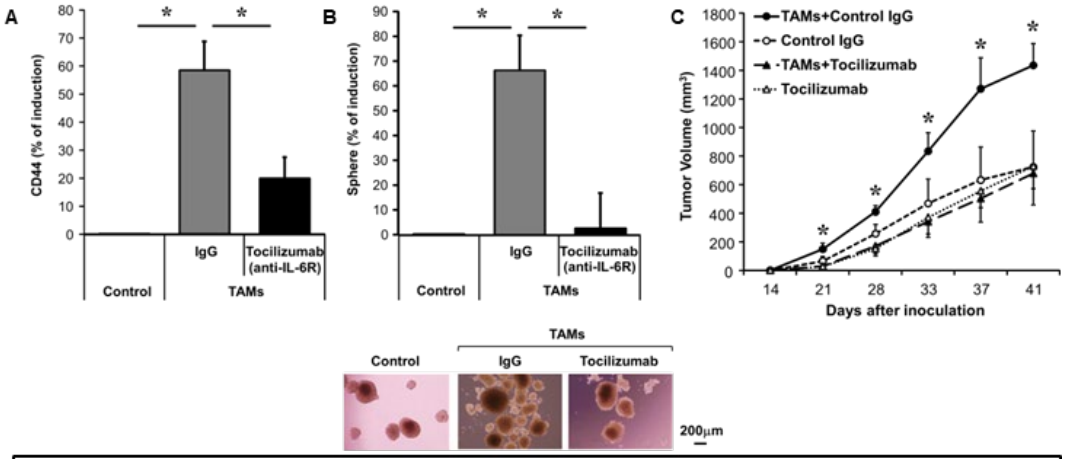

Figure 5. Co-cultures of HepG2 cells and TAMs performed as in Fig. 1 with presence of Tocilizumab (5 ug/mL) or control IgG followed by (A) FACS for CD44 (n=5) and (B) sphere assay (n=8). (C) Co-implantation of TAMs and HepG2 cells into NSG mice followed by i.p. Tocilizumab (20mg/kg) every week. (n=5 mice, 1 of 2 experiments shown) *p < 0.05.

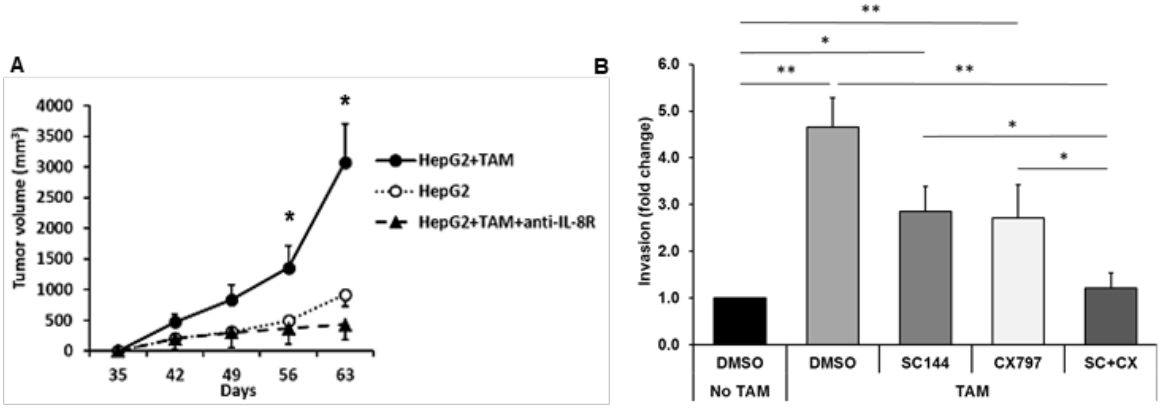

Figure 6. (A) Following co-culture in presence or absence of anti-IL-8 receptor antibody (anti-CXCR1 and anti-CXR2), HepG2 xenograft tumor growth following implantation into NSG mice (n=3-4 mice/group). *p<0.05 vs. HepG2 alone. (B) Invasion assays into Matrigel following TAM co-culture with HepG2 or Hep3B cells in presence or absence of gp130 inhibitor (SC144 0.1 uM) and/or CXCR2 inhibitor (CX797, 10uM). SC+CX is combined SC144 and CX797. * and **p < 0.05 vs. indicated comparisons, n=3-6 experiments.

2.2 Name and Description of the Investigational Agent

Nivolumab (Opdivo®) is a programmed death receptor-1 (PD-1) blocking, fully humanized, IgG4 antibody. It blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, releasing PD-1-mediated inhibition of the immune response. Nivolumab is FDA approved for treatment of patients with melanoma, non-small cell and small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, MSI-H or mismatch repair deficient colorectal cancer, and hepatocellular carcinoma.

BMS-986253 is a blocking, humanized, IgG1k antibody to IL-8. BMS-986253 binds soluble IL-8, thus disrupting IL-8's ability to bind to its receptors, CXCR1 and CXCR2. Disruption of IL-8 signaling through these receptors diminishes myeloid derived suppressor cell (MDSC) and TAM recruitment to the TME,

reduce CSC renewal, reverse EMT, and inhibit tumor angiogenesis. Phase I studies in advanced solid tumors have demonstrated safety at a dose range from 4 mg/kg up to and including 32 mg/kg IV every 2 weeks with no evidence of drug related toxicity (BMS Investigator Brochure). Recently a phase 1/2a study with Nivolumab (480 mg every 4 weeks) in combination with BMS-986253 (varying doses every 4 weeks) in cancer patients was shown to be tolerable (BMS Investigator Brochure).

2.2.1 Preclinical Data

All study drugs have initiated clinical studies. See sections 2.1, 2.2.2, 2.3, and 2.4.

2.2.2 Clinical Data to Date

While recently tyrosine kinase inhibitors such as sorafenib and regorafenib have had some efficacy in advanced HCC patients (5, 6), the immune oncology agent, Nivolumab (Nivo) (Opdivo®) has demonstrated safety and efficacy in HCC patients (CheckMate-040) resulting in its recent FDA approval for 2nd line in HCC patients (7). Radiographic objective response rates (ORR) are reported to be 15% with 3% having a CR and 42% having stable disease. Most recent updates on this trial (N=154) have shown that the median time to response was 2.8 months. The median DOR has not been reached after 48 months of follow up. Of those patients responding, 59% had a DOR of greater than 12 months. Median OS based on best overall response (RECIST v.1.1) and stratified as complete/partial response, stable disease, and progressive disease was not reached, 16.7 months, and 8.9 months, respectively (El-Khoueiry et al, ASCO-GI, 2018).

In the phase I study of BMS-986253 in solid tumor malignancy patients (CA027-001, Investigatory Brochure), there were no observed objective radiographic responses in the 15 participants. There were no dose limiting toxicities noted. AEs that were attributable to treatment were grade 1-2 in severity. There were no SAEs considered to be treatment related. There were no immune related AEs observed. The ongoing phase 1/2a study (CA027-002) with Nivolumab (480 mg every 4 weeks) in combination with BMS-986253 (variant doses every 4 weeks) in advanced cancer patients has shown tolerability with the combination.

2.2.3 Dose Rationale (if applicable)

BMS-986253 monotherapy in 15 advanced cancer patients has been performed with no dose limiting toxicities observed (CA027-001, Investigator Brochure). A dose range of 4-32 mg/kg every 2 weeks was evaluated. Only 5 of 15 participants were considered to have experienced an AE related to treatment with BMS-986253 and were grade 1-2 with no correlation to dose level. An ongoing phase 1/2a study (CA027-002) with Nivolumab (480 mg every 4 weeks) in combination with BMS-986253 in advanced cancer patients receiving BMS-986253 at 2400 mg every 4 weeks along with Nivolumab at 480 mg every 4 weeks has shown tolerability, therefore in order to ensure the maximum potential reduction in serum IL-8, the highest tolerated dose of BMS-986253 at 2400 mg is chosen for the present study along with Nivolumab at 240 mg every 2 weeks.

2.3 Rationale

Despite surveillance of high risk populations, many HCC patients present with advanced disease or progress despite initial therapies such as surgical resection or local-regional (LR) treatments (3, 4). While recently tyrosine kinase inhibitors such as sorafenib and regorafenib have had some efficacy in advanced HCC patients (5, 6), survival has only been extended for a median of 2.7-2.8 months. The immune oncology agent, Nivolumab (Nivo) (Opdivo®) has demonstrated safety and efficacy in HCC patients (CheckMate-040) resulting in its recent FDA approval for 2nd line in HCC patients (7). Radiographic objective response rates (ORR) using RECIST criteria are reported to be 15% with 3% having a CR and 42% having stable disease. Responding patients are still being followed and have an as yet “non-reached” median survival after greater than 45 months of follow up. Given HCC’s known prognostic link to the balance of immunosuppression versus immune activation within the tumor microenvironment (TME), ongoing studies of Nivolumab as possible 1st line therapy (Checkmate-459) are underway. Dosing of Nivolumab, 240 mg

IV, every 2 weeks has been shown to be well tolerated, particularly in patients with underlying liver disease, the main risk factor for HCC.

In order to maximize the potential response to immunotherapeutics, other targeting strategies in the TME should be investigated. TAMs and myeloid-derived suppressive cells (MDSCs) are the dominant immune suppressive cells within the TME (8). In HCC, TAMs have been directly linked to a worse prognosis (9, 10) and TAMs often reside at the invasive front of malignancies (11). We and others have shown that TAMs and their secreted factors, particularly IL-6 and IL-8, contribute to HCC CSC and EMT phenotype (12, 13) (**Fig. 1-2**, Appendix). Additionally, IL-6 and M-CSF are both known to contribute to monocyte differentiation into TAMs (14, 15). IL-8 has been independently linked to poor prognosis, being important for tumor angiogenesis. Indeed, we have shown that serum levels of IL-8 independently predicted worse survival in a cohort of HCC patients (16) (**Fig. 3**, Appendix). Additionally, a recent pan-tumor study in patients receiving nivolumab based therapy showed that patients with increased baseline IL-8 had worse overall survival and less responsiveness to nivolumab therapy (ASCO Meeting, 2018). Furthermore, we have shown that IL-6 and IL-8 are dominant cytokines released from TAMs in HCC (**Fig. 4**, Appendix). These cytokines are responsible for stimulating cancer stem cell (CSC) function as well as epithelial-mesenchymal transition (EMT) behavior (**Fig. 5-6**, Appendix). *Therefore, our overall hypothesis is that therapeutic agents directed at targeting the function of TAMs may provide additive or synergistic benefits to known checkpoint inhibitor drugs such as Nivolumab.*

With these aims toward disrupting TAM function in cancer for therapeutic effect, recent studies to verify dose and safety have been utilized for BMS-986253, an antibody to IL-8. A dose of BMS-986253 at 4 mg/kg up to 32 mg/kg IV every two weeks as monotherapy was found to be safe. Additionally, the combination of BMS-986253 (variant doses every 2-4 weeks) and Nivolumab (480 mg IV every 4 weeks) was found to be tolerable. Therefore in order to target TAM function in HCC more effectively, we will compare combination therapy of Nivolumab and BMS-986253 to Nivolumab monotherapy and evaluated for improved ORR along with other biologic correlates.

2.4 Potential Risks & Benefits

2.4.1 Known Potential Risks

The AEs reported for Nivolumab in HCC patients based upon the recent Checkmate 040 study (154 patients) and the package insert included the following: AST increase (5.8%, Grade 3-4 3.2%), ALT increase (7.8%, Grade 3-4 2.6%), ALP increase (5.6%, Grade 3-4 0%), bilirubin increase (1.9%, Grade 3-4 0%), hepatitis (0.6%, Grade 3-4 0.6%), other GI (25%, Grade 3-4 1.3%), endocrine AEs (8.4%, Grade 3-4 0%), pulmonary AE (1.3%, Grade 3-4 0.6%), renal AE (0.6%, Grade 3-4 0%), skin AE (31.8%, Gr 3-4 1.3%), and infusion reaction AE (3.9%, Grade 3-4 0%). All AEs were reversible with holding of dose. Thirteen patients discontinued treatment due to drug toxicity. The AEs observed and incidence in HCC patients were immune related and similar to that observed for use of Nivolumab in treatment of patients with other cancer types (7)(AASLD Annual Meeting, 2017) (Nivolumab package insert).

A phase I, dose escalation study (CA027-001, Investigator Brochure) of BMS-986253 monotherapy in 15 advanced cancer patients has been performed with no dose limiting toxicities observed. A dose range of 4-32 mg/kg was evaluated. Drug was given every 2 weeks. Only 5 of 15 participants were considered to have experienced an AE related to treatment with BMS-986253 and were grade 1-2. There was no correlation to dose level. The most frequent AEs (regardless of causality) were constipation, nausea and anemia. Six SAEs were reported, but none were attributable to study drug. There is an ongoing phase 1/2a study (CA027-002) with Nivolumab (480 mg every 4 weeks) in combination with BMS-986253 (variant doses every 2-4 weeks) in advanced cancer patients (n=92) with 31 patients receiving BMS-986253 2400 mg IV every 2 weeks and nivolumab 480 mg IV every 4 weeks which has shown tolerability with the combination. AEs that were attributable to treatment were grade 1-2 in severity. There was only one participant who discontinued treatment due to a grade 4 infusion reaction. In three other phase I studies involving either patients with progressive plaque psoriasis,

palmar-plantar pustulosis, or induced follicular rash in healthy volunteers, no dose limiting toxicities were observed and therefore no maximal tolerated dose was reached.

2.4.1.2 Other Risks of Study Participation

Additional risks associated with participation in this study, include the risk of phlebotomy, risks associated with CT/MRI scans, and breach of confidentiality. Risks associated with phlebotomy include weaknesses, redness, pain, bruising, bleeding, or infection at the needle site. Privacy protection procedures are in place and good clinical practice guidelines are followed for the study to minimize risks associated with research procedures and participation.

Risks associated with MRI
MRI uses strong magnetic fields and radiowaves to make images of the inside of your body. MRI does NOT involve high-energy radiation (like x-rays). For most people MRI is very safe. However, if you have anything made of metal on your skin or inside your body, MRI may not be safe for you, and you must tell study personnel before your scan.

Also, if you have any electronic devices on the outside or inside of your body, you must tell study personnel about those too. Some things, like tattoos, may have metal materials in them even though you might not realize it. For this reason, study personnel will give you a checklist of things that have metal or electronic parts in them. You must read the list carefully before your scan and put a checkmark next to everything that applies to you.

The following paragraphs will describe the possible risks of MRI. To reduce many of these risks, you will be given an emergency squeeze ball to hold in your hand during the scan. If you feel any discomfort you should squeeze the ball. This sets off an alarm that the technologist can hear. The technologist will then talk to you, and will stop the scan if you want. There is a microphone in the scanner so that you can communicate with the technologist. However, the scanner makes a lot of noise when it is running and the technologist may not always hear what you say. If you need to get the technologist's attention, you should squeeze the ball.

Remember, if at any point you feel uncomfortable and want to stop the scan, just squeeze the ball and tell the technologist.

Risks from metal
The strong magnetic field in the scanner will pull on things that contain certain types of metal. If someone takes a metal object into the scan room, it might fly towards the scanner and hurt you. For this reason, everyone (including you) must remove everything metal from their clothes and pockets before going into the scan room. Also, the door to the scan room will be kept closed during the scan to prevent unauthorized people from walking in.
If you have something metal inside your body, the scanner might pull on it and make it move. You must tell study personnel before your scan if you have anything metal inside your body.
Some types of metal might heat up when the scanner is running. If you feel any burning sensation during the scan, you should squeeze the emergency ball and the technologist will stop the scan.

Risks from electronic devices
If you have any electronic devices on the inside or outside of your body, the scanner might make them stop working properly. For this reason, you must tell study personnel before your scan if you have anything electronic on or in your body.

Burns
Metal is not the only thing that can cause burns in MRI. It's possible (although very rare) to get burned by touching the inside walls of the scanner or by making skin-to-skin contact. The technologist will give you a blanket or cushions so that you don't touch the inside walls of the scanner. You should also avoid letting your hands or legs touch each other. Remember, if you feel any burning sensation during the scan, you should squeeze the emergency ball and the technologist will stop the scan.

Tinnitus (ringing in the ears) and hearing loss
The scanner makes very loud sounds while it is running. You will be given earplugs or headphones to wear during the scan. Make sure you roll the earplugs tightly and let them expand in your ears so that they work properly. If the sound of the scanner is still so loud that it causes you discomfort, squeeze the emergency ball and tell the technologist. This is important because very loud sounds can cause ringing in the ears or even hearing loss.

Feeling warm or hot
The radiowaves used in MRI are like those your cellphone uses, but much stronger. Sometimes they are strong enough to make you feel warm (just like standing in bright sunshine makes you feel warm). MRI scanners are designed to try to avoid you getting too hot. However, if you start to feel uncomfortable, squeeze the emergency ball and tell the technologist.

Peripheral nerve stimulation (tingling or twitching)
The magnetic field inside the scanner changes very quickly while the scanner is running. If it changes too quickly, it can give you tingling sensations or make you twitch. MRI scanners are designed to try to avoid this. However, if you experience tingling or twitching, squeeze the emergency ball and tell the technologist.

Claustrophobia (discomfort in enclosed spaces)
Some people get panic attacks inside enclosed spaces. This is called ‘claustrophobia’, which means ‘fear of confined spaces’. If you know that you are claustrophobic, tell study personnel before your scan. Some people only find out they are claustrophobic when they have an MRI for the first time. If you feel anxious or panicky inside the scanner, squeeze the emergency ball and the technologist will get you out.

Quench
In very rare circumstances, the scanner can lose its magnetic field. This happens very suddenly and is known as a ‘quench’. The helium that helps keep the magnetic field strong will then escape from the scanner. The scanner is connected to a vent so that the helium will go outside the building. However, if for some reason the vent doesn’t work properly, helium might fill the scan room, making it difficult to breathe. In the very unlikely event of a quench, the technologists will get you out of the scanner immediately.

Gadolinium contrast (MRI dye)
You might need to have an injection of gadolinium contrast (a dye that lights up on the images). Sometimes the dye can cause side effects like headache, dizziness, or nausea (feeling slightly sick) for a short time after the injection. Some people might get an itchy skin rash, although this is uncommon (about 1 in 1000 people). It is also possible to have a serious allergic reaction called ‘anaphylactic shock’, which can cause swelling of the mouth and make it difficult to breathe. However, this is very rare (about 1 in 10,000 people). The technologist will tell you ahead of time when the dye is about to be injected, and will keep in contact with you to make sure that you’re OK. If you feel any discomfort, squeeze the emergency ball and the technologist will come into the room to check on you.

The dye leaves your body in your pee. Provided your kidneys are healthy, it should be almost all gone in about 24 hours. However, if you have kidney problems, you should tell study personnel before your scan. In rare situations, people with severe kidney problems have developed a serious condition called ‘nephrogenic systemic fibrosis’ from certain types of dye.

Fairly recently (in 2014) scientists discovered that if people get many injections of certain types of dye, some of the dye seems to stay in their brain for a long time afterwards. Doctors don’t know yet whether this is bad for you or not. However, if you have already had dye many times before, you should tell study personnel before your scan.

CT Scan risks (if unable to undergo MRI):

Radiation Exposure: During this study, you will have exposure to radiation from liver CT scans if you are unable to undergo MRI, as well as CT-guided biopsy. This radiation exposure is not necessary for your medical care and is for research purposes only. This means that you will be exposed to small doses or amounts of radiation. The risk from this amount of radiation is less than the risk from everyday exposure to the sun. The risks of receiving very small doses of radiation are thought to be low. These risks are not actually known.

Pregnant women cannot be exposed to radiation. Women must have a negative pregnancy test before they can have a CT scan.

2.4.2 Known Potential Benefits

Nivolumab has been evaluated in a phase II study in HCC patients (Checkmate 040 study) and was recently FDA approved for use in HCC patients. The ORR was noted to be 15% with 3% having a CR and 12% having a PR (7). Most recent updates on this trial (N=154) have shown that the median time to response was 2.8 months. The median DOR has not been reached after 48 months of follow up. Of those patients responding, 59% had a DOR of greater than 12 months. Median OS based on best overall response (RECIST v.1.1) and stratified as complete/partial response, stable disease, and progressive disease was not reached, 16.7 months, and 8.9 months, respectively (El-Khoueiry et al, ASCO-GI, 2018).

In the phase I study of BMS-986253 in solid tumor malignancy patients (CA027-001, Investigator Brochure), there were no observed objective radiographic responses in the 15 participants. In the phase 1/2a study evaluating the combination of BMS-986253 and Nivolumab (CA027-002) in advanced cancer patients there is no efficacy data available at the present time.

It is possible that some study subjects who receive the study therapies may experience an improvement in their cancer during the study. Others with HCC may benefit in the future from what is learned in this study.

3 Objectives and Purpose

3.1 Primary Objective

The primary objective is to determine the ORR of BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy using RECISTv.1.1 criteria. Additionally, the safety of the BMS-986253 in combination with Nivolumab will be determined.

3.2 Secondary Objectives

The secondary objectives are to determine the TTR, DOR, PFS, and OS for subjects receiving BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy. An additional secondary objective is to evaluate the tumor microenvironment (TME) using novel NYU technologies of 30-parameter flow cytometry and single cell RNAseq on pre- and on-treatment fresh core tumor biopsies.

4 Study Design and Endpoints

4.1 Description of Study Design

The trial is a phase II, randomized controlled, single blinded study evaluating 2 study arms: Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400 mg IV every 2 weeks(see Study Schema). Six patients will be observed for toxicity in each arm The trial will be performed at two sites. Holding of dose will occur if a dose limiting toxicity occurs on any arm.

4.2 Study Endpoints

4.2.1 Primary Study Endpoints

The primary endpoint will be the ORR of the Nivolumab and BMS-986253 combination, and the ORR of the Nivolumab monotherapy. ORR will be determined based upon RECIST v. 1.1 criteria. The safety of BMS-986253 in combination with Nivolumab will be determined.

4.2.2 Secondary Study Endpoints

The secondary endpoints will include determining the TTR, DOR, PFS, OS, and safety for both treatment arms. These endpoints will allow achievement of the secondary objectives for the study. Thus, these determinations will provide greater insight toward expected clinical response of BMS-986253 when combined with Nivolumab for use in HCC patients. Additionally, potential new insights into the management of side effects and increased safety is possible.

4.2.3 Exploratory Endpoints

Exploratory/translational endpoints will include detailed analysis of fresh pre-treatment and on-treatment (protocol at three months and at time of progression) core biopsies. Our collaboration team at NYU includes the ability to interrogate the TME in a novel, rigorous manner using 30-parameter platforms for single cell flow cytometry. This novel technology also has the ability to “tag” cell subsets/markers and perform single cell RNAseq. Using these techniques, we will aim to discover novel biomarkers predictive of response along with the ability to identify additional novel targets in patients who may “escape” or relapse to known immune oncology therapies.

5 Study Enrollment and Withdrawal

Advanced HCC patients who are not eligible for resection or other local-regional therapy, and are eligible for systemic treatment will be considered. Patients must be naïve to other systemic therapies. The study is a phase II design with 50 patients to be randomized 1:1 into the following arms (see Study Schema): Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400mg IV every 2 weeks.The first six patients will be monitored for Dose Limiting Toxicity in each arm. Dose Limiting Toxicities will be defined by toxicity occurring during the first 4 weeks of treatment on this study. If no drug related AE meeting DLT criteria is observed in any arm in >=4 of 6 patients, the study arms will continue as planned. If >2 out of 6 patients are observed to have related AE (i.e., AE with no clear alternative explanation) meeting DLT criteria that has not been observed in the use of nivolumab monotherapy as described in the package insert, then a lower dose strategy for BMS-986253 (1200 mg IV q 2 weeks) vs. discontinuation of the arm will be implemented in coordination with the DSMC and the study supporter. Should a lower dose strategy be chosen, DLTs will be observed in the first 6 subjects will be observed as above prior to expansion to 25 subjects.

The following will be considered DLTs:

• Any grade 4 toxicity

• Any grade 3 toxicity, with the exceptions of fatigue; rash that improves to grade 2 with medical management within 3 day; elevations of amylase and lipase in the absence of clinical pancreatitis; elevations in AST, ALT or alkaline phosphatase; nausea, vomiting or diarrhea that improves to grade 2 or lower, with maximal medical management within 3 days; and any grade 3 electrolyte abnormality that is corrected to grade 2 or lower within 48 hours; hypothyroidism that improves to grade 2 with medical management.

Asymptomatic lymphopenia or leukopenia of any grade will NOT be considered a DLT.

Any toxicity fitting the above criteria for the definition of a DLT and with an attribution of "related" to study treatment is required to be considered a DLT.

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Have histologically confirmed evidence of HCC, Childs-Pugh score of ≤7.
   a. Participants must be willing to provide specimen from fresh, pre- and on-treatment tumor core biopsies for histologic diagnosis and translational studies.
2. Radiographically measurable disease by RECIST1.1 in at least one site.
3. Deemed to not be a candidate for resection or other local-regional therapy.
4. Must not be receiving treatment with other investigational agents and must not have received any other systemic therapy prior to registration.
   a. Prior radioembolization, local ablative therapies (radiofrequency, microwave or cryoablation), radiation (external beam or stereotactic), or hepatic resection permitted if completed ≥ 4 weeks prior to study enrollment and if patient has recovered with ≤ grade 1 toxicity and if untreated measurable disease is present.
5. Be willing and able to provide written informed consent/assent for the trial.
6. Participants must be ≥ 18 years
7. Have a Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
8. If hepatitis B is present, participants must be on anti-viral HBV therapy.
9. All women of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a blood test to rule out pregnancy within 24 hours prior to start of study treatment
10. All women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study treatment (s) and for 4 months following discontinuation of study treatment.
11. Male participants must not donate sperm during this period.
12. Demonstrate adequate organ function as defined by the following required lab and acceptable range criteria:

<u>Adequate bone marrow function:</u>	
Absolute neutrophil count	> 1000/mcL
Platelet count	> 50,000/mcL
Hemoglobin	≥ 8.5 g/dL
<u>Adequate hepatic function:</u>	
Total bilirubin (ULN)	≤ 2 mg/dL or ≤ 1.5 times upper limit of normal
AST and ALT	≤ 5 times ULN
INR	≤ 1.5 times ULN
Albumin	≥ 2.8 g/dL
<u>Adequate renal function:</u>	
Creatinine	< 2.0 mg/Dl

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Women who are pregnant or breastfeeding.
2. Presence of other malignancies. Participants with active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ. NOTE: Patients with history of malignancy are not considered to have a “currently active” malignancy if they have completed therapy and are now considered by their physician to be at less than 30% risk for relapse.
3. Have active or history of Tuberculosis
4. Participants with known HIV positive status
5. Participants with known CNS metastases
6. Uncontrolled ascites
7. Uncontrolled encephalopathy
8. Uncontrolled gastro-esophageal varices. Prior organ allograft or allogeneic bone marrow transplantation
9. Participants with active, known, or suspected autoimmune disease. Participants with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, euthyroid participants with a history of Grave’s disease (participants with suspected autoimmune thyroid disorders must be negative for thyroglobulin and thyroid peroxidase antibodies and thyroid stimulating immunoglobulin prior to first dose of study treatment), psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

10. Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study treatment administration except for adrenal replacement steroid doses > 10 mg daily prednisone equivalent in the absence of active autoimmune disease. **Note**: Treatment with a short course of steroids (< 5 days) up to 7 days prior to initiating study treatment is permitted.

11. Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected treatment-related pulmonary toxicity.

12. Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:
    - -Myocardial infarction or stroke/transient ischemic attack within the past 6 months
    - -Uncontrolled angina within the past 3 months
    - -Any history of clinically significant arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes)
    - -History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, significant pericardial effusion, or myocarditis)
    - -Cardiovascular disease-related requirement for daily supplemental oxygen therapy.
13. Participants with ongoing or active, uncontrolled infections (afebrile for ≥ 48 hours off antibiotics). If hepatitis B is present, must be on anti-viral HBV therapy.
14. Must not have a psychiatric illness, other significant medical illness, or social situation, which, in the investigator’s opinion, would limit compliance or ability to comply with study requirements.
15. Any major surgery within 4 weeks of study treatment. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before
16. Any uncontrolled inflammatory disease including Crohn’s disease and ulcerative colitis
17. Treatment with botanical preparations (eg, herbal supplements, including potential drugs of abuse, or traditional Chinese medicines) intended for general health support or to treat the disease under study within 2 weeks prior to randomization/treatment.
18. Concomitant use of statins while on study.
19. Current or history of clinically significant muscle disorders (eg, myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels.
20. Known history of sensitivity to infusions containing Tween 20 (polysorbate 20) and Tween 80 (polysorbate 80).
21. Participants who have received a live / attenuated vaccine within 30 days of first treatment.

22. Concomitant use of any live / attenuated vaccine during treatment and until 100 days following last dose.

5.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

5.4 Vulnerable Subjects

Vulnerable subjects will not be eligible for enrollment into the study.

5.5 Strategies for Recruitment and Retention

Potential patients with advanced HCC will be identified in the multidisciplinary liver cancer programs at the participating sites. This may include review during multidisciplinary tumor boards to identify potential participating patients. Potential participating patients will be referred in to the site cancer center ambulatory clinics for formal screening and consent. It is anticipated that 90 patients total may need to be screened anticipating potential screening failures. The study title will be included on cancer center web content listing available clinical trials at individual study site. The study will also be listed on https://clinicaltrials.gov website.

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations.

Target enrollment for this study is 50 patients over 2 years. The target accrual goal is 25 patients per year. Patients will be recruited from physicians participating in this study. Consenting, screening, and treatment will take place at the NYU Langone Health PCC or participating sub-sites under the supervision of the Site PI. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

The Principal Investigator will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed.

2. Determine patient eligibility; see Section 5.1 and 5.2

3. Submit registration to NYU Langone Health Perlmutter Cancer Center CTO

4. Receive registration confirmation from the NYU Langone Health Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

The informed consent process and documentation follows established institutional guidelines.

5.6 Registration Procedures

5.6.1 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYULH PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist
3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

A unique patient study number will be issued once consent is received, due to serum IL-8 samples collected prior to eligibility confirmation. The patient will not be identified by name. Once remaining registration material is verified, the patient is considered accrued on study.

5.6.2 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's quarterly Data and Safety Monitoring report to the DSMC. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide remote extensive monitoring including real-time review of all eCRFs to ensure completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be completed within four weeks of enrollment.

5.6.3 Patient Registration at Additional Sites

Enrollment at addition sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyulangone.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyulangone.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. A unique patient study number will be issued once consent is received, due to serum IL-8 samples collected prior to eligibility confirmation. The NYU Langone Health

PCC CTO will provide the subject's unique study number via email. Once remaining registration material is verified a signed eligibility conformation worksheet email is sent. This number is unique to the participant and must be written on all data and correspondence for the participant.

The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Nina Beri. All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Subjects must not start any protocol procedures prior to registration; each participating institution will order the study agent directly from the supplier, Bristol-Myers Squibb (Nivolumab, BMS-986253).

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone Health PCC Clinical Trials Office and to their IRB as per site institutional policy.

Please email all SAEs to NYUPCCsafetyreports@nyulangone.org, Dr. Beri, PCC Assigned Medical Monitor, and the NYU Langone Health CTO Quality Assurance specialist.

5.7 Duration of Study Participation

Study participants will receive study drug until events such as (outlined in Section 5.9.1) a) disease progression, b) treatment related toxicity or other adverse event preventing continued participation, or c) withdrawal of consent. It is estimated that of the 50 enrolled, evaluable patients, that 50% will complete 17 cycles and 50% will complete an additional 17 cycles. Thus, the screening period and intervention period for 50% of participants will have a duration of 17.5 months and for 50% a duration of 34.5 months. The follow up period will occur for at least every 3 months for 1 year after last study treatment dosage, even in patients who discontinue the study drug. Thus the total study duration is estimated to be 20.5-23.5 months for 50% of participants and 34.5-37.5 months for 50% of participants.

5.8 Total Number of Participants and Sites

Recruitment will end when approximately 50 participants are randomized over 2 years. It is expected that approximately 70 participants will be screened in order to enroll and produce 50 randomized participants. There will be no international sites. Other U.S. sites may be considered to facilitate enrollment.

5.9 Participant Withdrawal or Termination

5.9.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

A subject has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion. The investigator and supporter have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for subject withdrawal from the study may include, but are not limited to:

- Subject withdrawal of consent at any time.
- Disease progression (if applicable)
- Intolerable toxicity (If applicable)
- Any medical condition that the investigator or supporter determines may jeopardize the patient's safety if s/he continues in the study or continues treatment with study drug.
- The investigator or supporter determines it is in the best interest of the patient.
- Failure of the subject to adhere to protocol procedure requirements
- Pregnancy (if applicable)
- Study termination by Supporter

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). All patients who withdraw from study drug prematurely will undergo end-of-treatment assessments within 30 days after the last dose, if possible. Regardless of the reason for withdrawal, effort shall be made to follow safety events from the time of withdrawal through resolution or until the event stabilizes. Subjects who discontinue study drugs will continue to be followed for adverse events for up to 100 days and for survival every 3 months (+/- 2 weeks) from the date of last dose of study drug(s) for up to 12 months.

5.9.2 Handling of Participant Withdrawals or Termination

Significant efforts will be made to continue follow-up of withdrawn or terminated participants or participants who discontinue study agent but remain in the study for follow-up, especially for safety and efficacy of secondary study endpoints. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). The PI and site PIs will attempt to obtain at a minimum survival data on all participants lost to follow-up. Methods that will be used prior to stating that a participant is lost to follow up will include at least three phone calls to participant or next-of-kin if possible. A certified letter will be mailed if the phone calls fail to secure follow up information.

Withdrawal from the study can be made in writing to the Principal Investigator, Dr. Nina Beri. Any samples/specimens remaining after formal withdrawal, will be destroyed/discarded per Institutional guidelines.

5.10 Premature Termination or Suspension of Study

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Dr. Nina Beri, BMS, and any regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.
Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

- Determination of futility

The study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the supporter, IRB and/or FDA.

6 Study Agent (Study drug, device, biologic, vaccine etc.) and/or Procedural Intervention

6.1 Study Agent(s) and Control Description

6.1.1 Acquisition

The study drugs will be shipped from Bristol-Myers Squibb at 2-8ºC (36-46ºF) and be stored in the study site cancer center pharmacy of each participating institution until use at the same temperature.

6.1.2 Formulation, Appearance, Packaging, and Labeling

Product Description / Class and Dosage Form	Potency/Route of Administration	Blinded or Open Label	Packaging / Appearance	Storage Conditions (Per Label)
Nivolumab (BMS-936558-01) Solution for Injection	100 mg (10 mg/mL)	Open label	Vial	Refer to the label on container
Nivolumab (BMS-936558-01) Solution for Injection	40 mg (10 mg/mL)	Open label	Vial	Refer to the label on container
BMS-986253 (BMS-986253) Solution for Injection	200 mg (20 mg/mL)	Open Label	Vial	Refer to the label on container
BMS-986253 (BMS-986253) Solution for Injection	1000 mg (100 mg/mL)	Open Label	Vial	Refer to the label on container
BMS-986253 (BMS-986253) Solution for Injection	1200 mg (100 mg/mL)	Open Label	Vial	Refer to the label on container

Please refer to the current version of the Investigator Brochures for complete preparation, storage, and handling information.

Nivolumab: Nivolumab is and IgG4 monoclonal antibody in a clear to opalescent, colorless to pale-yellow solution available for injection in a single dose 100 mg or 40 mg vial. See Package Insert (Appendix).

BMS-986253: BMS-986253 is a IgG1k monoclonal antibody in a clear to opalescent, colorless to pale-yellow solution available for injection in a single dose vial. Some particulates may be present. See Investigator Brochure (Appendix). Each vial contains 200 mg/vial (20 mg/mL), 1000 mg/vial (100mg/mL) or 1200 mg/vial (100 mg/mL)

All 2 trial drugs are manufactured and packaged by Bristol-Myers Squibb.

6.1.3 Product Storage and Stability

All three study drugs should be stored at 2-8°C (36-46°F) protected from light, and protected from freezing. BMS-986253 should be stored in original container.

6.1.4 Preparation

Nivolumab (Opdivo®): See Package Insert (Appendix). Withdraw the required volume of OPDIVO and transfer into an intravenous container.
• Dilute OPDIVO with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. The total volume of infusion must not exceed 160 mL.
• Mix diluted solution by gentle inversion. Do not shake.
• Discard partially used vials or empty vials of OPDIVO.

After preparation, store the OPDIVO infusion either:
• at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
• under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.
Do not freeze.

BMS-986253: See Investigator Brochure (Appendix). Vials are single use. Dilute drug into 0.9% sodium choloride injection. Administration of diluted BMS-986253 injection must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored for up to 24 hours refrigerated at 2° to 8°C (36° to 46°F) protected from light; 4 hours of the 24 hours can be at room temperature (15° to 25°C, 59° to 77°F) ambient light. The diluted solution in IV bag should not be shaken or frozen. Equilibration to room temperature is recommended for the infusion bag, drug product, or their combination prior to administration.

6.1.5 Dosing and Administration

Nivolumab will be administered by infusion over 30 minutes through an intravenous line containing asterile, non-pyrogenic, low protein binding in-line filter. BMS-986253 will be administered by infusion over 120 minutes through an intravenous line containing asterile, non-pyrogenic, low protein binding in-line filter. If the patient's weight is < 35 kg, the infusion will be administered over 180 minutes. Pore size of 0.2 micrometer to 1.2 micrometer is acceptable for Nivolumab and BMS-986253 (see package insert and IB, respectively).Do not co-administer other drugs through the same intravenous line. Flush the intravenous line at end of infusion. When administering BMS-986253 with Nivolumab, infuse Nivolumab first followed by a 30 minute period of observation followed by infusion BMS-986253 over 120 minutes on the same day. Use separate infusion bags and filters for each infusion.

6.1.6 Route of Administration

Intravenous (IV)

6.1.7 Dose Adjustments/Modifications/Delays

Recommendations for study drug modifications are provided in the tables below. The recommendations for Nivolumab monotherapy are from the Package Insert. Since no dose limiting toxicity has been observed for BMS-986253 monotherapy in phase I (Investigator Brochure) and the combination of Nivolumab and BMS-986253 is currently being evaluated in CA027-002 with no new safety signals noted,

the management plan for toxicity will be the same as for Nivolumab monotherapy however both agents will be withheld or discontinued based on the described AEs below.

There are no recommended dose modifications for hypothyroidism or hyperthyroidism.

Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions. Discontinue the study drug in patients with severe or life-threatening infusion reactions.

ADVERSE EVENT MANAGEMENT FOR NIVOLUMAB MONOTHERAPY OR FOR NIVOLUMAB IN COMBINATION WITH BMS-986253

Adverse Reaction	Severity*	Dose Modification
Colitis	Grade 2 diarrhea or colitis	Withhold dose[a]
	Grade 3 diarrhea or colitis	Withhold dose when single agent (Nivolumab monotherapy), Permanently discontinue when administered with additional study drug
	Grade 4 diarrhea or colitis	Permanently discontinue
Pneumonitis	Grade 2 pneumonitis	Withhold dose[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Hepatitis	If AST/ALT is within normal limits at baseline and increases to more than 3 and up to 5 times ULN	Withhold dose[b]
	If AST/ALT is more than 1 and up to 3 times ULN at baseline and increases to more than 5 and up to 10 times ULN	
	If AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 8 and up to 10 times ULN	
	If AST or ALT increase to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose[a]
	Grade 4 hypophysitis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose[a]
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Type I Diabetes Mellitus	Grade 3 hyperglycemia	Withhold dose[a]
	Grade 4 hyperglycemia	Permanently discontinue
Nephritis and Renal Dysfunction	Serum Cr more than 1.5 and up to 6 times the ULN	Withhold dose[a]
	Serum Cr more than 6 times the ULN	Permanently discontinue
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose[a]
	Grade 4 rash or confirmed SJS or TEN	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose[a]

	Immune-mediated encephalitis	Permanently discontinue
Other	Other Grade 3 adverse reaction First Occurrence	Withhold dose[a]
	Recurrence of same Grade 3 Adverse reactions	Permanently discontinue
	Life threatening or Grade 4 adverse reaction	Permanently discontinue
	Grade 3 myocarditis	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Grade 2 or 3 adverse reactions lasting 12 weeks or longer	Permanently discontinue

* Toxicity is graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5).
[a] Withhold all study drugs, resume treatment when adverse reaction improves to Grade 0 or 1.
[b] Withhold all study drugs, resume treatment when AST/ALT returns to baseline.

6.1.8 Duration of Therapy

Duration of therapy will be at least three cycles, unless AE requiring dose modification is required (6.1.7), at which point first radiographic imaging is performed. From a statistical standpoint, this will be an evaluable participant for objective response based on RECISTv1.1 criteria. One cycle is defined as 4 weeks.

6.1.9 Tracking of Dose

Dosing of drugs will occur under supervision in the infusion center at the study sites.

6.2 Study Agent Accountability Procedures

The study agents will be distributed to the pharmacy at their request to ensure dosing of all study participants with additional 2 doses surplus in case there is damage. Shipping requires 5-7 days with no deliveries on Mondays. Drug request forms will be provided to sites at study start. Receiving and documentation of adequate and safe handling will be performed by the pharmacy and records maintained by the study coordinator. Unused product will be returned to the supporter (Bristol-Myers Squibb).

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated by the study team.

Any unused drug and also at the final reconciliation of the site's drug supply at the end of the study will be shipped back to the supporter (Bristol-Myers Squibb, Princeton, NJ 08543).

7 Study Procedures and Schedule

7.1 Study Procedures/Evaluations

7.1.1 Study Specific Procedures

- Informed Consent
- Peripheral serum IL-8 determination (Pre- and On-treatment)

- Assessment of eligibility should include a review of permitted and prohibited medications.
- Toxicity Evaluation
- Study Drug Administration
- On-treatment biopsy

7.1.2 Standard of Care Study Procedures

- Medical history (by interview and from medical records, social history, past medical and surgical history)
- Symptom Assessment (complete review of systems)
- Medication history (complete medication history is needed, prescription and over-the-counter medications). Assessment of eligibility will include a review of permitted and prohibited medications.
- Physical examination (vital signs including height and weight, head and neck, respiratory, lymphatic, abdomen, cardiovascular, neurologic, musculoskeletal).
- Performance Status (ECOG)
- Radiographic or other imaging assessments. MRI or CT (3 phase liver protocol with IV contrast), CT chest
- Biological specimen collection and laboratory evaluations. See Section 7.2 Laboratory Procedures/Evaluations below.
- A discussion of if the results of any study specific procedures (e.g., radiographic or other imaging or laboratory evaluations) will be provided to participant.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Screening Laboratory Tests

- ***Hematology:*** *hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Biochemistry:*** *creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, sodium, glucose*
- ***Coagulation:*** *Prothrombin Time (International Normalized Ratio/INR)*
- ***Tumor Marker:*** *alpha fetoprotein (AFP)*
- ***Pregnancy test****, usually to be done within 24 hours prior to study intervention and results must be available prior to administration of study product.*

Post-enrollment Laboratory Tests

- ***Hematology:*** *hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count.*
- ***Biochemistry:*** *creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, alkaline phosphatase, sodium, glucose*
- ***Coagulation:*** *Prothrombin Time (International Normalized Ratio/INR)*
- ***Tumor Marker:*** *alpha fetoprotein (AFP)*

7.2.2 Other Assays or Procedures

Serum IL-8 determination: Venipuncture for blood into yellow top tube (2-3 mL) to collect blood/serum for IL-8 at screening and at beginning of cycle 4. Serum will be collected on site, frozen, and sent on dry ice for screening IL-8 assay at Rules Based Medicine. IL-8 assay will be performed using the Luminex

ELISA so that screening IL-8 level can be determined. Serum obtained may be saved frozen (-20ºC) in aliquots for later exploratory analysis.

Pre- (Standard of Care) and On-treatment (Translational/Correlative Study) Tumor Core Biopsies: Ultrasound guided or CT guided percutaneous core needle biopsies will be performed by Interventional Radiology. Core needle biopsies (6 cores) will be obtained using 14-18G needles as per Standard of Care techniques for both pre-treatment and on-treatment biopsies. Fresh cores (4 pre-treatment and 6 on-treatment) will be placed immediately in Miltenyi Tissue Storage Buffer on ice. Two cores (pre-treatment only) will go to pathology for SOC evaluation. Research samples will then be processed and analyzed at NYU (Welling Lab).

7.2.3 Specimen Preparation, Handling, and Storage

See sections 7.2.2 and 7.2.4

7.2.4 Specimen Shipment

Serum IL-8 determination: All serum samples for IL-8 determination will be sent frozen on dry ice via FedEx overnight shipping to Rules Based Medicine for analysis. Sera obtained at screening or cycle 4 may be stored frozen (-20ºC) and sent in batches on dry ice for analysis in batches at Rules Based Medicine. Serum specimens will only be sent on Mondays-Thursdays.

Pre-(Standard of Care) and On-treatment (Translational/Correlative Study) Tumor Core Biopsies: Core biopsies will be obtained at screening and 2 cores will be provided for clinical pathologic evaluation as part of standard of care practice. An additional 4 cores will be immediately placed in Miltenyi Tissue Storage Buffer on ice and sent to the Theodore H. Welling Liver Cancer Lab (Dr. Shanshan Wan and Dr. Theodore Welling, NYU Langone Health, Science Building, 4th floor, 435 E. 30th St., New York, NY 10016). Study sites separate from NYU will schedule and send core biopsy specimens on Mondays-Thursdays only, via Fed Ex, overnight. Cycle 3 tumor core biopsies will be processed in the same manner except that all 6 cores will go to Welling lab and no cores will go to SOC pathology.

As of February 2024, specimen analysis is complete, and no samples will be collected or stored for future analysis.

7.3 Study Schedule

7.3.1 Screening

Screening Visit (Day -20 to -1)

- Obtain informed consent of potential participant verified by signature on written informed consent for screening form.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform medical examinations needed to determine eligibility based on inclusion/exclusion criteria.
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1), AFP, IL-8 levels.
- MRI abdomen (or CT if not eligible), 3 phase IV contrast, liver protocol.
- CT chest (with or without IV contrast).
- Ultrasound or CT guided core tumor biopsy.
- Schedule study visits for participants who are eligible and available for the duration of the study.
- Provide participants with instructions needed to prepare for first study visit.
- Randomize participant to either Arm 1or Arm 2 of study treatment (see Study Schema).

7.3.2 Enrollment/Baseline

Enrollment/Baseline Visit (Visit 1, Day 1, Cycle 1)

- Verify inclusion/exclusion criteria.
- Record vital signs, results of physical examinations, and medical history.
- Collect blood for hematology, biochemistry, coagulation, and pregnancy test (Section 7.2.1).
- Administer the study treatment (Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400mg every 2 weeks..
- Observe for infusion reactions and treat if needed (see Package Insert for Nivolumab and Investigator Brochures for BMS-986253).

7.3.3 Intermediate Visits

7.3.3.1 Visit 2

Visit 2, Cycle 1 (Day 15 +/- 3)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1).
- Administer the study treatment (Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400 mg IV every 2 weeks.

7.3.3.2 Visit 3

Visit 3, Cycle 2 (Day 29 +/- 3)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1).

Administer the study treatment (Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400 mg IV every 2 weeks.

7.3.3.3 Visit 4

Visit 4, Cycle 2 (Day 45 +/- 3)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1).

Administer the study treatment (Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400 mg IV every 2 weeks.

7.3.3.4 Visit 5

Visit 5, Cycle 3 (Day 59 +/- 3)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1). AFP to be determined every 8 weeks for 12 months then every 12 weeks thereafter

- Collect blood for IL-8 level (Cycle 3 only)
- Administer the study treatment (Arm 1 (control) Nivolumab 240mg IV every 2 weeks monotherapy; Arm 2 Nivolumab 240 mg IV plus BMS-986253 2400 mg IV every 2 weeks.
- MRI abdomen (or CT if not eligible), 3 phase IV contrast, liver protocol. To be performed every 8 weeks for 12 months, then every 12 weeks thereafter
- CT chest (with or without IV contrast). To be performed every 8 weeks for 12 months, then every 12 weeks thereafter
- Tumor objective response determination (RECIST v. 1.1). To be performed every 8 weeks for 12 months, then every 12 weeks thereafter
- Ultrasound or CT guided core tumor biopsy (Cycle 3 only).

7.3.3.5 Visit 6

Visit 6, Cycle 3 (Day 74 +/- 3)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1).
- Administer the study treatment.

7.3.4 Final Study Visit

A final study visit will be scheduled if a treatment related or non-treatment related AE occurs such that further treatment is not advised, disease progression has occurred, or participant wishes to withdraw from the study (or other reasons as listed in Section 5.9).

For participants having suspected disease progression, consideration will be made for ultrasound or CT guided tumor biopsy as part of standard of care. For participants deemed to be deriving a clinical benefit despite evidence of disease progression, consideration will be made for continuation of study drug treatment. For example, appearance of new tumors if index tumors have had a response/stable disease will be one type of consideration. If tissue biopsy is obtained, clinical and translational core biopsy tissue will be obtained and processed as described (Section 7.2). Study participants will be informed regarding all results of diagnostic imaging studies and clinical pathology biopsy results.

- In order to allow continued administration of study treatment despite progression of disease, e.g. based on appearance of a new lesion, patients must have absence of symptoms and signs of clinically important morbidity due to disease progression (e.g. requirement for additional medical management to control symptoms or irradiations to prevent morbidity), absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g. spinal cord compression), and no decline in ECOG or Karnofsky performance status
- If a patient is treated past disease progression, the patient will be re-consented using a written informed consent document at that time.
- Patients treated past disease progression will then be re-evaluated at 3 month intervals with CT or MRI to determine if progression is confirmed.

If there are any ongoing AEs or SAEs, participants will continue to receive treatment and follow up as per standard of care. Documentation of resolution or continued progression of AEs/SAEs will be provided.

Final Study Visit (Visit Z, Day Z+/-3)

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).

- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1), AFP
- Ultrasound or CT guided biopsy if applicable
- Provide final instructions to participant with regard to management of AEs.

7.3.5 Withdrawal/Early Termination Visit

Significant efforts will be made to continue follow-up of withdrawn or terminated participants or participants who discontinue study agent but remain in the study for follow-up, especially for safety and efficacy of secondary study endpoints. Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs). Subjects whom do not wish to continue further follow-up can formally withdraw consent, having the below assessments obtained. The PI and site PIs will attempt to obtain at a minimum survival data on all participants lost to follow-up. Methods that will be used prior to stating that a participant is lost to follow up will include at least three phone calls to participant or next-of-kin if possible. A certified letter will be mailed if the phone calls fail to secure follow up information.

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1), AFP
- MRI abdomen (or CT if not eligible), 3 phase IV contrast, liver protocol if greater than 6 weeks since most recent evaluation radiographic evaluation
- Tumor objective response determination (RECIST v. 1.1).
- Provide final instructions to participant with regard to management of AEs.

7.3.6 Unscheduled Visit

Unscheduled visits may be required for example to evaluate a participant for a suspected AE or to evaluate for symptomatic possible disease progression requiring potential study termination and consideration of other treatments (e.g. symptomatic bony metastasis requiring radiation therapy). The visit will be documented as “Unscheduled Visit”.

- Record adverse events as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1), AFP

If clinically indicated:

- MRI abdomen (or CT if not eligible), 3 phase IV contrast, liver
- CT chest (with or without IV contrast).
- Tumor objective response determination (RECIST v. 1.1).

7.3.7 Follow-Up Visits

The follow-up period will occur for at least every 3 months for 1 year after last study treatment dosage, even in patients who discontinue the study drug.

- Record survival status
- Record adverse events and concomitant medications as reported by participant or observed by investigator.
- Record vital signs, results of medical history, physical exam, height/weight, performance status (ECOG).
- Collect blood for hematology, biochemistry, coagulation (Section 7.2.1), AFP
- Record new anti-cancer treatment since last study visit, if applicable
- MRI abdomen (or CT if not eligible), 3 phase IV contrast, liver protocol.
- CT chest (with or without IV contrast).

- Tumor objective response determination (RECIST v. 1.1).

7.4 Concomitant Medications, Treatments, and Procedures

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the CRF are concomitant prescription medications, over-the-counter medications and non-prescription medications.

7.5 Prohibited Medications, Treatments, and Procedures

Treatment with oral steroids, calcineurin inhibitors, immune suppressive, other immune stimulatory, or anti-proliferative agents will not be permitted. Treatment with other chemotherapeutic agents will not be permitted. If participants are found to be taking such medications after entering treatment in the trial, then the participant will be recorded as an AE and undergo early termination from the trial.

7.6 Prophylactic Medications, Treatments, and Procedures

Topical numbing medications such as Emla cream or lidocaine cream may be used at site of injection. Nivolumab can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. Nivolumab will be discontinued in patients with severe or life-threatening infusion reactions. The rate of infusion will be interrupted or slowed in participants with mild or moderate infusion reactions.

7.7 Rescue Medications, Treatments, and Procedures

Corticosteroids may be provided at the discretion of the site clinical investigators as rescue therapy for high grade treatment related AEs (e.g. pneumonitis), usually 1-2 mg prednisone equivalents/kg/day and then tapered to off as AE resolves.

7.8 Participant Access to Study Agent at Study Closure

If the study is for any reason terminated due to completed enrollment and follow up, unexpected toxicity, or demonstrated superiority of one of the arms, individual participants who are judged to be experiencing a clinical benefit will be considered for continued treatment with study drug after consultation with the medical monitor assigned by NYULH DSMC and the funding supporter (BMS). If there are patients that fall into this criteria, a protocol amendment will be submitted to provide the continued treatment with adequate justification in doing so.

8 Assessment of Safety

8.1 Specification of Safety Parameters

8.1.1 Definition of Adverse Events (AE)

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

8.1.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

8.1.3 Definition of Unanticipated Problems (UP)

Unanticipated Problems Involving Risk to Subjects or Others
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.2 Classification of an Adverse Event

8.2.1 Severity of Event

For AEs not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

8.2.2 Relationship to Study Agent

The clinician's assessment of an AE's relationship to study agents (drug,) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported. All AEs must have their

relationship to study agent assessed. In a clinical trial, the study product must always be suspect. To help assess, the following guidelines are used.

- **Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate etiology has been established.

8.2.3 Expectedness

The PI, Dr. Nina Beri, and the Medical Monitor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agents.

8.3 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate RF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study supporter of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The supporter should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.4 Reporting Procedures – Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULH IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, but no later than 5 working days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events* that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or supporter, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- Breach of confidentiality
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file

8.4.1 Adverse Event Reporting

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 100 days following the last administration of study treatment.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.4.2 Serious Adverse Event Reporting

Investigators and the protocol supporter must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 days of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm (see definitions, section 8.1)

Events should be reported using the NYU CTO Medical Events Form.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

Serious adverse event reporting will begin in conjunction with the date of participant's written consent. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the principal investigator and PCC Assigned Medical Monitor, with a notification email sent to NYUPCCsafetyreports@nyulangone.org and recorded on the case report form.

All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism and the NYU Langone Health IRB by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyulangone.org and PCC Assigned Medical Monitor whether full information regarding the event is known or not.

Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Supporter. For laboratory results, include the laboratory normal ranges.

All other serious adverse events must be reported to the supporter and DSMC's appointed medical monitor within 24 hours by e-mail (NYUPCCsafetyreports@nyulangone.org) or fax (212-263-0715). The Serious Adverse Event Form must also be emailed to the principal investigator and Clinical Trials Office (NYUPCCsafetyreports@nyulangone.org) or it can be faxed (212-263-0715), this documentation will be forwarded to the DSMC's appointed medical monitor within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. All SAEs that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug within 24 hours of becoming aware of the event. SAEs must be recorded on either MedWatch, or approved site SAE form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

The Sponsor will reconcile the clinical database AE cases (**case level only**) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com).

- The Investigator will request from BMS GPV&E, aepbusinessprocess@bms.com the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report. The investigator must verify and confirm all SAEs are captured in this report.

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 (Worldwide.Safety@bms.com).

Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the DSMC if meeting the requirements for expedited reporting, the study Supporter will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB, DSMC, and FDA.

8.4.3 Unanticipated Problem Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DSMC/study supporter. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DSMC/study supporter within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMC/study supporter within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 days of the IR's receipt of the report of the problem from the investigator.

8.4.4 Reporting of Pregnancy

If a study participant develops a pregnancy, this represents a study exclusion criteria and study drugs will be discontinued and the participant will be withdrawn from the study. The occurrence of the pregnancy will be reported the DSMC, BMS, the study PI and medical monitor, the IRB, and the FDA. The pregnancy must be reported immediately to the principal investigator, and the Clinical Trials Office, by emailing: NYUPCCsafetyreports@nyulangone.org, and the study supporter (NYU Langone Health PCC) will report to BMS in accordance with their outlined procedures. A Final Study Visit will be scheduled, however the participant will continue to be followed until pregnancy outcome and continuing safety follow up will occur.

8.5 Reporting Procedures – Notifying the Study Supporter

The study clinician will complete a SAE Form within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the DSMC/study supporter within 24 hours of site awareness. See Section 1, Key Roles for contact information.
- Other SAEs regardless of relationship will be submitted to the DSMC/study supporter within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the DSMC/study supporter and should be provided as soon as possible.

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects shall be provided promptly to the study supporter.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours of becoming aware of the event. SAEs must be recorded on either MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS on either the MedWatch or approved site SAE form. In addition the Pregnancy Surveillance Form (3 Parts) must be completed and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: +1 609-818-3804

Adverse Events that are routinely collected according to GCP shall be submitted to BMS every three (3) months by the last working day of the third month.

The Adverse Event information required to be sent to BMS is noted in an attached 'Bristol-Myers Squibb Early Asset Investigator Sponsored Research (ISR) Import Plan', which describes the method of collection and submission to BMS via the mailbox:
MG-RD-GPVE-PHARMACOVIGILANCE@bms.com
When the file is submitted to BMS, it must be noted the file contains

1) all Non Serious Adverse Events (only adverse events not previously submitted to BMS within the 3 months)

8.6 Reporting Procedures – Notifying the Study Supporter

Since multiple sites will be participating, the following describes events that must be reported to the study supporter (NYU Langone Health PCC) and the study supporter reports to BMS in an expedited fashion.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours of becoming aware of the event. SAEs must be recorded on either MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS. BMS will perform due diligence follow-up using the BMS Pregnancy Form which the investigator must complete.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: +1 609-818-3804

Initial Report: within 24 hours:

The following events must be reported to the study supporter (NYULMC PCC) by email within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Co-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to: NYUPCCsafetyreports@nyulangone.org

AND

Nina Beri, MD
Laura & Isaac Perlmutter Cancer Center
NYU Langone Health
240 East 38th Street, New York, NY 10016

Nina.Beri@nyulangonec.org
Phone: 212-731-5770

AND
PCC Assigned Medical Monitor

Events of Clinical Interest (any medical event that is deemed significant via Principal Investigator's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Supporter specifications

8.7 Reporting Procedures – Notifying the FDA

The study supporter is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports.

The following describes the IND safety reporting requirements by timeline for reporting and associated type of event:

- ***Within 7 calendar days*** *(via telephone or facsimile report)*
  Any study event that is:
  - associated with the use of the study drug
  - unexpected,
  - fatal or life-threatening

- ***Within 15 calendar days*** *(via written report)*
  Any study event that is:
  - associated with the use of the study drug,
  - unexpected, and
  - serious, but not fatal or life-threatening
    -or-
  - a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

Additional reporting requirements
Supporters are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Reporting Process
Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form; see Attachment1), or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 8.3. The contact information for submitting IND safety reports is noted below:

NYU Langone Health Contacts:

NYUPCCsafetyreports@nyulangone.org

AND

Nina Beri, MD
Laura & Isaac Perlmutter Cancer Center
NYU Langone Health
240 East 38th Street, New York, NY 10016

Nina.Beri@nyulangone.org
Phone: 212-731-5770

AND

PCC Assigned Medical Monitor

8.8 Reporting Procedures – Participating Investigators

In addition to reporting certain unanticipated problems and adverse events noted above to the FDA, it is the responsibility of the study supporter to report those same adverse events or findings to participating investigators at other study sites. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

8.9 Study Halting Rules

Administration of study agent will be halted when four grade 4 AEs and/or AEs that would require permanent discontinuation of study drugs (See Section 6.1.8) determined to be "probably related" are reported to the PI and the Medical Monitor. The study supporter and PI will notify investigators immediately when the third grade 4 event is reported and enrollment screens will stop accepting new study participants. The study supporter will inform the DSMC members within 24 hours of this occurrence and will provide the DSMC with AE listing reports. The DSMC will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMC will provide recommendations for proceeding with the study to the study supporter/NIH. The study supporter will inform the FDA of the temporary halt and the disposition of the study.

8.10 Safety Oversight

A Medical Monitor will be appointed to advise the study investigators and will monitor participant safety. The role of the Medical Monitor is to 1) Review all AEs on a regular basis throughout the trial; 2) be available to advise the investigators on trial-related medical questions or problems, and 3) evaluate cumulative participant safety data and make recommendations regarding the safe continuation of the study.

All Internal SAEs reported by the CTO, occurring to patients on clinical trials that are not monitored by any other institution or agency, are reported via email: NYUPCCsafetyreports@nyulangone.org and reviewed within 48 hours by the medical monitor. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of all SAEs on the study to date.
- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next scheduled study review.

Safety oversight will be under the direction of a DSMC composed of individuals with the appropriate expertise, including clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials. The DSMC will meet at least quarterly to assess safety and efficacy data on each arm of the study. The DSMC operates under the rules of an approved charter. The DSMC will provide its input to Bristol-Myers Squibb.

9 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Serious adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of serious adverse events via email initially, reviewed offline by the designated medical monitor, and presented at the next DSMC monthly meeting. The Data Safety and Monitoring Committee (DSMC) will review the study at least quarterly. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.1 Data Monitoring Committee

This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the NYULMC Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYULH PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by DSMC quarterly (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months. DSMC summary reports are available to facilitate the review and monitoring of this study. These reports include the following: patient listings and summary reports that describe study enrollment and accrual, eligibility, demographic characteristics, dose modifications, adverse experiences, subject's death and additional external published data if applicable to the study. Cumulative toxicities, SAEs, and AEs are reviewed, to identify possible adverse events with elevated frequency that is unexpected. Once a

recommendation is made if further action is required, the Investigator's must respond within of the time period specified in the DSMC letter.

10 Statistical Considerations

10.1 Statistical and Analytical Plans (SAP)

A formal SAP will be completed prior to database lock.

10.2 Statistical Hypotheses

The null hypothesis for the primary endpoint is that there is no difference in the ORR of the Nivolumab and BMS-986253 combinationand the ORR of the Nivolumab monotherapy.

The null hypothesis for the secondary endpoint is that there is no difference in TTR, DOR, PFS, OS, and safety for the Nivolumab and BMS-986253 combination and the Nivolumab monotherapy arm.

The alternative hypothesis for the primary endpoint is that there is a difference in the ORR of the Nivolumab and BMS-986253 combinationand the ORR of the Nivolumab monotherapy.

The alternative hypothesis for the secondary endpoint is that there is a difference in TTR, DOR, PFS, OS, and safety for the Nivolumab and BMS-986253 combinationand the Nivolumab monotherapy arm.

10.3 Analysis Datasets

The analysis dataset will be the Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants).

10.4 Description of Statistical Methods

10.4.1 General Approach

Descriptive statistics will be provided for every covariate and outcome by the studied arms. Continuous data will be presented as means with standard deviations, and categorical data will be presented as numbers with percentages. All p-values will be two sided. Normality assumptions will be checked and log transformation will be considered if normality assumption is violated.

10.4.2 Analysis of the Primary Efficacy Endpoint(s)

ORR will be defined as the best objective response using RECIST v.1.1 criteria based on MRI or CT scan evaluations following treatment. ORR will be compared by two-sample proportion test between BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy. P-values will be two-sided and any p-values less than 0.05 will be significant. No adjustment to significance determination for multiple comparisons will be made.

10.4.3 Analysis of the Secondary Endpoint(s)

Secondary Endpoints, including TTR, DOR, PFS, OS, and exploratory analysis of the HCC TME, will be performed. TTR and DOR will be described and PFS and OS will be compared between subjects receiving BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy. Kaplan-Meier method will be used to analyze the median TTR, DOR, PFS, and OS. Categorical variables will be compared by two-sample proportion test, survival outcomes will be compared by log rank test, and continuous outcome will be compared by two-sample t-test.

10.4.4 Safety Analyses

Descriptive statistics will be provided for every safety endpoints by the studied arms. The occurence of safety endpoints will be compared between BMS-986253 in combination with Nivolumab in comparison to Nivolumab monotherapy.

The first six patients assigned in each arm will be monitored for AEs meeting DLT criteria as specified in Section 5. Dose Limiting Toxicities will be defined by toxicity occurring during the first 4 weeks of treatment on this study. If no treatment related AE is observed in >=4 of 6 patients, the study will continue as planned. If >2 out of 6 patients are observed to have treatment related AE (i.e., AE with no clear alternative explanation) meeting DLT criteria that has not been observed in the use of nivolumab monotherapy as described in the package insert, then a lower dose strategy for BMS-986253 (1200 mg IV q 2 weeks) vs. discontinuation of Arm 2 will be implemented in coordination with the DSMC and the study supporter.

10.5 Sample Size

Group sample sizes of 25 in Nivolumab combination group and 25 in Nivolumab-only monotherapy group achieve 80% power to detect a difference between the group ORRs of 34%. The ORR in Nivo-only group is assumed to be 15%. The ORR in Nivolumab combination group is assumed to be 49% under the alternative hypothesis. The test statistic used is the two-sided Z-Test with unpooled variance. The significance level of the test is 0.05.

The powered sample size and expected ORR is based upon results from the phase II study of nivolumab in HCC as well as other checkpoint inhibitors (e.g. pembrolizumab) in HCC. If the results do not show significant efficacy, the HRs and 95% CIs will be estimated to quantify the magnitude of the efficacy in each treatment arm. If results are sufficiently promising, then the protocol may be amended to expand the cohort to allow comparison between treatments with higher confidence.

10.6 Randomization

The randomization list will be generated by the biostatistics department according to the proposed sample size and study design and uploaded into the REDCap randomization module. All centers will receive randomization assignment from NYU as the coordinating center. If a patient is randomized, but not ultimately treated, then the coordinating center (NYU PCC) must be notified. Randomization will be stratified within center.

11 Source Documents and Access to Source Data/Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. It is acceptable to use CRFs as source documents. If this is the case, it should be stated in this section what data will be collected on CRFs and what data will be collected from other sources.

Trialmaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data

requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or Trial master. Relevant source documentation to be reviewed by the assigned QA specialist throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Concurrent medications
3. Treatment records
4. Adverse events

12 Quality Assurance and Quality Control

This study will be monitored according to the monitoring plan detailed below. Sub-site monitoring will follow parameters detailed in Section 12.1. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents. If an on-site monitoring visit is necessary, the Investigator will provide access to all study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and ensure there is adequate space to conduct the monitoring visit. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform NYU PCC CTO and BMS of any audit requests by health authorities, and will provide BMS with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

At the NYU Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

In addition, the quality assurance unit will monitor this trial every 4-6 weeks; this includes real- time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

12.1 Monitoring of Other Participating Institutions

Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with a Site Investigator and staff. If remote EMR access is not available, then the Site Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), before emailing all requested documents to the quality assurance specialist within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high- priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Supporter or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

13 Ethics/Protection of Human Subjects

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

13.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 Informed Consent Process

13.3.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product. The following consent materials are submitted with this protocol: Informed Consent.

13.3.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the signed informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

A copy of the signed informed consent document will be stored in the subject's research record. The consent process, including the name of the individual obtaining consent, will be thoroughly documented in the subject's research record. Any alteration to the standard consent process (e.g. use of a translator, consent from a legally authorized representative, consent document presented orally, etc.) and the justification for such alteration will likewise be documented.

The informed consent process and documentation will follow established institutional guidelines.

13.3.3 Informed Consent

Consent will be obtained only by a participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read; a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

13.3.4 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

13.3.5 Patient Informed Consent at Additional Sites

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is NYULH policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials, unless Fellows are listed as co-investigators.

The Investigator must ensure that each participant is fully informed about the nature and objectives of the study and possible risks associated with participation. All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant and by the person obtaining the consent. The participant must be given 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.

All parties will ensure protection of participant personal data and will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, NYULH Perlmutter Cancer Center (PCC) will maintain high standards of confidentiality and protection of participant personal data.

The informed consent form must be in compliance with ICH/GCP, local regulatory requirements, and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB and NYULH before use.

13.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the supporter(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information

concerning the study or the data will be released to any unauthorized third party without prior written approval of the supporter.

The study monitor, other authorized representatives of the supporter, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Health. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by NYU Langone Health research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Health.

13.4.1 Research Use of Stored Human Samples, Specimens, or Data

As of February 2024, specimen analysis is complete, and no samples are left in storage.

- Intended Use: Samples and data collected under this protocol may be used to study hepatocellular carcinoma and its tumor microenvironment. No genetic testing will be performed other than tumor mutational analysis.
- Storage: Access to stored samples will be limited using the PI, Dr. Theodore Welling. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using Trialmaster.

Disposition at the completion of the study: All stored samples will be sent to the study primary investigator, Dr. Welling. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking. However, withdrawal of consent with regards to specimens storage will not be possible after the study is completed.

13.5 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at NYU Langone Health. After the study is completed, the coded and de-identified, archived data will be archived at the Perlmutter Cancer Center Clinical Trials Office. Permission to transmit data to the Clinical Trials Office will be included in the informed consent. Storage of samples, specimens, and data are required in order for subjects to participate in the study.

Any leftover materials from the biological samples collected per protocol will be stored and used for future research. The storage of samples and data for future research will be used to research into the causes of hepatocellular carcinoma, its complications, and other conditions for which individuals of hepatocellular carcinoma are at increased risk, and to improve treatment. There can also be other research aims that are unknown at this time. Data and samples will be kept for 15 years, or until samples are completely used and/or data is no longer needed, whichever comes first. With the participant's approval and as approved by local IRs, de-identified biological samples will be stored at the Theodore H. Welling Liver Cancer Laboratory. The Theodore H. Welling Liver Cancer Laboratory will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant. Samples will be labeled with freezer viable

labels and stored in freezers that are temperature monitored with emergency back-up generators. The linking key will remain with the PI, Theodore H. Welling. As of February 2024, specimen analysis is complete, and no samples are left in storage.

True genetic testing will not be done on the samples stored for future research, and no results will be shared with the study participants,

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological sample storage will not be possible after the study is completed. Subjects will be able to withdraw their consent by writing to the Principal Investigator of the study. Upon receipt of the subject's written statement, the Principal Investigator and affiliated laboratory members will ensure the stored samples are discarded.

When the study is completed, access to study data will be provided through the Perlmutter Cancer Center Clinical Trials Office by the permission of Dr. Beri.

14 Data Handling and Record Keeping

14.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Trialmaster, a 21 CFR Part 11-compliant data capture system provided by Data Core. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

14.2 Study Records Retention

Study documents will be retained for the longer of 3 years after close-out, 5 years after final reporting/publication, or 2 years after the last approval of a marketing application is approved for the drug for the indication for which it is being investigated or 2 years after the investigation is discontinued and FDA is notified if no application is to be filed or if the application has not been approved for such indication. No records will be destroyed without the written consent of the supporter, if applicable. It is the responsibility of the supporter to inform the investigator when these documents no longer need to be retained.

14.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

All protocol deviations must be addressed in study source documents, reported to NYULH PCC CTO and BMS Program Official.

Protocol deviations must be reported to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. All protocol deviations must be addressed in study source documents and reported to IRB Program Official at the time of annual continuing review. If a protocol deviation is determined to be reportable new information, the IRB will be notified immediately.

14.4 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is supportered by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the supporter or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

- NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

15 Study Finances

15.1 Funding Source

This study is financed through funding from Bristol-Myers Squibb.

15.2 Costs to the Participant

There are no additional costs to the study participants.

15.3 Participant Reimbursements or Payments

No subjects will receive payments or stipends for participation in this research study. BMS will provide coverage of tests and procedures that are not covered by the participant's insurance/standard of care (e.g. IL-8 serum measurements and on-treatment biopsy).

16 Study Administration

16.1 Study Leadership

The Steering Committee will govern the conduct of the study. The Steering Committee will be composed of the PI, Dr. Nina Beri, representatives of the PCC CTO, and the PI of the clinical sites. The Steering Committee will meet in person or via teleconference at least monthly, these meetings are facilitated by CTO's quality assurance specialists.

17 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the NYU PCC CTO has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by the NYU Langone Conflict of Interest Management Unit (CIMU) with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study supporter prior to participation in this study. All NYULH investigators will follow the applicable conflict of interest policies.

18 References

1. El-Serag HB. Hepatocellular carcinoma. *The New England journal of medicine.* 2011;365(12):1118-27.
2. Sawyers CL, Abate-Shen C, Anderson KC, Barker A, Baselga J, Berger NA, et al. AACR Cancer Progress Report 2013. *Clin Cancer Res.* 2013;19(20 Suppl):S4-98.
3. Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: A multicenter prospective study. *Hepatology (Baltimore, Md.* 2016;63(3):827-38.
4. Bruix J, Reig M, and Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology.* 2016;150(4):835-53.
5. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *The New England journal of medicine.* 2008;359(4):378-90.
6. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2017;389(10064):56-66.
7. El-Khoueiry AB, Sangro B, Yau T, Crocenzi TS, Kudo M, Hsu C, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. *Lancet.* 2017;389(10088):2492-502.
8. Wan S, Kuo N, Kryczek I, Zou W, and Welling TH. Myeloid cells in hepatocellular carcinoma. *Hepatology.* 2015.
9. Wu K, Kryczek I, Chen L, Zou W, and Welling TH. Kupffer cell suppression of CD8+ T cells in human hepatocellular carcinoma is mediated by B7-H1/programmed death-1 interactions. *Cancer research.* 2009;69(20):8067-75.
10. Kuang DM, Zhao Q, Peng C, Xu J, Zhang JP, Wu C, et al. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. *The Journal of experimental medicine.* 2009;206(6):1327-37.
11. Ruffell B, and Coussens Lisa M. Macrophages and Therapeutic Resistance in Cancer. *Cancer Cell.*27(4):462-72.
12. Wan S, Zhao E, Kryczek I, Vatan L, Sadovskaya A, Ludema G, et al. Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. *Gastroenterology.* 2014;147(6):1393-404.
13. Fernando RI, Castillo MD, Litzinger M, Hamilton DH, and Palena C. IL-8 signaling plays a critical role in the epithelial-mesenchymal transition of human carcinoma cells. *Cancer Res.* 2011;71(15):5296-306.
14. Duluc D, Delneste Y, Tan F, Moles MP, Grimaud L, Lenoir J, et al. Tumor-associated leukemia inhibitory factor and IL-6 skew monocyte differentiation into tumor-associated macrophage-like cells. *Blood.* 2007;110(13):4319-30.
15. Grugan KD, McCabe FL, Kinder M, Greenplate AR, Harman BC, Ekert JE, et al. Tumor-Associated Macrophages Promote Invasion while Retaining Fc-Dependent Anti-Tumor Function. *The Journal of Immunology.* 2012;189(11):5457-66.
16. Welling TH, Fu S, Wan S, Zou W, and Marrero JA. Elevated serum IL-8 is associated with the presence of hepatocellular carcinoma and independently predicts survival. *Cancer Invest.* 2012;30(10):689-97.

19 Attachments

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Investigator Agreement (for any investigator, other than supporter-investigator, who participates in the study)
- Sample Consent Form
- Study Procedures Flowchart/Table

- Study Monitoring Plan
- Core Lab Instructions To Investigators
- Specimen Preparation And Handling (e.g. for any specialized procedures that study team must follow to process a study specimen, and/or prepare it for shipment)
- Nivolumab Package Insert
- BMS-986253 Investigator Brochure
- Women of Childbearing Potential Definitions and Methods of Contraception

20 Schedule of Events

STUDY DAY ►	**Pre-study, screening (Day -20 to -1)**	**C1D1**	**C1D15 (+/- 3 days)**	**C2D1 (Day 29+/- 3 days)**	**C2D15 (Day 45+/- 3 days)**	**C3D1 (Day 59+/- 3 days)**	**C3D15 (Day 74+/- 3 days)**	**Subsequent Visits* (Estimate 24 visits average)**	**Follow Up[F]**
Study Team Procedures									
Informed Consent	X								
Medical History	X		X	X	X	X	X	X	X
Physical Exam	X		X	X	X	X	X	X	X
Vital Signs	X		X						X
Weight	X		X	X	X	X	X	X	X
Height	X								X
ECOG Performance Status	X		X	X	X	X	X	X	X
Toxicity Evaluations (AE reporting)		X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
RECIST v. 1.1[A]	X					X		X	X[F]
Study Drugs[B]		X	X	X	X	X	X	X	
Venipuncture	X	X	X	X	X	X	X	X	
Laboratory Assessments									
CBC, CMP, INR	X	X	X	X	X	X	X	X	X

AFP[C]	X					X		X	X[F]
TSH Testing	X	X		X		X		X	
Venipuncture	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test		X							
Translational Peripheral Blood Sample[D]	X					X			
Tumor Biopsy	X					X			
Fresh frozen tissue from core biopsy (Processing)	X					X			
Imaging Assessments									
Imaging[E]	X					X		X	X[F]

[A] every 8 weeks for 12 months, see Schema
[B] Arm 1: Nivolumab 240 mg IV every 2 weeks; Arm 2: BMS-986253 2400mg IV + Nivolumab 240mg IV every 2 weeks;
[C] AFP to be checked pre-study and at every 8 weeks for 12 months, see Schema
[D] IL-8 level and other, cycle 3 only
[E] 3-phase liver CT, or MR abdomen with contrast every 8 weeks for 12 months, see Schema
[F] every 3 months for 1 year, See Schema
*Scheduled treatment visits occurring after Cycle3