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Clinical Protocol BMS CA209-956

An Open-Label Preoperative Pilot Study Evaluating Nivolumab (Anti-PD-1 Antibody) Alone Versus Nivolumab Plus Ipilimumab (Anti-CTLA-4 Antibody) in Patients with Resectable HCC

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Table 1. LIST OF ABBREVIATIONS

Abbreviation	Term
ANC	Absolute Neutrophil Count
BID	Twice a Day
BMS	Bristol-Myers Squibb Company
CAT (or CT scan)	Computed Axial Tomography
CBC	Complete Blood Count
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECOG PS	Eastern Cooperative Oncology Group Performance Status
HCV	Hepatitis C virus
HBV	Hepatitis B virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
HCC	Hepatocellular Carcinoma
ICF	Informed Consent Form
IRB	Institutional Review Board
irRC	Immune related Response Criteria
MRI	Magnetic Resonance Imaging
NAFLD	Non-alcoholic fatty liver disease
PD	Progressive Disease
PD-1	Programmed Death Receptor-1
PFS	Progression Free Survival
PO	By Mouth
PR	Partial Response
QD	Once Daily
SAE	Serious Adverse Event
SD	Stable Disease
TTP	Time to Tumor Progression
UNOS	United Network for Organ Sharing

1.0 RESEARCH HYPOTHESIS

Anti-PD1 antibody (nivolumab) alone or in combination with anti-CTLA-4 antibody (ipilimumab) can be safely administered and may induce augmented immunological and clinical responses in patients with resectable hepatocellular carcinoma (HCC).

2.0 OBJECTIVES

Primary Objective:

1. To evaluate the safety and tolerability of therapy with nivolumab alone or nivolumab + ipilimumab in resectable HCC in the context of presurgical therapy.

   Note: As of January 8, 2020, 30 patients have been enrolled and 27 patients have been randomized. The PI decided to stop enrollment since the study has reached its primary endpoint of safety.

Secondary Objectives:

1. To assess the efficacy of presurgical nivolumab alone or nivolumab + ipilimumab therapy in HCC by estimating the objective response rate (ORR) and time to progression (TTP) per RECIST 1.1 progression-free survival (PFS).

Exploratory Objectives:

1. To assess the ***immunological/biomarker changes*** in tumor tissues and peripheral blood in response to nivolumab alone or nivolumab + ipilimumab in HCC therapy (pre- vs post-treatment), and explore any potential association between these biomarker measures and antitumor response and immune-related response criteria (iRC) assessed by MD Anderson Department of Diagnostic Imaging.

3.0 DISEASE BACKGROUND

3.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is a highly lethal malignancy of worldwide significance and has become increasingly important in the United States. Overall, it is the most common

primary liver cancer, the sixth most common cancer, and the third most common cause of cancer-related deaths worldwide [1]. Various risk factors are responsible for the majority of HCC cases. these include liver cirrhosis (multiple etiologies), hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, alcohol abuse, and non-alcoholic fatty liver disease [2]. Notably, although treatment for HCV has dramatically improved over the past several years, HCC incidence in the United States is rising especially among patients chronically infected with HCV. This is likely due to the long latency period between initial HCV infection and HCC incidence [3, 4].

Treatment options for HCC depend on the cancer stage at initial presentation and degree of synthetic liver dysfunction. Although a number of different staging systems have been used to provide accurate prognostic assessment (i.e. AJCC, Okuda, GRETCH, CLIP, etc.), all have limitations. The Barcelona Clinic Liver Cancer staging system provides an easy reference algorithm that links HCC stage and evidence-based treatment recommendations (Fig. 1) [5-7].

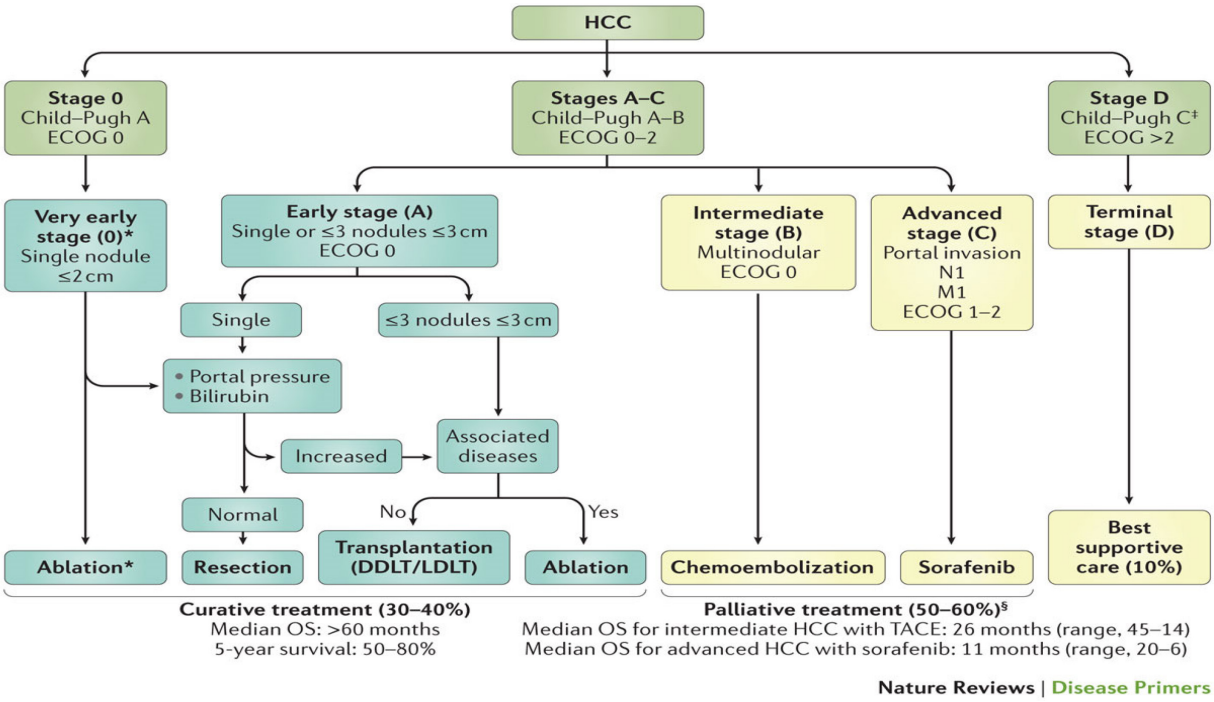

Figure 1: BCLC staging system and therapeutic strategy. Llovet, J. M. *et al.* (2016) Hepatocellular carcinoma *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.18

3.2 Standard Therapy for Hepatocellular Carcinoma

Surgical Resection and Liver Transplantation

The only potentially curative treatment modalities for HCC include surgical resection (partial hepatectomy) and liver transplantation. Unfortunately, the actual number of patients who qualify for these modalities is small (approximately 10-30%) because most patients present with locally advanced or metastatic disease, or have significant liver dysfunction that precludes curative options. Surgical resection is typically considered for patients with a solitary tumor of any size who have adequate liver remnant and no evidence of major vascular invasion or portal hypertension [8]. Recent evidence has shown that partial hepatectomy procedures in carefully selected patients can be done with low operative morbidity and mortality [9, 10]. However, despite these favorable surgical outcomes, in those patients who are fortunate to undergo surgical resection, tumor recurrence is common. In fact, the 5-year tumor recurrence rate following surgical resection have been reported to be as high as 70% [11-13].

Although there is no FDA-approved medication for use in the adjuvant setting after surgical resection, the recently reported phase III STORM trial evaluated the efficacy and safety of sorafenib, an antiangiogenic agent approved for use in advanced HCC [14]. In this study, 1,114 HCC patients with a complete radiological response after surgical resection or local ablative therapy were given sorafenib 400 mg or placebo twice a day for a maximum of 4 years. Treatment related adverse events were high in both study groups and there was no difference seen between the two groups in regard to recurrence-free survival (RFS), time to recurrence (TTR) or overall survival (OS). At this time, there remains no evidence to support a particular adjuvant therapy in HCC. Of note, our pilot study is important as it will generate for the first time PFS data in HCC with combination nivolumab plus ipilimumab.

Liver transplantation is the other potentially curative treatment option for HCC patients that removes both the underlying HCC tumors and background cirrhosis. In 1996, Mazzaferro and colleagues proposed the Milan criteria (single lesion ≤ 5 cm or 2-3 lesions each ≤ 3 cm, no macrovascular invasion, no extrahepatic disease) for patients with small, unresectable HCC in the setting of cirrhosis [15]. For patients meeting this criterion who underwent orthotropic liver transplantation, the OS and RFS rates at 4 years were 85% and 92%, respectively. Subsequent studies have confirmed the results reported in this initial Mazzaferro study. Because of this, the United Network for Organ Sharing (UNOS) has adopted the Milan criteria for determining candidates for liver transplantation with HCC. Moreover, in 2001, Yao and colleagues proposed expanded criteria (UCSF Criteria) for HCC liver transplantation (single lesion ≤ 6.5 cm or 2-3 lesions, each ≤ 4.5 cm + sum of lesions ≤ 8 cm, no macrovascular invasion, no extrahepatic disease) that demonstrated 1- and 5-year survival rates of 90% and 75%, respectively [16]. Because

UNOS specifies that patients undergoing evaluation for liver transplantation are not eligible for partial hepatectomy, liver transplantation is usually reserved for those patients with early-stage HCC and moderate to severe cirrhosis (i.e., Child's Pugh B or C). On the other hand, partial hepatectomy is considered for those patients with mild cirrhosis (i.e., Child's Pugh A) having an HCC tumor amenable to resection as deemed by the performing surgeon.

Local-regional therapies for HCC

Conceptually, local-regional therapies are designed to induce local tumor necrosis and are indicated for those patients with primarily liver-only disease but who are not resection or transplantation candidates. Even though there is no absolute HCC size-cut off for use of these treatment modalities, there are a number of contraindications to use. These include poor synthetic liver function (i.e. Child Pugh C), elevated bilirubin > 2.5, significant ascites, hepatic encephalopathy, recent variceal bleeding, and main portal vein thrombosis. Local-regional therapies are generally divided into two categories: ablation and arterially directed therapies.

Ablative modalities include thermal ablation (radiofrequency ablation or microwave ablation), cryoablation, or chemical ablation (percutaneous ethanol infusion or acetic acid injection). Ablative procedures may be curative in treating tumors ≤ 3 cm and have shown increased overall survival in tumors 3 - 5 cm in largest diameter [17-19] . Radiofrequency ablation (RFA), which we consider the most commonly used method of the ablative options, involves the local application of radiofrequency thermal energy to small HCC lesions. In fact, some centers even consider RFA the treatment of choice for small tumors (<2 cm) in an appropriate location. This is based on studies demonstrating similar outcomes for these tumors when compared to surgical resection with less cost and procedure-related complications [20].

Arterial directed therapies involve selective catheter-based infusion of particular substances into the hepatic artery. These therapies are possible because the liver has a dual blood supply; the portal vein supplies blood to normal liver parenchyma whereas the hepatic artery supplies blood to HCC lesions. Such modalities are particularly attractive because all tumors, irrespective of location, can be treated with an arterial approach provided the blood supply to the tumor can be manipulated without causing undo harm to surrounding, normal tissue. In general, arterial based treatments are used for larger tumors not amenable to resection, transplantation or an ablative approach. Currently available arterial directed therapies include transarterial bland embolization, transarterial chemoembolization, transarterial radioembolization and yttrium-90 microspheres.

External-beam Radiation Therapy (EBRT)

Because HCC is a radiosensitive tumor, EBRT can be employed in patients with unresectable or inoperable HCC to deliver high doses of radiation to the underlying HCC tumors while sparing the normal liver parenchyma. Like arterial based approaches, EBRT can be used to treat all tumor regardless of location. Specific EBRT modalities include intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and proton beam therapy (PBT). Notably, SBRT is usually considered in patients with liver-only disease who have failed ablative or arterial-based approaches, and for those with partial vein thrombosis [21].

Sorafenib for advanced HCC

Sorafenib is an orally bioavailable agent originally developed as a Raf kinase inhibitor. Further studies revealed that sorafenib was also a potent inhibitor of vascular endothelial growth factor receptors (VEGFR-1, -2, and -3), as well as platelet derived growth factor receptor (PDGFR), KIT and FLT3. Currently, sorafenib is the only FDA-approved therapy for advanced or unresectable HCC. This approval was based on the phase III SHARP study, which evaluated 602 patients with advanced HCC who had not received previous systemic therapy who received either sorafenib (400 mg BID) or placebo [22]. Median overall survival was 10.7 months in the sorafenib group compared to 7.9 months in the placebo group; there was also a benefit in time to symptomatic progression (5.5 months for sorafenib vs. 2.8 months for placebo). Additionally, in the phase III Asia-Pacific study, 226 patients with advanced HCC were randomized to receive either sorafenib (400 mg BID) or placebo [23]. This study, which included a large number of HBV infected patients, also demonstrated improved OS (6.5 months vs. 4.2 months) and TTP (2.8 months for 1.4 months) for the sorafenib group.

Of note, there currently is no second line therapy approved for advanced HCC.

Regorafenib for advanced HCC

Regorafenib is an orally bioavailable agent that inhibits multiple membrane-bound and intracellular kinases involved in cell growth (RET, VEGFR-1, VEGFR-2, VEGFR-3, KIT, PDGFR-alpha, PDGFR-beta, FGFR1, FGFR2, TIE2, DDR2, Trk2A, Eph2A, RAF-1, BRAF, SAPK2, PTK5 and ABI). Although regorafenib is not yet approved for advanced HCC, the recently reported phase III RESORCE Trial evaluated 573 patients with intermediate or advanced stage HCC who had been previously treated with sorafenib (data unpublished). Patients were randomized 2:1 to receive either regorafenib 160 mg daily or placebo for 1-3 of each four-week cycle. This trial, which has not been formally published, demonstrated improvements in both

median OS (10.6 months vs. 7.8 months) and PFS (3.1 months vs. 1.5 months) for the regorafenib group.

Other systemic therapies for advanced HCC

Multiple chemotherapy regimens and targeted agents have been tested in advanced HCC with modest benefit; however, no single regimen has shown superiority to any other. Most randomized trials have demonstrated median OS benefits of < 12 months. Monotherapy agents that have been tested in HCC include doxorubicin, epirubicin, mitoxantrone, 5-fluorouracil (5-FU), capecitabine, gemcitabine, irinotecan, thalidomide, cisplatin, bevacizumab (VEGF inhibitor) and ramicirumab (VEGF inhibitor). In addition, a number of combination chemotherapy regimens have also been tested with limited clinical efficacy. These include FOLFOX (infusional 5-fluorouracil, leucovorin, oxaliplatin), cisplatin doublets, gemcitabine doublets and PIAF (cisplatin, interferon alpha, doxorubicin, and infusional 5-FU). Notably, our group recently performed a clinical trial which tested the efficacy of modified PIAF in patients without cirrhosis or hepatitis who had initially unresectable HCC [24]. Our results demonstrated an ORR=36% and a rate of conversion to curative surgery = 33%.

3.3 Anti-PD1 (Nivolumab)

3.3.1 Mechanism of Action

Immune activation is tightly regulated by co-stimulatory (e.g. CD28 and ICOS) and co-inhibitory (e.g. CTLA-4 and PD-1) receptors expressed on T cells. Agonistic antibodies against co-stimulatory T cell receptors and blocking antibodies against co-inhibitory T cell surface receptors have both been shown to potentiate T cell activation for tumor cell killing.

PD-1 (programmed death receptor-1) is mainly expressed by activated $CD4^+$ and $CD8^+$ T cells, as well as APCs. It has two ligands, PD-L1 and PD-L2, with distinct expression profiles [25]. PD-L1 is expressed not only on APCs, but also on non-hematopoietic cells, including tumor cells. Expression of PD-L2 is largely restricted to APCs including macrophages and myeloid dendritic cells, as well as mast cells. The role of PD-1 as a negative regulator of T cells was best demonstrated by the finding that PD-1 deficient mice developed significant autoimmunity with high titers of autoantibodies [26, 27]. Subsequently, blocking antibodies against PD-1 were shown to activate immune responses that resulted in reduction of tumor metastasis and tumor growth in a number of experimental tumor models [28, 29]. Consistent with the immune inhibitory role of PD-1/PD-L1/2 signaling, forced expression of PD-L1 in murine tumor cell lines allowed increased tumor growth in vivo, which was otherwise kept in check by T cells. The inciting effect of PD-L1

on tumor growth was reversed by blocking anti-PD-L1 antibodies [30]. Patients with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than those with low levels of PD-L1 expression.

Notably, the PD-1 pathway regulates T cell responses in chronic inflammatory liver conditions (HBV, HCV, autoimmune hepatitis, and NAFLD) that are responsible for the large majority of HCC. Interestingly, in a previous study examining the PD-1 expression profiles, it was shown that patients with chronic inflammatory hepatitis have significantly increased numbers of PD-1 expressing lymphocytes [31]. Subsequent reports have confirmed that there is up-regulation of PD-1 in patients infected with HBV or HCV [32, 33].

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

3.3.2 Nivolumab in Hepatocellular Carcinoma

El-Khoueiry AB, et al. presented results from the interim analysis of the phase 1/2 nivolumab trial (CA209-040) in patients with advanced hepatocellular carcinoma at the 2015 annual ASCO meeting [34]. In the presentation, the dose escalation study demonstrated safety and tolerability of nivolumab at 0.1 mg/kg to 10 mg/kg in patients with HCC due to HCV, HBV or who were uninfected with viral hepatitis. The only grade 4 adverse event was elevated lipase (1 patient) while grade 3 elevations in liver enzymes were seen in 9 patients (AST = 5, ALT = 9). 3 mg/kg was selected for the dose expansion in the uninfected and HCV cohorts; the dose escalation for the HBV cohort was ongoing. In 42 patients evaluable to response, the ORR by RECIST 1.1 criteria was 19% (8) with 2 patients achieving a complete response. The preliminary overall survival at 12 months was 62% (95% CI 42-76%). Moreover, Sangro B, et al. recently presented interim results of 214 patients in the expansion CheckMate-040 study who received Nivolumab 3 mg/kg every 2 weeks [35]. This report demonstrated a preliminary ORR = 16%.

Because of these results, a phase III study comparing nivolumab to sorafenib for patients with advanced HCC has been launched in the frontline setting with an estimated enrollment of 726 patients and primary completion date of July 2017 (NCT02576509).

3.3.3 Summary of Results from Nivolumab Program

For a complete review of clinical information, please refer to the nivolumab Investigator Brochure.

3.3.3.1 Summary of Safety

In clinical trial CA209001 (n = 39), patients received a single dose of nivolumab with possible retreatment at 3 months. The most frequent adverse events (AEs) were fatigue (56%), nausea (44%), proteinuria (38%), constipation (33%), back pain (33%), dry mouth (28%), vomiting (28%), rash (26%) and dyspnea (26%). There was no clear correlation between the incidence or severity of AEs and the nivolumab dose levels (0.3, 1, 3, or 10 mg/kg IV single dose, with possible retreatment at 3 months). Among 39 (100%) patients who had at least one AE, 32 (82%) had Grade 3 or 4 AEs. Three treatment-related severe adverse events (SAEs) were reported: hypothyroidism (Grade 2), colitis (Grade 3), and anemia (Grade 2). Among 12 deaths, none were considered drug-related.

In CA209003 (n = 306), as of the database lock date of 18-March-2013, nivolumab-related AEs of any grade occurred in 75.2**%** of patients [36]. The most frequent drug-related AEs occurring in ≥ 5% of patients included fatigue (28.1%), rash (14.7%), diarrhea (13.4%), pruritus (10.5%), nausea (9%), decreased appetite (9%), and fever (6%). The majority of AEs were low grade, with Grade 3/4 drug-related AEs observed in **14%** of patients. The most common Grade 3/4 drug-related AEs occurring in ≥ 1% of patients were fatigue (2%), pneumonitis (1%), diarrhea (1%), AST/ALT increase (0.3% each) Drug-related SAEs occurred in **17%** of patients. Grade 3/4 drug-related SAEs occurring in ≥ 1% of patients were: pneumonitis (1.3%), and diarrhea (1%). The spectrum, frequency, and severity of nivolumab-related AEs were generally similar across dose levels and histological subtypes. Other drug-related AEs included vitiligo, hepatitis, hypophysitis, and thyroiditis.

Hepatic or gastrointestinal events were managed with treatment interruption and administration of corticosteroids, and were generally completely reversible. Endocrine events were managed with hormone replacement therapy. Several patients in these categories successfully reinitiated treatment with nivolumab. Drug-related pneumonitis occurred in 3% of patients; Grade ≥ 3 pneumonitis developed in 3 patients (1%). No clear relationship was identified between the

occurrence of pneumonitis and tumor type, dose level, or the number of doses received. Low-grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In three patients, infliximab and/or mycophenolate were utilized for additional immunosuppression, with unclear effectiveness. There were three (1%) drug-related deaths due to pneumonitis. In two of these cases, the patients did not receive the early and aggressive intervention (including systemic corticosteroid therapy) that is likely key in the management of this toxicity, while in the third case, other anti-cancer agents (erlotinib and vinorelbine) may have contributed to the fatal event.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the Investigator Brochure.

3.3.3.2 Summary of Clinical Activity

In CA209001 and CA209003, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, non-small cell lung cancer (NSCLC), and colorectal cancer (CRC). Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg) and across dosing schedules (every 2 weeks dosing for CA209003, single administration with possibility of retreatment at 3 months in CA209001).

In CA209001, all treated patients (n = 39) were evaluable for tumor response [37]. Partial response (PR) was reported in 3 patients and stable disease (SD) was reported in 10 patients. Patients with PRs included 1 patient with CRC treated at 3 mg/kg and 1 patient each with melanoma and RCC, both treated at 10 mg/kg. Tumor responses were maintained in these patients as of their last radiological tumor assessments at 26, 3, and 18 months, respectively as of the clinical data cut-off date. The patient with RCC had received multiple prior therapies, including sunitinib and sorafenib. In 2 of the 10 patients with SD, stable disease was maintained for more than 6 months.

In CA209003, as of the database lock date of 18-March-2013, a total of 306 patients with melanoma, RCC, and NSCLC were evaluated for clinical activity [36]. A response of either CR or PR, as determined by the investigator based on modified RECIST 1.0, has been reported at all dose levels. No responses (CR or PR) have been reported in patients with colorectal carcinoma or castrate-resistant prostate cancer.

3.3.3.3 Clinical Pharmacology Summary

Single dose pharmacokinetics (PK) of nivolumab was evaluated in patients with multiple tumor types in CA209001 whereas multiple dose PK is being evaluated in patients in CA209003.

In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from ~350 patients from CA209001, CA209002, and CA209003.

Single dose PK of nivolumab was evaluated in 39 patients with multiple tumor types in study MD1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear in the range of 0.3 to 10 mg/kg with dose- proportional increase in Cmax and AUC (INF) with low to moderate inter-subject variability observed at each dose level (i.e., CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab is 17 to 25 days, which is consistent with half-life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in investigator brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 patients from CA209001, CA209002, and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of nivolumab.

3.4 Ipilimumab (Yervoy): Background

Ipilimumab (anti-CTLA-4) is a fully humanized IgG1 monoclonal antibody to cytotoxic T-cell lymphoma-4 (CTLA-4). Ipilimumab is an approved therapy for metastatic melanoma and has demonstrated improved overall survival as monotherapy (as compared to peptide vaccine gp100) and in combination with dacarbazine (as compared to dacarbazine alone) [38, 39]. It has been studied in combination with multiple standard-of-care therapies including chemotherapy for squamous and non-squamous NSCLC and radiotherapy for hormone resistant prostate cancer [40].

Ipilimumab toxicity profile includes side effects associated with an immune mechanism of action (immune-related adverse events, irAEs). At 3 mg/kg given every 3 weeks as monotherapy [38], the following AEs were observed in at least 10% of subjects: fatigue (42%), diarrhea (33%), nausea (35%), decreased appetite (27%), vomiting (24%), pruritus (24%), constipation (21%), rash (19%), cough (16%), abdominal pain (15%), headache (15%) and pyrexia (12%). Additional irAEs occurring in < 10% of subjects but with clinical relevance included: colitis (8%); endocrinopathies (8%) including hypothyroidism, hypopituitarism, hypophysitis, adrenal insufficiency, increased

serum thyrotropin and decreased corticotropin; hepatotoxicity (4%) including hepatitis and elevations in AST/ALT; and vitiligo (2%). Other reported irAEs include nephritis, pneumonitis, meningitis, pericarditis, uveitis, iritis and hemolytic anemia. Overall irAEs occurred in approximately 60% of subjects, of which 13% were Grade 3-4, and 0.8% were Grade 5 [38, 40]. Seven deaths were associated with an irAE - GI perforation (4), colitis (1), liver failure (1), and Guillain-Barré Syndrome (1). In addition, 1 subject in the ipilimumab plus gp100 group of MDX010-20 clinical trial had a Grade 4 skin irAE (Stevens Johnson syndrome/toxic epidermal necrolysis/Lyell's syndrome), but died due to a treatment-related acute respiratory distress syndrome. The irAEs are related to T-cell activation and can be serious or life threatening. Specific management guidelines were addressed by Weber et al [41].

3.4.1 Ipilimumab in Hepatocellular Carcinoma

There are currently no published data testing ipilimumab in HCC. However, Checkmate 040, which is currently enrolling, is testing the combination of nivolumab plus ipilimumab in patients with advanced HCC.

Interestingly, anti-CLTA-4 therapy (tremelimumab) was previously tested in a pilot study to evaluate the safety, preliminary antitumor/antiviral effect of tremelimumab in patients with HCC and chronic HCV [42]. In the 21 patients enrolled in this study, 20 were evaluable for toxicity and 17 for tumor response. Tremelimumab had an acceptable safety profile with only 1 patient developing grade 3 toxicity (encephalopathy); the partial response rate was 17.6% and disease control rate was 76.4%.

3.4.2 Nivolumab in combination with ipilimumab in melanoma

Since anti-PD1 and anti-CTLA-4 use distinct mechanisms for immune activation from anti-CTLA-4 and anti-PD1 as well as supportive preclinical data, a phase I study was conducted on nivolumab and ipilimumab combination therapy in patients with advanced melanoma [43]. In this trial, patients were treated with intravenous doses of nivolumab and ipilimumab in patients every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses.

A total of 53 patients received concurrent therapy with nivolumab and ipilimumab, and 33 received sequenced treatment. The ORR (according to modified WHO criteria) for all patients in the concurrent-regimen group was 40%. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for ≥24 weeks) was observed in 65% of patients. At

the maximum doses that were associated with an acceptable level of adverse events (nivolumab at a dose of 1 mg per kilogram of body weight and ipilimumab at a dose of 3 mg per kilogram), 53% of patients had an objective response, all with tumor reduction of 80% or more

Grade 3 or 4 adverse events related to therapy occurred in 53% of patients in the concurrent-regimen group but were qualitatively similar to previous experience with monotherapy and were generally reversible. Among patients in the sequenced-regimen group, 18% had grade 3 or 4 adverse events related to therapy and the objective-response rate was 20%.

A follow-up phase 3 study examined 945 previously untreated patients with advanced melanoma [44]. Patients were randomized in a 1:1:1 ratio to receive one of three regimens: nivolumab 3 mg/kg every 2 weeks plus placebo; nivolumab 1 mg/kg every 3 weeks plus ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks; or ipilimumab 3mg/kg every 3 weeks for 4 doses plus placebo. The investigator-assessed ORR for the 3 treatment regimens were 43.7% (95% CI, 38.1 to 49.3) in the nivolumab alone group, 57.6% (95% CI, 52.0 to 63.0) in the combination nivolumab plus ipilimumab group, and 19% (95% CI, 14.9 to 23.8) in the ipilimumab alone group. The median progression-free survival was 6.9 months (95% CI, 4.3 to 9.5), 11.5 months (95% CI, 8.9 to 16.7), and 2.9 months (95% CI, 2.8 to 3.4), respectively. In addition, grade 3-4 treatment-related adverse events occurred in 16.3% in the nivolumab group, 55% in the nivolumab-ipilimumab group, and 27.3% in the ipilimumab group, with diarrhea and fatigue being the most common adverse events.

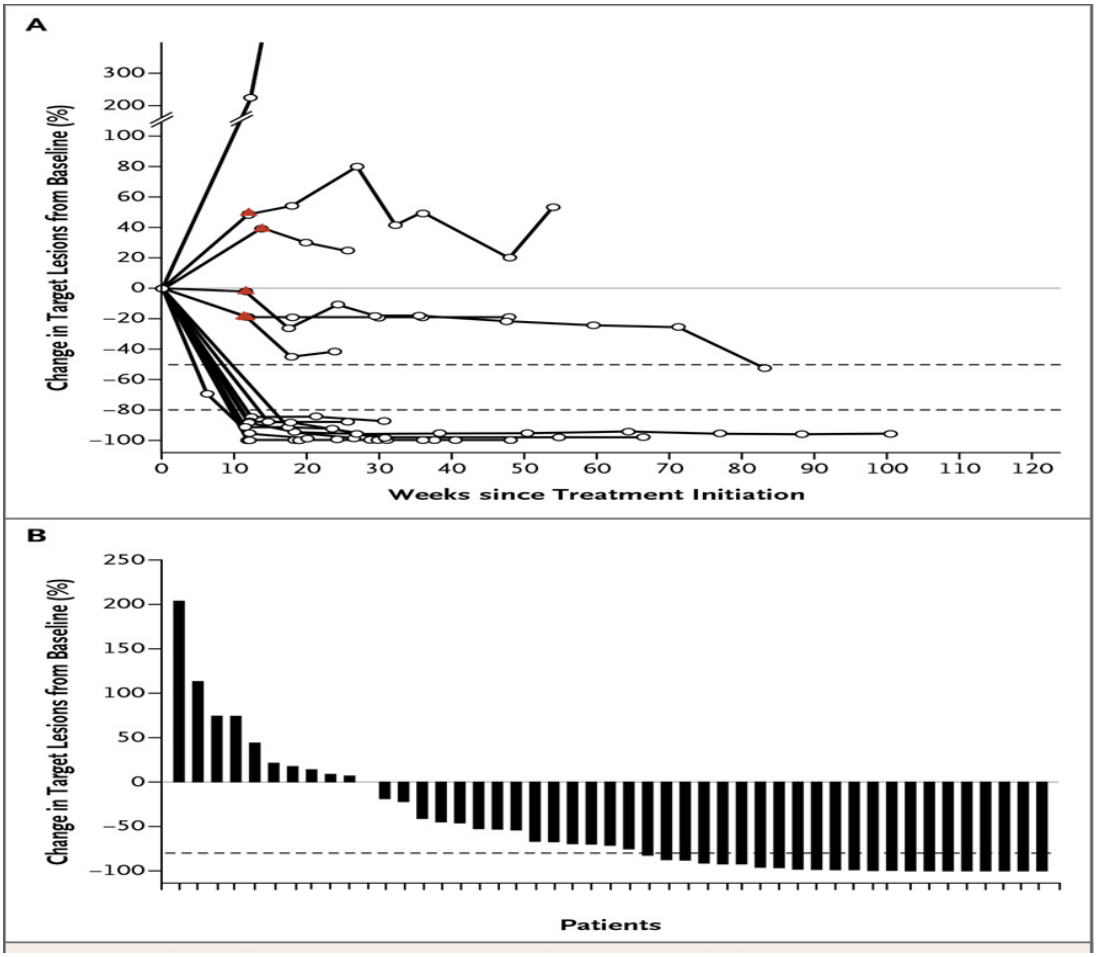

Figure 1. Clinical Activity in Patients Who Received the Concurrent Regimen of Nivolumab and Ipilimumab. **Panel A** shows changes from baseline in the tumor burden. **Panel B** shows a representative waterfall plot of the maximum percentage change in target lesions, as compared with baseline measurements.

3.4.3 Nivolumab in combination with ipilimumab in other malignancies

Recently, interim data from phase 1 studies in NSCLC and MSI-high colorectal cancer testing combination nivolumab and ipilimumab were presented. In particular, CheckMate 012 in first-line advanced NSCLC tested nivolumab and ipilimumab in the following combinations: nivolumab 1mg/kg plus ipilimumab 1 mg/kg every 3 weeks x 4 cycles then nivolumab 3 mg/kg every 2 weeks; nivolumab 1 mg/kg every 2 weeks plus ipilimumab 1 mg/kg given every 6 weeks; nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 12 weeks; and nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks [45]. Of notable interest, the nivo 3 Q2W + ipi 1 Q12 (n=38) and nivo 3 Q2W + ipi Q6W (n=39) showed improved toxicity profiles,

and grade 3-4 treatment-related adverse events were 37% and 33%, respectively. In addition, the confirmed ORR for these two groups were 47% (95% CI, 31 to 64) and 39% (95% CI, 23 to 55), respectively.

Based upon these data, it is important to determine whether combination therapy with nivolumab and ipilimumab can offer similar clinical benefit to patients with resectable or unresectable HCC, a disease in which there is no standard preoperative therapy.

3.4.5 Study Rationale

As mentioned, surgical resection or liver transplantation are the only potentially curative treatment modalities for localized HCC in select patients. Local-regional therapies (ie: ablation, arterial-based therapies, or EBRT) can palliate and sometimes downstage non-resectable lesions, but are not typically curative procedures. Sorafenib is the only FDA-approved systemic therapy for advanced HCC. Therefore, patients with unresectable HCC have poor survival and there is a high recurrence rate (~50% or more) for those receiving potentially curative therapy. Novel treatment approaches taking advantage of the higher response rates seen in early-phase HCC studies and long-term survival of immunotherapies clearly need to be studied in order to improve the treatment of HCC. As a basis for future research in HCC, immunological pathways in response to monotherapy versus combinational therapy need to be evaluated in the context of clinical outcome in order to identify predictive and prognostic biomarkers as well as other potential therapeutic targets.

Anti-PD-1 antibody, nivolumab, has recently been shown in a phase 1-2 clinical trial on 42 patients with advanced or unresectable HCC to result in 19% ORR; many of these responses were durable with a response duration of 1-8+ months in patients achieving a PR [34]. Subsequent analysis of 214 patients on this study confirmed a 16% ORR. Of note, these response rates compare favorably to those seen for sorafenib where the ORR = 2% (without any observable CRs). Anti-CTLA-4 antibody, ipilimumab, has not been tested in HCC. However, an alternative anti-CLTA-4 blocking agent, tremelimumab, has been reported to have a partial response rate of 17% in patients with HCC and chronic HCV [42].

Based on strong preclinical data supporting the hypothesis that PD-1 and CTLA-4 are both non-redundant pathways that negatively regulate effector T cells, multiple recent clinical studies in other cancer types suggest that combination nivolumab and ipilimumab may induce even greater anti-tumor responses than either agent alone. While this combination has yet to be tested in HCC, considering the immunosuppressive environment especially characteristic of hepatitis-related HCC, combination therapy may lead to enhanced responses.

Lastly, multiple recent studies have demonstrated that checkpoint inhibitors can be safely administered in the preoperative setting. For example, two preoperative trials have evaluated anti-CTLA-4 antibody therapy prior to curative surgery both in early stage breast cancer [46] and bladder cancer [47]. In addition, anti-PD-1 antibody therapy is current being tested in the preoperative setting in renal cell carcinoma at MD Anderson.

Based upon the above functional mechanisms and clinical activities of nivolumab and ipilimumab, we propose to use nivolumab alone, or nivolumab + ipilimumab in the presurgical setting for a number of reasons. First, it will offer patients with resectable HCC the promising clinical benefits of nivolumab and ipilimumab. This may result in improved recurrence rates for those patients receiving curative surgery. Second, it will allow us to further evaluate potentially synergistic or additive activities on HCC between nivolumab + ipilimumab. Third, this proposed trial will allow us to evaluate the immunological pathways in HCC tissues after treatment with nivolumab alone, or with nivolumab + ipilimumab, to interrogate potential predictive/prognostic biomarkers of clinical response.

We **hypothesize** that therapy with nivolumab alone, or combination therapy with nivolumab + ipilimumab will have acceptable safety profile and may lead to measurable immunological changes, with identification of novel biomarkers that can be used for correlation of clinical outcomes in patients with resectable HCC.

4.0 Study Population

For entry into the study, the following criteria MUST be met within 4 weeks (+/- 7 days) prior to 1st dose of therapy on this trial. Any exceptions from the protocol-specific selection criteria must be approved by principle investigator. A PI override will be submitted to the UTMDACC IND Office before obtaining UTMDACC IRB approval for enrolling a patient on an active protocol who has a minor deviation from the stated eligibility criteria which will not affect the analysis or interpretation of the study.

4.1 Inclusion Criteria

Signed written informed consent

1. Patients must give written informed consent prior to initiation of therapy, in keeping with the policies of the institution. Patients with a history of major psychiatric illness must be judged able to fully understand the investigational nature of the study and the risks associated with the therapy.

Target population

2. Patients with histologically confirmed HCC (Documentation of original biopsy for diagnosis is acceptable if tumor tissue is unavailable) or clinical diagnosis by AASLD criteria in cirrhotic subjects is required (presence of arterial hypervascularity with venous washout). For subjects without cirrhosis, histological confirmation is mandatory. The determination of resectability status will ultimately lie in the clinical judgment of the surgical oncologist and medical oncologist involved in the care of the patient.

3. Patient must have measurable disease defined as a lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) and measures ≥ 15 mm with conventional techniques or ≥ 10 mm with more sensitive techniques such as MRI or spiral CT scan.

4. Patient can have had prior treatment for HCC including prior surgery, radiation therapy, local-regional therapy (abalation or arterial directed therapies), and systemic therapy including sorafenib or chemotherapy (but not anti-PD-1 or anti-CTLA-4 therapy)

5. ECOG performance status ≤ 1.

6. Within 14 days of the first dose of study drug, patients must have adequate organ and marrow function as defined below:

    - Absolute neutrophil count ≥ 1,500/μL
    - Platelets ≥100,000/μL
    - Hgb > 9.0 g/dL (may be transfused or receive epoetin alfa [e.g., Epogen®] to maintain or exceed this level)
    - Total bilirubin ≤ 1.5 mg/dl
    - Serum creatinine ≤ 1.5 times the upper limit of normal or estimated CrCL >40mL/min.
    - AST (SGOT) and/or ALT (SGPT) ≤ 5 X institutional upper limit of normal

Age and Sex

7. Men and women ≥ 18 years of age

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

9. Women must not be breastfeeding

10. WOCBP must agree to follow instructions for method(s) of contraception from the time of enrollment for the duration of treatment with study drug (s) plus 5 half-lives of study drug (s) plus 30 days (duration of ovulatory cycle) for a total of 5 months post treatment completion.

11. Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug (s) plus 90 days (duration of sperm turnover) for a total of 7 months post-treatment completion.

12. Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, WOCBP must still undergo pregnancy testing as described in these sections.

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

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

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

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Abstinence is only acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation

methods) and withdrawal are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Male Condom without spermicide*
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Female Condom*

*A male and female condom must not be used together

4.2 Exclusion Criteria

Any of the following criteria will disqualify the patient from participation:

Target Disease Exceptions

1. Any other malignancy from which the patient has been disease-free for less than 2 years, except for non-melanoma skin cancer, or in situ carcinoma of any site.

Medical History and Concurrent Disease

2. Patients who have organ allografts.
3. Patients who have had a major surgical procedure, open biopsy, or significant traumatic injury with poorly healed wound within 6 weeks prior to first dose of study drug; or anticipation of need for major surgical procedure during the course of the study (other than defined by protocol); fine needle aspirations or core biopsies within 7 days prior to first dose of study drug. NOTE: Patients will be allowed to start cycle 1 day 1 therapy after 24 hours from pre-treatment biopsy.
4. Autoimmune disease: Patients with a history of inflammatory bowel disease (including crohn's disease and ulcerative colitis) are excluded from this study as are patients with a history of autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis

[scleroderma], systemic lupus erythematosus, autoimmune vasculitis [e.g., wegener's granulomatosis]).

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

6. Any underlying medical condition, which in the opinion of the Investigator, will make the administration of study drug hazardous or obscure the interpretation of adverse events, such as a condition associated with frequent diarrhea.

7. Patients who have had a history of acute diverticulitis, abdominal fistula, gastrointestinal perforation, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis which are known risks factors for bowel perforation, should be excluded from the study.

8. Patients who have a primary brain tumor (excluding meningiomas and other benign lesions), any brain metastases, leptomeningeal disease, seizure disorders not controlled with standard medical therapy, or history of stroke within the past year.

9. History of serious systemic disease, including myocardial infarction or unstable angina within the last 12 months, history of hypertensive crisis or hypertensive encephalopathy, uncontrolled hypertension (blood pressure of >140/90 mmHg) at the time of enrollment, New York Heart Association (NYHA) Grade II or greater congestive heart failure, unstable symptomatic arrhythmia requiring medication (patients with chronic atrial arrhythmia, i.e., atrial fibrillation or paroxysmal supraventricular tachycardia are eligible), significant vascular disease or symptomatic peripheral vascular disease.

10. Patients who have history of other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that might affect the interpretation of the results of the study or render the subject at high risk from treatment complications.

11. Patients who are on high dose steroid (e.g. > 10 mg prednisone daily or equivalent) or other more potent immune suppression medications (e.g. infliximab)

12. Patients who have had influenza, hepatitis, or other vaccines within a month prior to initiation of study drugs.

13. Patients who have clinical history of coagulopathy, bleeding diathesis or thrombosis within the past year.

14. Patients who have serious, non-healing wound, ulcer, or bone fracture.

15. Pregnancy (positive pregnancy test) or lactation.

16. Patients with prior orthotropic liver transplantation.

17. Patients with cirrhosis and severe synthetic liver dysfunction (Child Pugh B-C).

Prohibited Therapies and/or Medications

18. Patients must not have received prior anticancer therapy with anti-CLTA-4 or anti-PD1 for HCC. Patients receiving any concomitant systemic therapy for HCC are excluded.

19. Patients must not be scheduled to receive another experimental drug while on this study.

20. Patients who require ongoing anticoagulation will be excluded. Only aspirin will be permitted. Pre and post-surgical prophylactic anti-coagulation treatment is permitted.

21. Patients must not require total parenteral nutrition with lipids.

Other Exclusion Criteria

22. Any patients who cannot be compliant with the appointments required in this protocol must not be enrolled in this study.

5.0 TREATMENT PLAN

5.1 Registration

This is a randomized preoperative pilot study evaluating nivolumab alone or in combination with ipilimumab in patients with resectable HCC. Patients will be registered by the responsible study nurse or research coordinator.

5.2 Data Collection

Data will be collected and stored in an approved database as required.

5.3 Study Design and Duration

This is a pilot, randomized, open-label study of preoperative nivolumab alone (Arm A) or nivolumab plus ipilimumab (Arm B) in patients with resectable HCC. **A total of 30 patients will be enrolled as follows: Arm A (15 patients) and Arm B (15 patients)**. Patients will be randomized into either Arm A or B.

> Note: As of January 8, 2020, 30 patients have been enrolled and 27 patients have been randomized. The PI decided to stop enrollment since the study has reached its primary endpoint of safety.

During screening, patients will be evaluated by a surgeon to determine if they are good candidates for conservative hepatic resection or liver resection with curative intent. All patients will also be required to provide a pre-treatment biopsy with documented tumor involvement by pathologist review.

Originally, this study included a third arm (Arm C) in which 15 unresectable patients were to receive nivolumab 240 mg IV every 2 weeks for 3 doses plus ipilimumab 1 mg/kg IV on day 1 of therapy (3 doses of nivolumab, 1 dose of ipilimumab; 6 weeks) followed by post-treatment biopsy. The study objective in Arm C was to estimate the conversion rate to surgery for potentially resectable patients. However, the study has been amended in June 2019 to remove exclude this objective and enrollment of Arm C (Appendix II).

Patients in **Arm A (resectable cohort)** will receive nivolumab at 240 mg IV every 2 weeks for 3 doses followed by liver imaging and hepatic resection on day 1 of week 7, followed (after 4 weeks from surgery) by nivolumab 480 mg IV every 4 weeks in the adjuvant setting until disease progression or for 2 years, whichever is sooner. Patients in **Arm B (resectable cohort)** will receive nivolumab 240 mg IV every 2 weeks for 3 doses plus ipilimumab 1 mg/kg IV on day 1 of therapy (3 doses of nivolumab, 1 dose of ipilimumab) followed by hepatic resection followed (after 4 weeks from surgery) by nivolumab 480 mg IV every 4 weeks plus ipilimumab 1 mg/kg IV every 6 weeks to 4 doses in the adjuvant setting. Adjuvant therapy will start after 4 weeks from surgery with nivolumab 480 mg IV every 4 weeks (Both Arms A and B) plus ipilimumab 1 mg/kg IV every 6 weeks (in Arm B only) for up to 4 doses in the adjuvant setting until disease recurrence or for total of 2 years from first cycle, whichever is sooner. For Arm B, ipilimumab will be administered before nivolumab since the toxicities for ipilimumab are already well-known. Since the doses of nivolumab and ipilimumab either as monotherapy or combination are within maximum tolerated doses as previously defined, no dose increases or reductions will be allowed.

Patients will return at week 6 for a pre-surgical evaluation. A small portion of patients with rapid disease progression (We anticipate 1-3 of a total of 30 patients in Arms A and B) may not have hepatic resection per discretion of the treating surgical and medical oncologists. These patients will be off protocol and treated with other standard or investigational agents. They will be asked to return for an optional biopsy that will be scheduled in place of their surgery. For patients who had significant progression of disease pre-operatively but are still eligible for hepatic resection or transplantation, they will be treated with other investigational agents vs. observation post-operatively as there is no standard adjuvant therapy in surgically resected HCC.

After finishing the last treatment, hepatic resection or biopsy will occur on day 1 of week 7 (+/- 7 days). We will obtain surveillance scans (MRI of abdomen and pelvis with/without contrast, and CT chest with/without contrast of chest) 8 weeks after surgery. Patients who show significant progression of disease post-operatively will be taken off study and an optional biopsy will be taken at that time for immunological analysis.

Patients who complete the study or discontinue study treatment should be scheduled for an end of treatment visit (EOT) as soon as possible. All patients who complete the study or discontinue treatment will have a safety follow-up visit 30 (+/- 14 days) after the last dose of study drug or surgery, whichever comes last. Please refer to **Figure 2** below for the study design.

Patients will receive baseline staging studies with CT or MRI and be assessed for treatment response by scans: MRI or CT of abdomen and pelvis with/without contrast, and CT chest with/without contrast of chest (according to RECIST 1.1 and irRC) at week 6 (+/- 7 days). Each patient will have post-surgical (day 1 of week 11 +/- 7 days), staging studies as above. Subsequently, restaging will be carried out every 12 weeks unless, in the investigators' opinion, follow-up intervals need to be shorter. Studies to confirm a complete response or document progressive disease will be performed as needed. Patients will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1/irRC-defined progression if they are deemed by the investigator to be deriving clinical benefit and tolerating study drug(s), as described in Section 8.3.

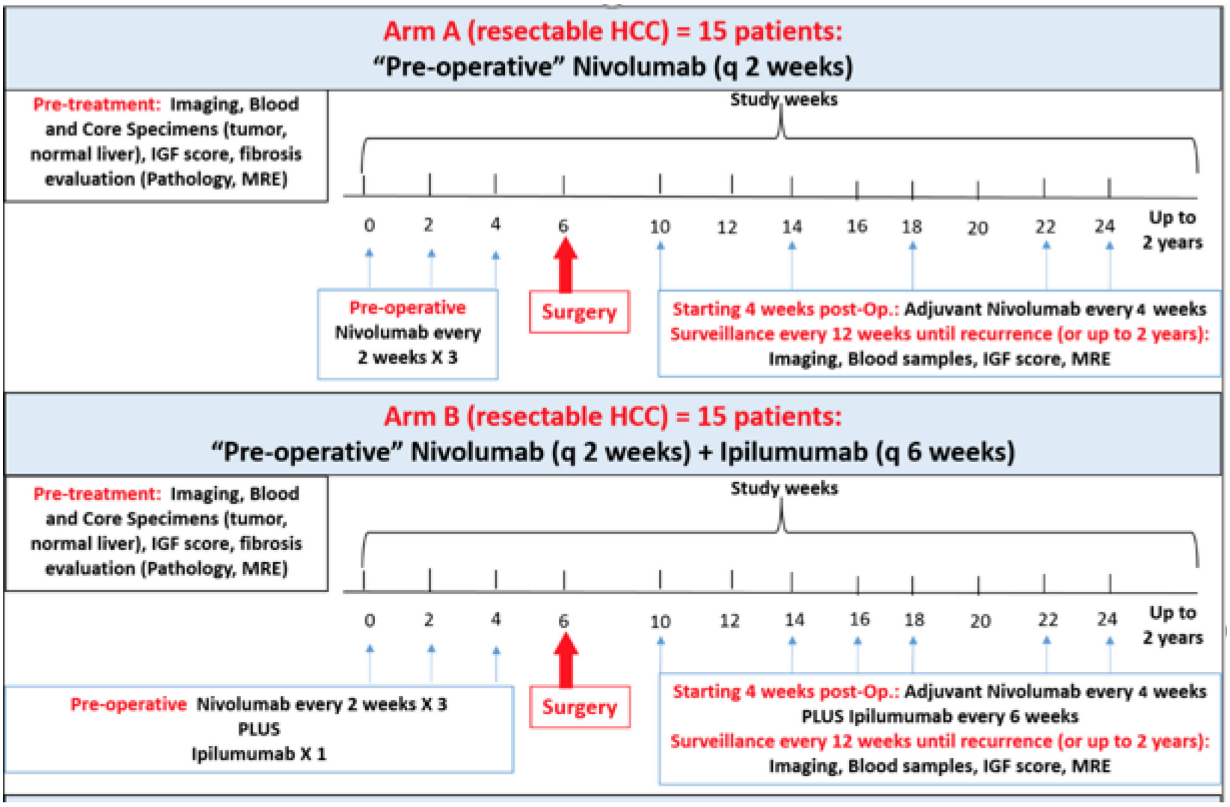

Figure 2. Study Design of preoperative nivolumab alone or in combination with ipilimumab. There are 2 arms to this study: A) Nivolumab monotherapy in resectable HCC; B) Combination nivolumab plus ipilimumab in resectable HCC.

6.0 STUDY MEDICATIONS

6.1 Nivolumab (Anti-PD1, nivolumab)

The vials are not subject specific although there will be specific vial assignments by subject distributed by the Pharmacy in order to track drug usage and re-supply.

6.1.1 Dose Calculation of nivolumab

Nivolumab will be dosed at the the currently FDA-approved dose of 240 mg/dose every two weeks or 480 mg/dose every 4 weeks. The flat dose was recently deemed similar to the 3mg/kg dosing that was previously used. Dose adjustment is not allowed.

6.1.2 Preparation and Dispensing of Nivolumab

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

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Nivolumab vials must be stored at a temperature of 2°C to 8°C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the Investigator Brochure section for "Recommended Storage and Use Conditions". Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab is to be administered as a 30 +/- 15-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or D5W for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

6.1.3 Administration of nivolumab

Patients in all two arms (a total of 30 will receive preoperative treatment with nivolumab as a 30 +/- 15-minute IV infusion on Day 1 of a treatment cycle every 2 weeks for arms A and B. Post-surgery adjuvant maintenance nivolumab will be given at 480 mg IV every 4 weeks until disease progression or intolerability. There will be no nivolumab dose escalations or reductions allowed. Patients in each arm may be dosed no less than 12 days from the previous dose. All post-surgical patients may be dosed no less than 12 days from the previous dose. If a subject cannot receive a following dose of the cycle within the designated time frame, it will be omitted and the next dose received will be considered Day 1 of the next cycle.

Nivolumab should be administered under the supervision of a physician experienced in the use of IV agents. Nivolumab is administered as an IV infusion only.

Calculate **Total Infusion Volume** as follows:
(Total nivolumab dose in mg ÷ 10 mg/mL) + dilution volume = total infusion volume in mL

Calculate **Total Drug Concentration** as follows:
Total nivolumab dose in mg ÷ Total infusion volume nivolumab dose in ml = total infusion volume in mg/mL.
Total concentration cannot be below 0.35 mg/mL.

Calculate **Rate of Infusion** as follows:
Total infusion volume in mL ÷ 30 minutes = rate of infusion in mL/min.

Example:
Flat dosing of 240 mg of nivolumab used.
The total infusion volume would be **24** mL (240 mg ÷ 10 mg/mL = 24 mL) if no dilution volume is added.
The total drug concentration would be **10** mg/mL (240 mg ÷ 24 mL = 10 mg/mL).
The rate of infusion would be **0.80** mL/min in 30 minutes (24 mL ÷ 30 minutes = 0.80 mL/min).

6.1.4 Patient Monitoring During Infusion

Patient vital signs should be monitored prior to dosing, about 15 minutes after initiation of the infusion (then every 15-20 minutes as indicated), at 30 and 60 minutes after completion of the infusion, or longer if indicated, until the vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing, every 30 minutes during dosing, and 1-hour post dosing. All vital sign time points will be afforded a 10-minute window.

6.1.5 Treatment of nivolumab Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations for nivolumab related infusion reactions are provided below and may be modified based on MD Anderson treatment standards and guidelines, as appropriate:

- **For Grade 1 symptoms** (Mild reaction; infusion interruption not indicated; intervention not indicated):
    - Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic pre-medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.
- **For Grade 2 symptoms** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):
    - Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
- **For Grade 3 or Grade 4 symptoms** [Severe reaction, Grade 3: prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltrates), Grade 4: life-threatening; pressor or ventilatory support indicated]:
    - Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg

of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Institutional guidelines will be followed for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids).

6.2 Ipilimumab (BMS-734016)

Ipilimumab is a human immunoglobulin G (IgG1) κ anti-CTLA-4 monoclonal antibody (mAb). It is supplied in clear, colorless solution at a concentration of 5 mg/ml in 40ml vial.

Ipilimumab (BMS-734016) Injection (5 mg/ml), must be stored refrigerated (2 - 8°C) with protection from light. In preparation of infusion, ipilimumab may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers at room temperature or refrigerated (2°C - 8°C) for up to 24 hours. Drug must be completely delivered to the subject within 24 hours of preparation. This includes any time in transit plus the total time for the infusion.

6.3.1 Dose Calculation of Ipilimumab

Total dose should be calculated as in the following example:

Subject's actual body weight in kg x 1 mg = total dose in mg

Therefore, a subject weighing 70 kg who is to receive a dose of 1 mg/kg would be administered 70 mg of ipilimumab (70 kg x 1 mg/kg = 70 mg). Dose adjustment is not allowed.

6.3.2 Administration of Ipilimumab

Each patient in Arm B is to receive ipilimumab at 1 mg/kg dose IV every 6 weeks of treatment for up to 4 dses after surgery. Ipilimumab will be administered as a 90 +/- 15-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

Please refer to the ipilimumab Investigator Brochure for further details regarding preparation/administration.

6.3.3 Patient monitoring during Ipilimumab infusion

Patient vital signs should be monitored prior to dosing, about 15 minutes after initiation of the infusion (then every 15-20 minutes as indicated), at 30 and 60 minutes after completion of the infusion, or longer if indicated, until the vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing, every 30 minutes during dosing, and 1-hour post dosing. All vital sign time points will be afforded a 10-minute window.

6.3.4 Treatment of Ipilimumab infusion Reactions

Since ipilimumab contains only human protein sequences, it is less likely that any allergic reaction will be seen in patients. However, it is possible that infusion of ipilimumab will induce a cytokine release syndrome that could be evidenced by fever, chills, rigors, rash, pruritus, hypo- or hypertension, bronchospasm or other symptoms. No prophylactic pre-medication will be given unless indicated by previous experience in an individual patient.

Reactions should be treated based upon the following recommendations:

<u>For mild symptoms (e.g., localized cutaneous reactions such as mild pruritus, flushing, rash</u>):

- Decrease the rate of infusion until recovery from symptoms, remain at bedside and monitor patient;
- Complete the ipilimumab infusion at the initial planned rate;
- Diphenhydramine 50 mg IV will be given prior to subsequent doses for patient who experience infusion reactions of ≥ grade 1.
- Premedication with diphenhydramine may otherwise be given at the discretion of the Investigator for subsequent doses of ipilimumab.

<u>For moderate symptoms (any symptom not listed above [mild symptoms] or below [severe symptoms] such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg):</u>

- Interrupt ipilimumab;
- Administer diphenhydramine 50 mg IV;
- Monitor patient closely until resolution of symptoms;
- Corticosteroids may abrogate any beneficial immunologic effect, but may be administered at the discretion of the treating physician;
- Resume ipilimumab infusion after recovery of symptoms;
- At the discretion of the treating physician, ipilimumab infusion may be resumed at *one half the initial infusion rate, then increased incrementally to the initial infusion rate.*

- If symptoms develop after resumption of the infusion, the infusion should be discontinued and no additional ipilimumab should be administered that day;
- The next dose of ipilimumab will be administered at its next scheduled time and may be given with pre-medication (diphenhydramine and acetaminophen) and careful monitoring, following the same treatment guidelines outlined above;
- At the discretion of the treating physician additional oral or IV antihistamine may be administered prior to dosing with ipilimumab.

For severe symptoms (e.g., any reaction such as bronchospasm, generalized urticaria, systolic blood pressure <80 mm Hg, or angioedema):

- Immediately discontinue infusion of ipilimumab, and disconnect infusion tubing from the subject;
- Consider bronchodilators, epinephrine 1 mg IV or subcutaneously, and/or diphenhydramine 50 mg IV, with Solu-Medrol 100 mg IV, as needed.
- Patients should be monitored until the Investigator is comfortable that the symptoms will not recur;
- No further ipilimumab will be administered;

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

7.0 DOSE MODIFICATIONS

Based upon toxicity profiles on past clinical trials (e.g. nivolumab plus ipilimumab in melanoma [43, 44]), the doses of nivolumab and ipilimumab proposed in this protocol are within the maximum tolerated doses. Therefore, dose reductions or modifications of nivolumab and/or ipilimumab will not be allowed.

For detailed management of toxicities related to nivolumab or ipilimumab, please refer to Appendix 1 (AE I-O Algorithms). If a patient experiences a grade 3 or greater drug-related adverse event after a dose of nivolumab or ipilimumab, and did not respond to steroid treatment within 2 weeks (i.e. improve from G4 to $\leq$ G3; or from G3 to $\leq$ G2), then the next dose will not be administered and the patient will proceed to surgery after the adverse event has resolved or been ameliorated sufficiently so that the patient can proceed safely to surgery. If a patient experiences a grade 3 or greater non-drug related adverse event after a dose of nivolumab or ipilimumab then the patient may receive additional doses of nivolumab or ipilimumab, at the discretion of the PI, if the grade 3 or greater event has resolved or has been reduced sufficiently as assessed by the treating PI prior to administration of the additional doses of nivolumab or ipilimumab.

8.0 DISCONTINUATION OF THERAPY

Patients MUST be discontinued from study therapy AND withdrawn from the study for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality or inter-current illness which, in the opinion of the Investigator, indicates that continued treatment with study therapy is not in the best interest of the subject
- Termination of the study by MD Anderson Cancer Center
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

8.1 Discontinuation Criteria of Nivolumab and Ipilimumab

Nivolumab and Ipilimumab administration should be discontinued for the following:

- Any Grade ≥ 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related bronchospasm, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 5-10x ULN for > 2 weeks
      - AST or ALT > 10x ULN
      - Total bilirubin > 5x ULN
      - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
  - Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the PI for Grade 4 amylase or lipase abnormalities.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the principle investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the principle investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the UTMDACC IND Office must be notified. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or inter-current illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin: Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the PI for Grade 3 amylase or lipase abnormalities.
- Any Grade 3 colitis, neurologic toxicity, symptomatic pancreatitis, or pneumonitis.
- Any Grade ≥3 Stevens-Johnson Syndrome of Toxic Epidermal Necrolysis(TEN).

8.2 Continued Treatment beyond Progression of Disease

Accumulating evidence indicates a minority of patients treated with immunotherapy may derive clinical benefit from continued treatment despite initial evidence of progressive disease [48]. For this reason, patients receiving nivolumab +/- [ipilimumab] will be permitted to continue study therapy beyond initial investigator-assessed RECIST 1.1-defined progression as long as they meet the 2 criteria listed below.

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression post-surgery must be discussed with the MDACC IND Office and documented in the study records.

Patients should discontinue study therapy upon evidence of further progression, defined as an additional 10% or greater increase in tumor burden from time of initial progression (including all target lesions and new measurable lesions).

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

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

8.3 Destruction of Study Drug

Nivolumab and ipilimumab are to be destroyed onsite. It is the Investigator's responsibility to ensure that arrangements have been made for disposal and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

8.4 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by BMS. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 CONCOMITANT THERAPY

Concurrent medications related to co-morbidity (e.g. hypertension, diabetes, etc.) and pre-medications prescribed by the protocol for infusion reactions will be recorded in the database. Hydration, supportive medications, and routine surgical drugs will not be recorded in the database. The patient will provide a list of medications taken within 4 weeks prior to screening, and will provide a new list during each clinic visit (see section 10.0). The name, dose, date of start, date of stop (if use for short term), indication of the medication will be listed.

The patient should not start a new prescription medication or over-the-counter medication before consulting with the study investigator, except in the case of a medical emergency. No other cancer/investigational therapies should be started during the current study without consulting with the study investigator.

10.0 STUDY ASSESSMENTS AND PROCEDURES

Table 1: Study Assessments and Procedures for Arm A

Trial Period:	**Screening Phase**	**Treatment Cycles. 3 cycles (2-Week Cycles) planned before surgery then after surgery (4-Week Cycles), patients may receive up to 2 years of therapy depending on response and every restaging scans every 12 weeks**							**End of Treatment**	**Post-treatment**		
Title:	**Screening**				**Surgery**				**Discontinue**	**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Treatment Cycle/Day:	**0**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7+D1**	At time of discon	30 days post last dose	Every 9 weeks post-discon	Every 12 weeks
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±7	±3	±3	±3	±3	±7	±7	±7
Administrative Procedures												
Informed consent	X											
Informed consent for future biomedical research (optional)	X											
Inclusion/exclusion criteria	X											

Trial Period:	**Screening Phase**	**Treatment Cycles. 3 cycles (2-Week Cycles) planned before surgery then after surgery (4-Week Cycles), patients may receive up to 2 years of therapy depending on response and every restaging scans every 12 weeks**							**End of Treatment**	**Post-treatment**		
Title:	**Screening**				**Surgery**				**Discontinue**	**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Treatment Cycle/Day:	**0**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7+D1**	At time of discon	30 days post last dose	Every 9 weeks post-discon	Every 12 weeks
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±7	±3	±3	±3	±3	±7	±7	±7
Demographics and medical history	X											
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X		
Post-study anticancer therapy status										X	X	X
Survival status												X
Clinical Procedures/Assessments												
Review adverse events	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination	X								X	X		
Directed physical examination [c]		X	X	X	X	X	X	X				
Child-Pugh score	X											
Height, weight, and vital signs (T, P, RR, BP)[c]	X	X	X	X	X	X	X	X	X			
12-Lead electrocardiogram	X											
Upper endoscopy[p]	X											
ECOG performance status	X[e]	X	X	X	X	X	X	X	X			
Nivolumab administration		X[b]	X	X		X[b]	X	X				
LOCAL Laboratory Assessments												
Pregnancy test[d]	X	X				X				X		
PT/INR and PTT	X[e]	X	X	X	X	X	X	X	X	X		
CBC with differential[f]	X[e]	X	X	X	X	X	X	X	X	X		

Trial Period:	**Screening Phase**	**Treatment Cycles. 3 cycles (2-Week Cycles) planned before surgery then after surgery (4-Week Cycles), patients may receive up to 2 years of therapy depending on response and every restaging scans every 12 weeks**							**End of Treatment**	**Post-treatment**		
Title:	**Screening**				**Surgery**				**Discontinue**	**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Treatment Cycle/Day:	**0**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7+D1**	At time of discon	30 days post last dose	Every 9 weeks post-discon	Every 12 weeks
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±7	±3	±3	±3	±3	±7	±7	±7
Chemistry panel[f]	X[e]	X	X	X	X	X	X	X	X	X		
Urinalysis[g]	X[e]	X	X	X	X		X[q]		X			
T3, FT4, TSH , ACTH, and total cortisol[g]	X[e]	X	X	X	X		X[q]		X	X		
AFP[p]	X[e]	X			X		X[q]		X	X		
C -Reactive protein, amylase, lipase		X			X		X[q]		X			
Serum IGF	X[q]	X			X		X[q]		X			
Hepatitis C antibody (HCV Ab, anti-HCV)	X											
Anti-HBc (Total and IgM), anti-HBs, HBsAg	X											
If Anti-HCV (Hepatitis C antibody) positive:												
• HCV genotype	X											
• HCV viral load[n]	X	X			X		X[q]		X			
If (1) HBsAg positive or (2) anti-HBc positive, anti-HBs negative, and HBsAg negative:												
• Anti-HDV	X											
• Anti-HBe and HBeAg	X											

Trial Period:	**Screening Phase**	**Treatment Cycles. 3 cycles (2-Week Cycles) planned before surgery then after surgery (4-Week Cycles), patients may receive up to 2 years of therapy depending on response and every restaging scans every 12 weeks**							**End of Treatment**	**Post-treatment**		
Title:	**Screening**				**Surgery**				**Discontinue**	**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Treatment Cycle/Day:	**0**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7+D1**	At time of discon	30 days post last dose	Every 9 weeks post-discon	Every 12 weeks
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±7	±3	±3	±3	±3	±7	±7	±7
• HBV viral load[n]	X				X		X[q]		X			
• Anti-HBc (total), anti-HBs, and HBe Ag	X											
CENTRAL Laboratory Assessments												
Blood for genetic analysis		X										
Whole blood for biomarker studies (serum and plasma)[h]		X	X	X	X		X[q]		X			
Whole blood for correlative studies (RNA and DNA)[h]		X	X	X	X		X[q]		X			
Tumor tissue collection[j]	X				X							
Efficacy Measurements												
Tumor imaging[k]	X[i, n]				X		X[q]		X			

AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; Anti-HBc (total) = Total hepatitis B core antibody; Anti-HDV = hepatitis D virus antibody (previously known as 'delta'); anti-HBs = hepatitis B surface antibody; BP = blood pressure; CBC = complete blood count; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; FT4 = free thyroxine; HBeAb or anti-HBe = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HBcAg = hepatitis B core antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCV Ab = hepatitis C antibody; INR = international normalized ratio; P = pulse; Q12W = every 12 weeks; RR = respiratory rate; T = temperature; PT = prothrombin time; T3 = triiodothyronine; TSH = thyroid-stimulating hormone, ACTH = adrenocorticotropic hormone .

a. In subjects that experience site-assessed PD or start a new anti-cancer therapy, contact should be made (example; by telephone) q12W to assess for survival status.
b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ±3 days until the end of treatment and ±7 days during follow-up. Nivolumab is given every 4 weeks after surgery.
c. Height will be measured at Visit 1 only.
d. For women of reproductive potential, a urine or serum pregnancy test should be performed within 24 hours prior to C1D1, C5D1 and 30 days post treatment. May use screening pregnancy test if performed within 24 hours of first dose. A serum test can be done if urine is not appropriate. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of a positive test results. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
e. ECOG Performance Status and laboratory tests for screening and determining eligibility are to be performed within 28 days prior to the first dose of trial treatment.
f. CBC with differential and chemistry to be performed every 2 weeks before surgery. After surgery, CBC with differential and chemistry are performed on every nivolumab administration day.
g. Urinalysis and thyroid/hormonal function tests will be performed at every cycle before surgery, at time of surgery (C4D1), at C6D1 and at every restaging thereafter (q12 weeks).
h. Blood will be collected prior to dose one (C1D1), Cycle 2 and 3 (before the 2nd and 3rd dose of Nivolumab), at time of surgery (C4D1), at 8 weeks after surgery (C6D1), at every restaging thereafter (q12 weeks), and finally at treatment discontinuation (confirmed progression or end of therapy).
i. Screening tumor imaging will be performed within 28 days prior to allocation for confirmation of baseline measurable disease per RECIST 1.1 as required prior to subject allocation, then at time of surgery. After surgery, imaging will be repeated and therapy starts at C7D1, then surveillance imaging will be repeated q12W (72±7 days).
j. Biopsies will be required pre-treatment and at time of surgery.
k. The first on-study imaging time point will be performed at 6 weeks around time of surgery (42±7 days) calculated from the date of allocation and then 8 weeks after surgery, and will continue to be performed q12W.
l. SAEs will be followed through 100 days following cessation of treatment, or 100 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.
m. HBV/HCV viral loads (for subjects who have known history of chronic infection) will be measured during screening, then at C1D1, at time of surgery (C4D1), at 8 weeks after surgery (C6D1), at every restaging thereafter (q12 weeks), and at time of discontinuation.
n. The following imaging studies are required at screening, at time of surgery, at 8 weeks after surgery, then at every restaging thereafter (q12 weeks): CT chest with or without contrast; MRI of abdomen and pelvis with or without contrast unless patient has contraindication for MRI or severely claustrophobic.
o. Every time imaging is done for re-staging (q12 weeks).

Trial Period:	Screening Phase	Treatment Cycles. 3 cycles (2-Week Cycles) planned before surgery then after surgery (4-Week Cycles), patients may receive up to 2 years of therapy depending on response and every restaging scans every 12 weeks							End of Treatment	Post-treatment		
Title:	**Screening**				**Surgery**				**Discontinue**	**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Treatment Cycle/Day:	**0**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7+D1**	At time of discon	30 days post last dose	Every 9 weeks post-discon	Every 12 weeks
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±7	±3	±3	±3	±3	±7	±7	±7

p. Unless performed within 6 months of enrollment day.
q. Starting with Cycle 6, assessments are to be done q12 weeks.

Table 1: Study Assessments and Procedures for Arm B

Trial Period:	Screening Phase	Treatment Cycles. 3 cycles (2-Week Cycles) planned before surgery then after surgery (4-Week Cycles), patients may receive up to 2 years of therapy depending on response and every restaging scans every 12 weeks							End of Treatment	Post-treatment		
Title:	**Screening**				**Surgery**				**Discontinue**	**Safety Follow-up[m]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Treatment Cycle/Day	**0**	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7+D1**	At time of discon	30 days post last dose	Every 9 weeks post-discon	Every 12 weeks
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±7	±3	±3	±3	±3	±7	±7	±7
Administrative Procedures												
Informed consent	X											
Informed consent for future biomedical research (optional)	X											
Inclusion/exclusion criteria	X											
Demographics and medical history	X											
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X		

Post-study anticancer therapy status										X	X	X
Survival status												X
Clinical Procedures/Assessments												
Review adverse events	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination	X								X	X		
Directed physical examination[c]		X	X	X	X	X	X	X				
Child-Pugh score	X											
Height, weight, and vital signs (T, P, RR, BP)[c]	X	X	X	X	X	X	X	X	X			
12-Lead electrocardiogram	X											
Upper endoscopy	X											
ECOG performance status	X[e]	X	X	X	X	X	X	X	X			
Nivolumab administration		X[b]	X	X		X[b]	X	X				
Ipilimumab administration		X[b]				X[r]						
LOCAL Laboratory Assessments												
Pregnancy test[d]	X	X				X				X		
PT/INR and PTT	X[e]	X	X	X	X	X	X	X	X	X		
CBC with differential[f]	X[e]	X	X	X	X	X	X	X	X	X		
Chemistry panel[f]	X[e]	X	X	X	X	X	X	X	X	X		
Urinalysis[g]	X[e]	X	X	X	X		X[q]		X			
T3, FT4, TSH , ACTH, and total cortisol[g]	X[e]	X	X	X	X		X[q]		X	X		
AFP[o]	X[e]	X			X		X[q]		X	X		
C -Reactive protein, amylase, lipase		X			X		X[q]		X			
Serum IGF	X[q]	X			X		X[q]		X			
Hepatitis C antibody (HCV Ab, anti-HCV)	X											
Anti-HBc (Total and IgM), anti-HBs, HBsAg	X											
If Anti-HCV (Hepatitis C antibody) positive:												
• HCV genotype	X											
• HCV viral load[n]	X	X			X		X[q]		X			

If (1) HBsAg positive or (2) anti-HBc positive, anti-HBs negative, and HBsAg negative:												
• Anti-HDV	X											
• Anti-HBe and HBeAg	X											
• HBV viral load[m]	X				X		X[q]		X			
• Anti-HBc (total), anti-HBs, and HBe Ag	X											
CENTRAL Laboratory Assessments												
Blood for genetic analysis		X										
Whole blood for biomarker studies (serum and plasma)[h]		X	X	X	X		X[q]		X			
Whole blood for correlative studies (RNA and DNA)[h]		X	X	X	X		X[q]		X			
Tumor tissue collection[j]	X				X							
Efficacy Measurements												
Tumor imaging[k]	X[i,n]				X		X[q]		X			

AFP = alpha fetoprotein; aPTT = activated partial thromboplastin time; Anti-HBc (total) = Total hepatitis B core antibody; Anti-HDV = hepatitis D virus antibody (previously known as 'delta'); anti-HBs = hepatitis B surface antibody; BP = blood pressure; CBC = complete blood count; Discon = discontinuation; ECOG = Eastern Cooperative Oncology Group; FT4 = free thyroxine; HBeAb or anti-HBe = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBV = hepatitis B virus; HBcAg = hepatitis B core antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HCV Ab = hepatitis C antibody; INR = international normalized ratio; P = pulse; Q12W = every 12 weeks; RR = respiratory rate; T = temperature; PT = prothrombin time; T3 = triiodothyronine; TSH = thyroid-stimulating hormone, ACTH = adrenocorticotropic hormone .

a. In subjects that experience site-assessed PD or start a new anti-cancer therapy, contact should be made (example; by telephone) q12W to assess for survival status.
b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ±3 days until the end of treatment and ±7 days during follow-up. Nivolumab is given every 4 weeks after surgery.
c. Height will be measured at Visit 1 only. Timepoints of directed physical examination will follow nivolumab and ipilimumab administration day.
d. For women of reproductive potential, a urine or serum pregnancy test should be performed within 24 hours prior to C1D1, C5D1 and 30 days post treatment. May use screening pregnancy test if performed within 24 hours of first dose. A serum test can be done if urine is not appropriate. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of a positive test results. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
e. ECOG Performance Status and laboratory tests for screening and determining eligibility are to be performed within 28 days prior to the first dose of trial treatment.
f. CBC with differential and chemistry to be performed every 2 weeks before surgery. After surgery, CBC with differential and chemistry are performed on every nivolumab and ipilimumab's administration day.

g. Urinalysis and thyroid/hormonal function tests will be performed at every cycle before surgery, at time of surgery (C4D1), at C6D1 and at every restaging thereafter (q12 weeks).
h. Blood will be collected prior to dose one (C1D1), Cycle 2 and 3 (before the 2nd and 3rd dose of Nivolumab), at time of surgery (C4D1), at 8 weeks after surgery (C6D1), at every restaging thereafter (q12 weeks), and finally at treatment discontinuation (confirmed progression or end of therapy).
i. Screening tumor imaging will be performed within 28 days prior to allocation for confirmation of baseline measurable disease per RECIST 1.1 as required prior to subject allocation, then at time of surgery. After surgery, imaging will be repeated and therapy starts at C7D1, then surveillance imaging will be repeated q12W (72±7 days).
j. Biopsies will be required pre-treatment and at time of surgery.
k. The first on-study imaging time point will be performed at 8 weeks around time of surgery (42±7 days) calculated from the date of allocation and then 8 weeks after surgery, and will continue to be performed q12W.
l. SAEs will be followed through 100 days following cessation of treatment, or 100 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.
m. HBV/HCV viral loads (for subjects who have known history of chronic infection) will be measured during screening, then at C1D1, at time of surgery (C4D1), at 8 weeks after surgery (C6D1), at every restaging thereafter (q12 weeks), and at time of discontinuation.
n. The following imaging studies are required at screening, at time of surgery, at 8 weeks after surgery, then at every restaging thereafter (q12 weeks): CT chest with or without contrast; MRI of abdomen and pelvis with or without contrast unless patient has contraindication for MRI or severely claustrophobic.
o. Every time imaging is done for re-staging (q12 weeks).
p. Unless performed within 6 months of enrollment day.
q. Starting with Cycle 6, assessments are to be done q12 weeks.
r. Ipilimumab 1 mg/kg IV is administered in the adjuvant setting, starting with Cycle 5, every 6 weeks to 4 doses maximum.

10.1 Procedures by Visit

The Time and Events Schedule above (Table 1 - attached) summarizes the frequency and timing of various measurements. The evaluations and procedures for patients enrolled in this study at specific time points are further described in the following sections.

10.1.1 Screening/Pre-study (Day -28 to Day -1)

The following procedures will be completed for each patient prior to inclusion in the study. All screening diagnostic imaging studies MUST be performed within 28 days of the first treatment.

- Confirmation of the eligibility of patients (see Section 4 for detailed Inclusion/Exclusion criteria)
- Histologic diagnosis of HCC
- Demographics
- Medical history relevant to the patient's cancer
- Vital sign measurements including weight, height, temperature, pulse, oxygen saturation by pulse oximetry, and resting systolic and diastolic blood pressure
- Complete physical examination
- ECOG Performance Status
- Clinical laboratory tests
- Hematology: CBC
- Serum Chemistry Panel
- T3 (free), T4 (free) & TSH
- ACTH and Total Cortisol
- Amylase and Lipase
- Hepatitis B and C screening tests
- AFP (alpha fetoprotein)
- Serum IGF
- Blood samples for Immune Testing
- Urinalysis: Gross examination including specific gravity, protein, glucose, and blood; microscopic examination including WBC/HPF, RBC/HPF and any additional findings.
- A pregnancy test will be done for women of childbearing potential every 4 weeks during enrollment, beginning 24 prior to starting therapy, and prior to post-operative nivolumab treatment as explained in Section 4.1.
- Chest radiography
- Diagnostic imaging, including CT of the chest, abdomen and pelvis or MRI abdomen/pelvis.

- EKG
- Current medications
- Baseline signs and symptoms
- Tumor tissue Collection-
- Diagnostic/confirmatory biopsy

10.1.2 Pre-surgical Phase

Patients who complete the screening evaluations and are confirmed to be eligible for the study will begin treatment on this study.

Eligible patients in Arm A will receive nivolumab at 240 mg IV every 2 weeks for 3 doses (6 weeks) followed by hepatic resection.

Eligible patients in Arm B will receive nivolumab 240 mg IV every 2 weeks for 3 doses plus ipilimumab 1 mg/kg IV on day 1 of therapy (3 doses of nivolumab, 1 dose of ipilimumab; 6 weeks) followed by hepatic resection.

The following procedures will be performed within +/- 3 days of each scheduled visit or as indicated in Section 10.

- Vital sign measurements including weight, temperature, pulse, oxygen saturation by pulse oximetry, and resting systolic and diastolic blood pressure.
- Vital sign measurements of pulse, oxygen saturation by pulse oximetry, and systolic and diastolic blood pressure will be collected every 30 minutes for the duration of nivolumab +/- ipilimumab infusion, 1 hour following the completion of the infusion, and routinely unless otherwise indicated.
- Physical examination
- ECOG Performance Status
- Blood samples for Immune Tests
- Hematology: (see Section 10, PT and PTT will be done at baseline and prior to surgery or future procedures)
- Serum chemistry (see Section 10)
- Amylase & Lipase
- AFP
- T3 (free), T4 (free) & TSH (see Section 10)
- A pregnancy test will be done for women of childbearing potential on the day of starting therapy as explained in Section 4.1.
- Concomitant medications (see Section 9)

- Adverse event assessment
- Each patient will be restaged with CT of the chest, abdomen and pelvis or MRI abdomen/pelvis at baseline, prior to surgery, 8 weeks post-surgery follow up, and during future follow up visits (every 12 weeks) as indicated in Section 10, unless, in the investigators' opinion, follow-up intervals need to be shorter. Studies to confirm a complete response or document progressive disease will be performed as needed.Unscheduled visits are permitted to evaluate adverse events and possible disease progression.

10.1.3 Pre-surgical Visit

During the Pre-Surgical Evaluation, the patient will have labs and imaging performed and be assessed by the physician and surgeon to determine if they are still good candidates for surgery. For the pre-surgical visit, patients will return to the clinic at week 6 (+/- 7 days). The following assessments will be conducted during this visit:

- Vital Signs Measurement
- Physical examination
- ECOG Performance Status
- Blood samples for Immune Tests
- Hematology, PT and PTT
- Serum chemistry (see Section 10)
- Amylase and Lipase
- AFP
- T3 (free), T4 (free) & TSH (see Section 10)
- ACTH and Total Cortisol
- Concomitant medications (see Section 9)
- Adverse event assessment
- Each patient will be restaged with CT of the chest, abdomen and pelvis or MRI abdomen/pelvis at baseline, prior to surgery, 8 weeks post-surgery follow up, and during future follow up visits (every 12 weeks) as indicated in Section 10, unless, in the investigators' opinion, follow-up intervals need to be shorter. Studies to confirm a complete response or document progressive disease will be performed as needed.

10.1.4 Surgery Visit

During the Surgical Visit the patient will have a hepatic resection or biopsy performed by the surgeon and tissue will be collected. For the surgical visit, patients will return to the clinic at week 7 (+/- 7 days). The following assessments will be conducted during this visit:

- Surgery or biopsy

- Tumor tissue collection for immune tests
- Additional safety lab tests at the surgeon's discretion
- Tumor tissue collection for immunological testing (at surgery).
- As an optional procedure, tissue will also be collected during procedures performed while patients are enrolled in this study. No new procedures will be required. This tissue will also be banked for future research related to immunological response.

10.1.5 Post-surgical Follow-Up (4 Weeks Post Surgery) & Post-Op Nivolumab or Nivolumab/Ipilimumab Maintenance

The Post-Surgical Follow Up begins for all patients after surgery. Patients will return to the clinic for a follow-up visit 4 weeks postsurgery. The following assessments will be conducted during this visit:

- Vital Signs Measurement
- Physical examination
- ECOG Performance Status
- Blood samples for Immune Tests
- Hematology
- Serum chemistry (see Section 10)
- Amylase and Lipase
- AFP
- T3 (free), T4 (free) & TSH (see Section 10)
- Concomitant medications (see Section 9)
- Adverse event assessment
- Each patient will be restaged with CT of the chest, abdomen and pelvis or MRI abdomen/pelvis at baseline, prior to surgery, 8 weeks post-surgery follow up, and during future follow up visits (every 12 weeks) as indicated in Section 10, unless, in the investigators' opinion, follow-up intervals need to be shorter. Studies to confirm a complete response or document progressive disease will be performed as needed.

Patients will be followed for clinical responses, anti-cancer medications and delayed autoimmune toxicity and TTP. If a possible delayed Immune-related adverse event (IRAE) is suspected, the patient will be requested to return to the Investigator's clinic or office for a physical examination and blood work, and other relevant laboratory assessments. All patients will be followed for immune-related adverse events for at least 30 days after finishing therapy.

10.1.6 End of Treatment Visit

Patients who complete the study or discontinue study treatment should be scheduled for an EOT visit as soon as possible, at which time all of the assessments listed for the EOT visit will be performed. At the time of study early withdrawal, the reason for early withdrawal and any new or continuing AEs should be documented. If study drug administration is discontinued, the reason for discontinuation will be recorded.

10.1.7 Safety Follow-up Visit

All patients who discontinue study treatment will have a safety follow-up visit for safety evaluations 30 days (+/- 14 days) after the last dose of study drug or surgery, whichever comes last. If study drug administration is discontinued, the reason for discontinuation will be recorded.

10.2 Details of Procedures

10.2.1 Study Materials

BMS will provide nivolumab and ipilimumab.

10.2.2 Safety Assessments

Adverse events will be assessed at each patient visit, documented in the medical record, and entered into CRFs. Patients who report visual changes on therapy will be referred to Ophthalmology for evaluation of potential inflammatory or immune-related adverse events (uveitis, optic neuritis, etc.) In addition, any occurrence of a SAE from the time of the first protocol specific intervention forward, until 100 days after the last dose of study drug, will be reported. Refer to safety reporting Section 10.3.

Safety will be evaluated for all treated patients using the NCI CTCAE version 4.0 (http://ctep.cancer.gov). Safety assessments will be based on medical review of AE reports and the results of vital sign measurements, physical examinations and clinical laboratory tests.

10.3 Criteria for Evaluation

10.3.1 Safety Evaluation

Refer to Common Terminology Criteria Adverse Events (CTCAE) version 4.0 (http://ctep.cancer.gov)

10.3.1.1 Medical History, Physical Exam, Physical Measurements

Physical examination will be performed at the time points outlined in Section 10.0. If the screening physical is conducted within 24 hours of dosing on Cycle 1 Day 1, then a single examination may count as both the screening and pre-dose evaluation. Pertinent medical history (physician discretion) will be recorded.

10.3.1.2 Vital Signs

Blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry and temperature will be obtained as outlined in Section 10.0. Orthostatic (supine and standing) blood pressure and heart rate are to be measured for any subject who experience lightheadedness, dizziness, syncope or any similar complaints.

10.3.1.3 ECOG Status

ECOG performance status will be evaluated continuously and documented at Screening and at each visit as outlined in Section 10.0.

10.3.1.4 Assessment of Baseline Symptoms

Baseline signs and symptoms present within 2 weeks of starting therapy, whether or not related to current disease will be documented. Assessment of these baseline signs and symptoms will be done at each treatment and Follow-Up Visit (see Section 10.1). Any worsening by > 1 Grade change from baseline is to be documented as an adverse event.

10.3.1.5 Adverse Event Monitoring

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

Adverse events will be evaluated according to the NCI CTCAE Version 4.0 on a continuous basis starting from when the patient takes the first dose of nivolumab or ipilimumab to follow up visits. Events, such as abnormal laboratory values, considered by the principal investigator to be not clinically significant (related to the study or study drug) will not be documented. **The investigator (or physician designee) is responsible for verifying and**

providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled. If abnormal lab values, which were not pre-existing or which worsened after the first dose of study drug, meet Common Terminology Criteria (CTC) for reporting as adverse events (AE), they will be documented in the AE source document and captured in the CORe/PDMS Database. For the lab results that do not meet the CTC for reporting as an AE, they will be considered not clinically significant (NCS). No additional documentation will be required to neither specify NCS lab results nor require physician investigator signature.

Adverse events will be treated appropriately. Such treatment may involve changes in nivolumab or ipilimumab therapy including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Refer to Sections 6.1-3 for treatments of nivolumab or ipilimumab infusion reaction and toxicities.

Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit of any changes in severity, the suspected relationship to nivolumab or ipilimumab, the interventions required to treat it, and the outcome. Reporting of adverse events will be done according to NCI CTCAE version 4.0. The following items will be recorded at least:

- Event description
- Date of onset of AE
- CTCAE grade/severity (1, 2, 3, 4, 5)
- Relationship to treatment with nivolumab or ipilimumab (unrelated, unlikely, possible, probable, highly probable/definite)
- Action taken (none, temporarily discontinued agent, drug treatment given/specify, permanently discontinued agent, non-drug treatment given/specify, hospitalization)
- Date of AE stop
- Outcome (recovered without sequelae, recovered with sequelae, ongoing, worsened, death)
- Serious AE (yes, no)
- Serious Adverse Events (SAEs) must be collected from the time of the first protocol specific intervention until 100 days after the last dose of study drug.

Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

10.3.2 Laboratory Test Assessments

Any abnormal laboratory test result considered clinically significant by the Investigator must be recorded.

10.3.2.1 Serum Chemistry

Serum chemistry tests include: LDH, glucose, total protein, albumin, BUN or urea, creatinine, ALT, AST, serum alkaline phosphatase, direct and total bilirubin, sodium, potassium, chloride, HCO3, calcium, magnesium, and uric acid. Serum Chemistry is to be obtained as outlined in Section 10.0. Three (3) ml of blood will be drawn for serum chemistry, exclusive of TSH. In addition, TSH, free T3, free T4, ACTH and total cortisol will also be obtained as described in Section 10.0 to monitor endocrine side effects of nivolumab or ipilimumab. Lastly, AFP for tumor marker assessment will also be monitored.

10.3.2.2 Hematology

CBC with differential are to be obtained as outlined in Section 5.1. Complete Blood Count (CBC) with differential includes hemoglobin, hematocrit, white blood cells, platelets, neutrophils, lymphocytes, eosinophils and monocytes. PT and PTT will be drawn at baseline and prior to surgery or future procedures. Additional draws must be incorporated to monitor recovery from any hematologic laboratory AE. Two and a half (2.5) ml blood will be drawn for hematology.

10.3.2.3 Tumor Tissue

Available tumor tissue, obtained at pre-treatment and the time of surgical resection or biopsy (if unresectable) will be collected for immune monitoring studies as described below (Section 10.3.3).

10.3.3 Immune Tests

The Immunotherapy Platform will perform immune monitoring, including but not limited to evaluation of CD4 and CD8 T cells in peripheral blood and available tumor samples as previously published [52-59]. All samples will be collected and analyzed as per a separate IRB-approved lab protocol.

All blood collection will be compliant with institutional safety standards and will not exceed the maximum blood draw per venipuncture policy.

10.3.4 Evaluation of Clinical Responses

10.3.4.1 Efficacy Assessments

Progression-free survival (PFS) and objective response rate (ORR), each based on RECIST 1.1 criteria, are two of the primary efficacy assessments of this study. See Sections 12.2.2.1 and 12.2.2.4 for the definitions of ORR and PFS, respectively.

10.3.4.2 Criteria for Progression and Responses

Evaluation of response will follow the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines. All tumor measurements must be recorded in centimeters.

- Target Lesions:

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum of longest diameters will be used as the reference by which the objective tumor response is characterized.

- Non-target Lesions:

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

- Evaluation of Target Lesions:
  - Complete Response: The disappearance of all target lesions.
  - Partial Response: At least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter.
  - Progressive Disease: At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.
  - Stable Disease: Insufficient shrinkage to qualify for partial response, or insufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.
- Evaluation of Non-target Lesions:
  - Complete Response: The disappearance of all non-target lesions.

- Incomplete Response/Stable Disease: The persistence of one or more non-target lesion(s)
- Progressive Disease: The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

- Evaluation of Best Overall Response: (see Table 4)

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Table 4. Evaluation of Best Overall Response

Target Organ Lesions	Non-Target Organ Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.3.4.3 Immune related Response Criteria (irRC)

Table 5. irRC outcome measures [64]

New, measurable lesions	Incorporated into tumor burden
New, non- measurable lesions	Do not define progression (but precludes irCR)
Non-index lesions	Contribute to defining irCR (complete disappearance is required
Complete response (CR)	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart
Partial response (PR)	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart
Stable disease (SD)	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
Progression of disease (PD)	≥25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart

Note: According to the irRC, disease progression of non-index lesions or appearance of new non-measurable lesions will not classify the subject as PD, and therefore the subject may stay in the study if it is the in the subject's best interest. A confirmatory tumor assessment may be performed no less than 4 weeks after the first indication of progression to provide additional data for the investigator to decide if the subject should stay in the trial or be discontinued due to clinical progression based on the investigator's decision.

10.3.4.4 Time -to- Event Assessment of Response

Time to Response: From the start of study drug to the first observation of a response (the first of two confirmatory measurements).

Duration of Response: From the first observation of a response (the first of the two confirmatory statements) to the first observation of progressive disease, or to death due to any cause, or early discontinuation of treatment due to progressive disease.

Time to Progression: From the start of study drug to the first evidence of progression.

11.0 ADVERSE EVENT REPORTING

11.1 Serious Adverse Event Reporting (SAE) for M. D. Anderson-sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of study drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

11.2 Reporting to FDA

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

11.3 Investigator Communication with Supporting Companies

- Adverse events classified as "serious" require expeditious handling and reporting to BMS to comply with regulatory requirements.
- All SAEs whether related or unrelated to nivolumab or ipilimumab must be immediately reported to BMS (by the investigator or designee) within 24 hours of becoming aware of the event, using the M. D. Anderson SAE forms. If only limited information is initially available, follow-up reports are required. The original SAE form must be kept on file at the study site.

All SAEs should be faxed (or emailed) to BMS at:

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

- For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the FDA as soon as possible and, in no event, later than 7 days (death or life-threatening event) or 15 days (all other SAEs) after the investigator's or institution's initial receipt of the information. The investigator will provide BMS with a simultaneous copy of all adverse events filed with the FDA. SAEs will be reported on the MDACC SAE Form.

- AE Reporting Period: For nivolumab and ipilimumab, all AEs must be collected which occur after the first dose through within 100 days of discontinuation of dosing or completion of the patient's participation in the study if the last scheduled visit occurs at a later time. In addition, the Investigator should notify BMS of any SAE that may occur after this time period which they believe to be certainly, probably, or possibly related to nivolumab and/or ipilimumab.
    - Worldwide.Safety@bms.comaepbusinessprocess@bms.com

Notes:

- Cancer/Overdose: An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. For reporting purposes, any form of overdose, regardless of adverse outcome, will be considered as an important medical event and reported immediately to BMS.
- Hospitalizations (exceptions): Criteria for hospitalizations not reported as SAEs include admissions for:
    - Planned as per protocol medical/surgical procedure
    - Routine health assessment requiring admission for baseline/trending of health status documentation (e.g., routine colonoscopy)
    - Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial; appropriate documentation required)
    - Admission encountered for other life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

11.4 Pregnancy

Patients must agree to use adequate contraception (barrier method of birth control) prior to study entry, and for up to 23 weeks after the last study drug dose (for female study participants) or up to 31 weeks after the last study drug dose (for male study participants). The treating physician, principle investigator and BMS should be notified immediately, should a patient or patient's sexual partner become pregnant or suspect she is pregnant while participating in this study.

12.0 STATISTICAL METHODOLOGY

12.1 Preliminaries and Objectives

This is a randomized, pilot trial of nivolumab (Arm A) or nivolumab + ipilimumab (Arm B) as pre-operative treatment for patients with hepatocellular carcinoma who are eligible for surgical resection. Each patient in both Arms A and B will be given nivolumab at 240 mg every 2 weeks

for a total of 6 weeks. Patients in Arm B will additionally be treated concurrently with ipilimumab at 1mg/kg every 6 weeks. No dose increases or reductions will be allowed for nivolumab or ipilimumab. Surgical resection or post-treatment biopsy will occur within 4 weeks after finishing the last cycle of therapy. The rationale is that nivolumab and ipilimumab activate the immune system via distinct mechanisms and therefore, the combination of nivolumab and ipilimumab may result in synergistic activation of the immune system against hepatocellular carcinoma. The primary objective is to assess the safety and tolerability of nivolumab +/- ipilimumab. Secondary objectives include estimating the ORR and TTP of the 2 different arms. Exploratory objectives include evaluating the pre- and post-treatment immunological changes in tumor tissues and peripheral blood.

As of January 8, 2020, 30 patients have been enrolled and 27 patients have been randomized. The PI decided to stop enrollment since the study has reached its primary endpoint of safety.

12.2 Endpoints

12.2.1 Primary Endpoint: Safety

Safety will be recorded through the incidence of adverse events, serious adverse events and specific laboratory abnormalities (worst grade) in each treatment arm. Toxicities will be graded using the NCI CTCAE version 4.0. For trial monitoring and decisions about future trials, extreme toxicities (TOX) will be defined as any grade 3 or higher adverse event that is possibly, probably, or definitely related to any therapy received on this protocol and occur within the first 6 weeks of therapy with one exception. Any grade 3 or higher adverse event that is potentially treatable with steroids will only count as an extreme toxicity if it does not improve to grade 1 or better within 2 weeks. Additionally, a delay of greater than 3 months from the expected surgery date will count as a TOX.

Success will be predefined as having at least 13 of 15 subjects receiving their assigned therapy without grade 3 or higher adverse events necessitating a delay in the pre-established surgical resection date (a clinically driven end-point defined by the multidisciplinary MD Anderson hepatocellular cancer team).

12.2.2 Secondary Endpoints

12.2.2.1. Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the number of subjects with a best response of CR or PR after 12 weeks of therapy by RECIST 1.1 criteria divided by the number of randomized subjects as described in Section 10.3.4.2

12.2.2.2. Time to progression (TTP)

TTP is defined as the time from the start of study drug to the first documented tumor progression or recurrence of tumor as determined by the investigator using RECIST 1.1 or iRC criteria. Patients who are alive and free of known progression at the time of analysis will be censored on the date of last tumor assessment.

*12.2.2.3 **PFS***

PFS is defined as the time from the start of treatment to date of PD or recurrence or date of death whichever occurs first if patients have a event, or to the last follow-up date if patients are alive without PD.

12.2.3 Exploratory Endpoints

Tissue and blood immune monitoring will be conducted through the Immunotherapy Platform based on samples collected at the following time points: 1) Pre-treatment; 2) time of surgical resection or biopsy (if unresectable); and 3) at time of discontinuation (peripheral blood collection).

12.3 Sample Size

Up to 30 patients will be enrolled, for 15 patients each in arm. This sample size is based on having sufficient patients to assess toxicities in each arm while providing preliminary estimates of secondary endpoints for future trials.

12.4 Randomization

Patients in the resectable cohorts will be randomized in a 1:1 fashion through the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct), which is housed on a secure server at MDACC and maintained by the MDACC Department of Biostatistics. Access to the website will be gained through usernames and passwords provided by the MDACC Department of Biostatistics to personnel responsible for enrolling patients. Training on the use of

the Clinical Trial Conduct website to enroll patients on the study will be provided by the study biostatistician for study personnel.

12.5 Safety Monitoring

All patients who receive at least one dose of nivolumab or nivolumab plus ipilimumab will be considered evaluable for toxicity.

Safety assessments will include a comprehensive evaluation of AEs and/or toxicity based on:

- Results of monitoring vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- Results of clinical chemistry, hematology/coagulation, complement testing, thyroid function testing, and urine analysis tests
- ECG results
- Changes in physical examination
- Need for concomitant medications
- ISRs
- ECOG performance status

12.6 Data Analyses

This is a two arm, open-label pilot study evaluating nivolumab alone or in combination with ipilimumab in the preoperative or prebiopsy setting. Since no effective treatments are available in this setting, a response rate of 15% (within 95% CI) is considered acceptable – i.e., the signal for launching further, larger studies with nivolumab or nivolumab + ipilimumab in this patient population is ≥ 1 response in the current study (each arm). If no response is observed, the treatment with nivolumab alone or in combination with ipilimumab will be considered ineffective. A total of 15 patients will be enrolled in each arm and treated to rule out a response rate of 15% or less with 90% power when at least one response is observed. In other words, with 15 patients treated, the probability of observing at least one response is more than 90% if the response rate is at least 15%. Descriptive statistics including with 90% confidence interval will be computed. Observed response profile, clinical benefit rate at 6 months and TTP along with relevant confidence intervals will be used to guide future development decisions.

Total evaluable patients	Number of responders	Response rate	Lower 90% CI*	Upper 90% CI*
15	0	0%	<1%	18%
15	1	7%	<1%	27%
15	2	13%	2%	36%
15	3	20%	6%	44%
15	4	27%	10%	51%
15	5	33%	14%	58%
15	6	40%	19%	64%
15	7	47%	24%	70%
15	8	53%	30%	76%
15	9	60%	36%	81%
15	10	67%	43%	86%
15	>10**	>67%	>43%	>86%

* Exact confidence interval computed by the method of Clopper and Pearson (Biometrika 26:404-413, 1934)

The Kaplan-Meier method will be used to estimate probability of PFS for each treatment arm.

Our exploratory objectives are to characterize the immune response for both treatment arms and its correlation to treatment response. Immune responses, such as infiltration of CD8+/CD4+ T cells and dendritic cells, and cytokine levels in blood, will be compared between pre-treatment and post-treatment via paired t-test and Wilcoxon signed rank test. The overall treatment response rate will be summarized descriptively by dose with the n, percentage, and 95% CIs. Comparison of the response rates between two treatment arms will be made via Fisher's exact test Association

between the binary overall treatment response and immune responses will be assessed by two-sample t-test and Wilcoxon rank sum test.

The Investigator is responsible for completing a Safety/Efficacy Summary Report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 5 evaluable patients per arm, complete 14 weeks of study treatment, and every 5 evaluable patients per arm, thereafter. On every summary submission, toxicity will be assessed at week 6, and response at week 14 of study treatment.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

13.0 ADMINISTRATIVE SECTION

13.1 Compliance with the Protocol and Protocol Revisions

The study must be conducted as described in the final approved protocol. Documentation of approval signed by the chairperson or designee of the IRB(s) must be sent to BMS protocol managers by the PI/research team. All revisions (protocol amendments, administrative letters, and changes to the informed consent) must be submitted to BMS protocol managers. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

13.2 Informed Consent

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB. The consent form must be sent to BMS for review prior to IRB approval.

13.3 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) on each individual treated with nivolumab +/- [ipilimumab]. The investigator is required to

retain, in a confidential manner, the data pertinent to the study. CORe/PDMS will be used as the electronic case report form for this study. All protocol specific data, including adverse events, will be entered into CORe/PDMS. This study will be monitored for compliance by the IND Office.

13.4 Institutional Review Board (IRB)

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

The Investigator should provide the IRB with reports, updates and other information (e.g., Amendments, Administrative Letters) according to regulatory requirements or Institution procedures. A detailed list of required regulatory documents also to be submitted to BMS will be sent upon final approval of the protocol.

13.5 Record Retention

The Investigator must retain nivolumab and nivolumab plus ipilimumab disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) for the maximum period required by applicable regulations and guidelines, or Institution procedures. If the Investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator, IRB). Documentation of such transfer must be provided to BMS.

References:

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Appendix I: AE I-O Algorithms

GI Adverse Event Management Algorithm

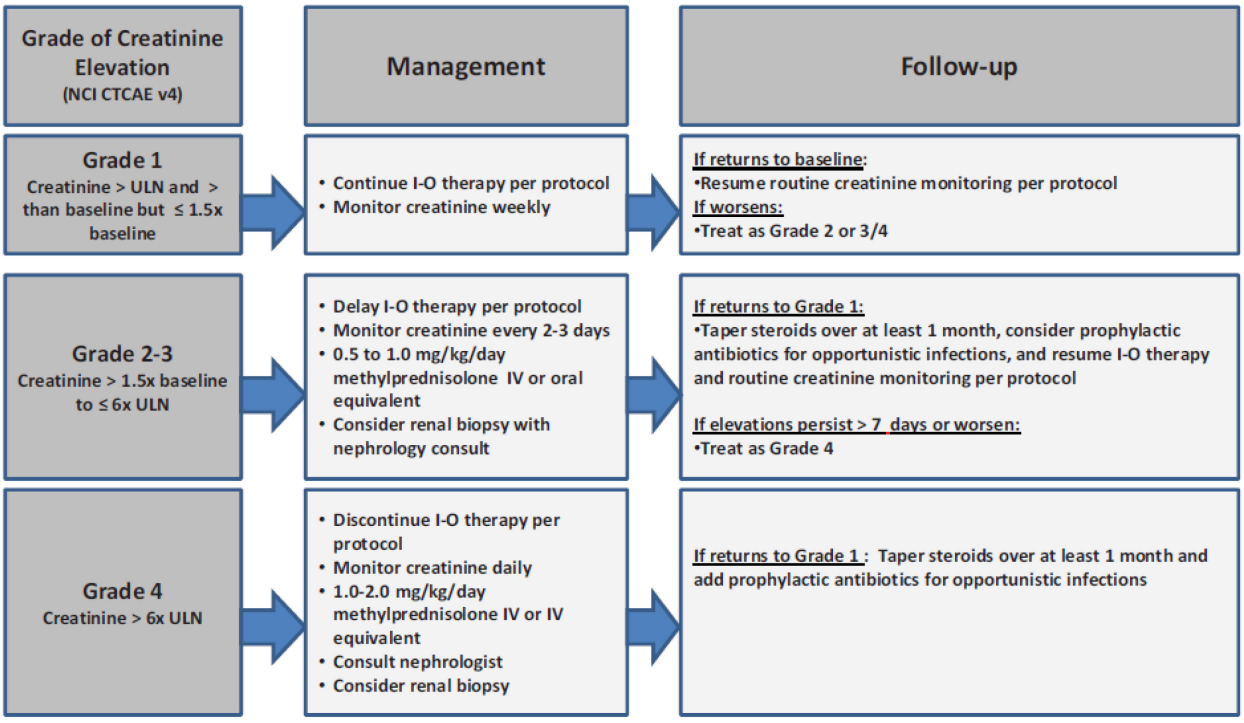
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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

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

Renal Adverse Event Management Algorithm

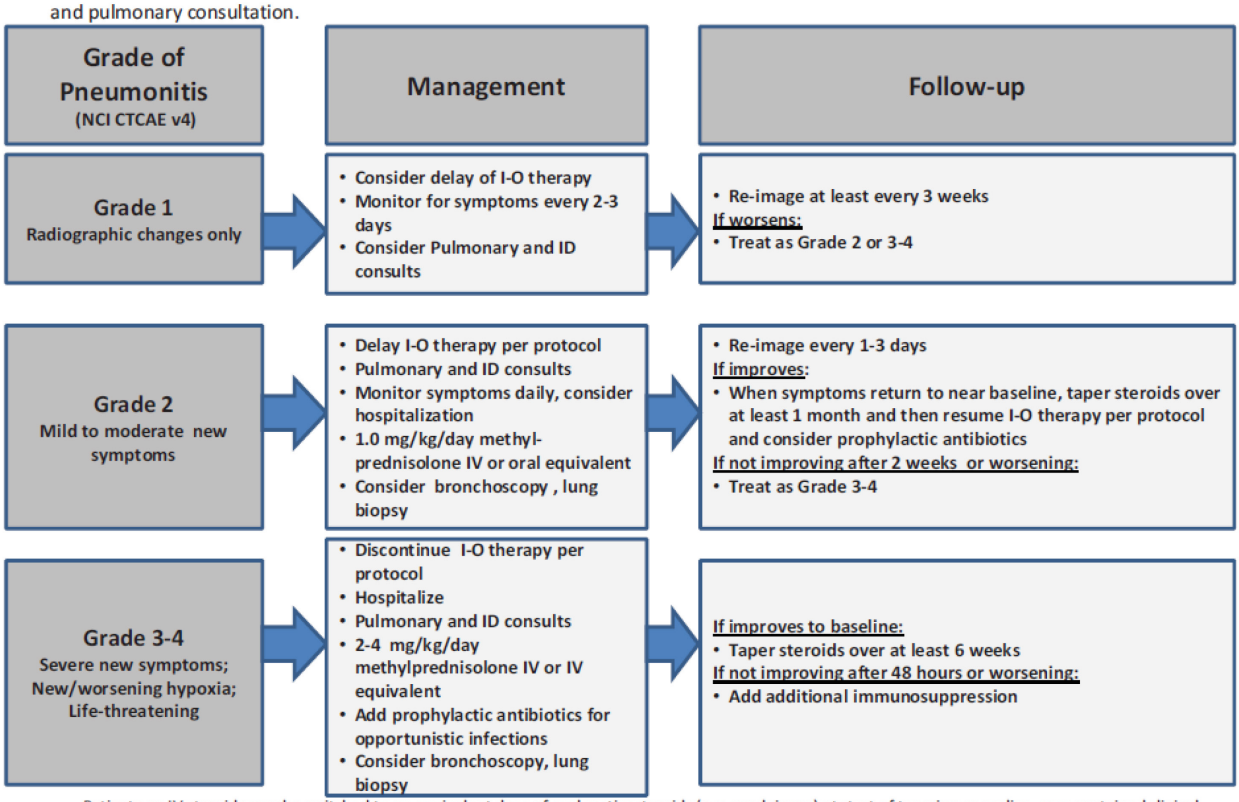
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

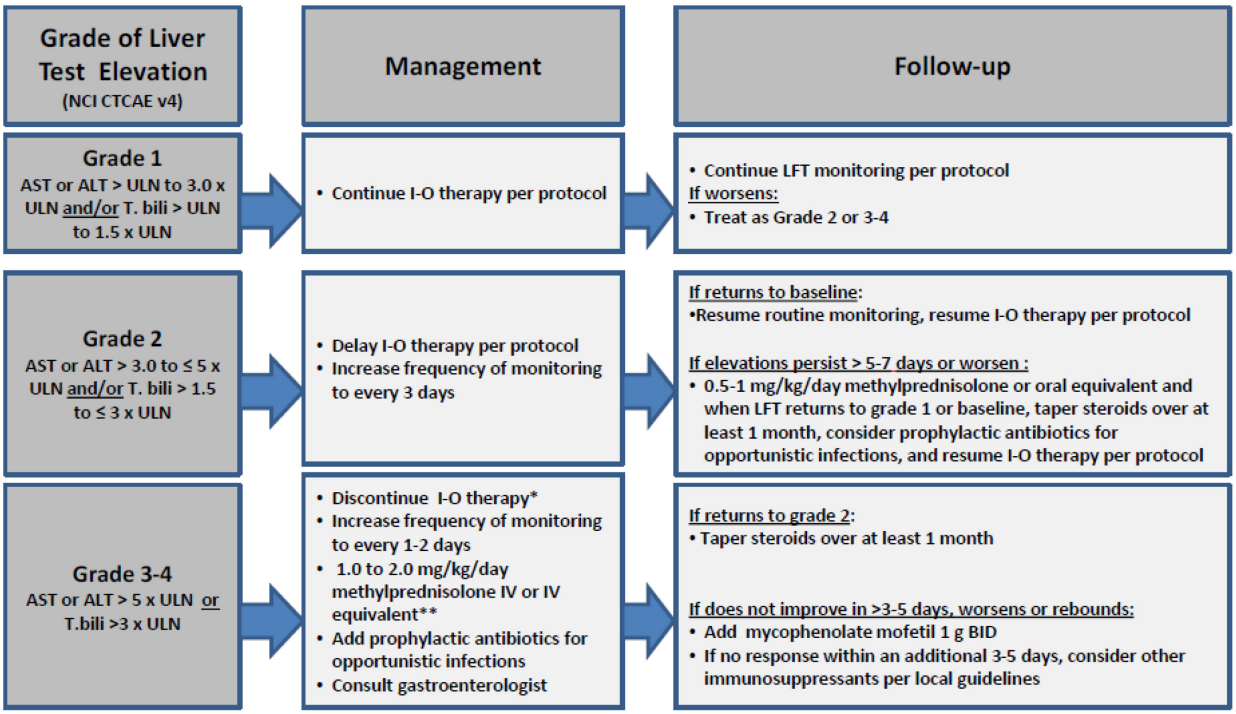
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



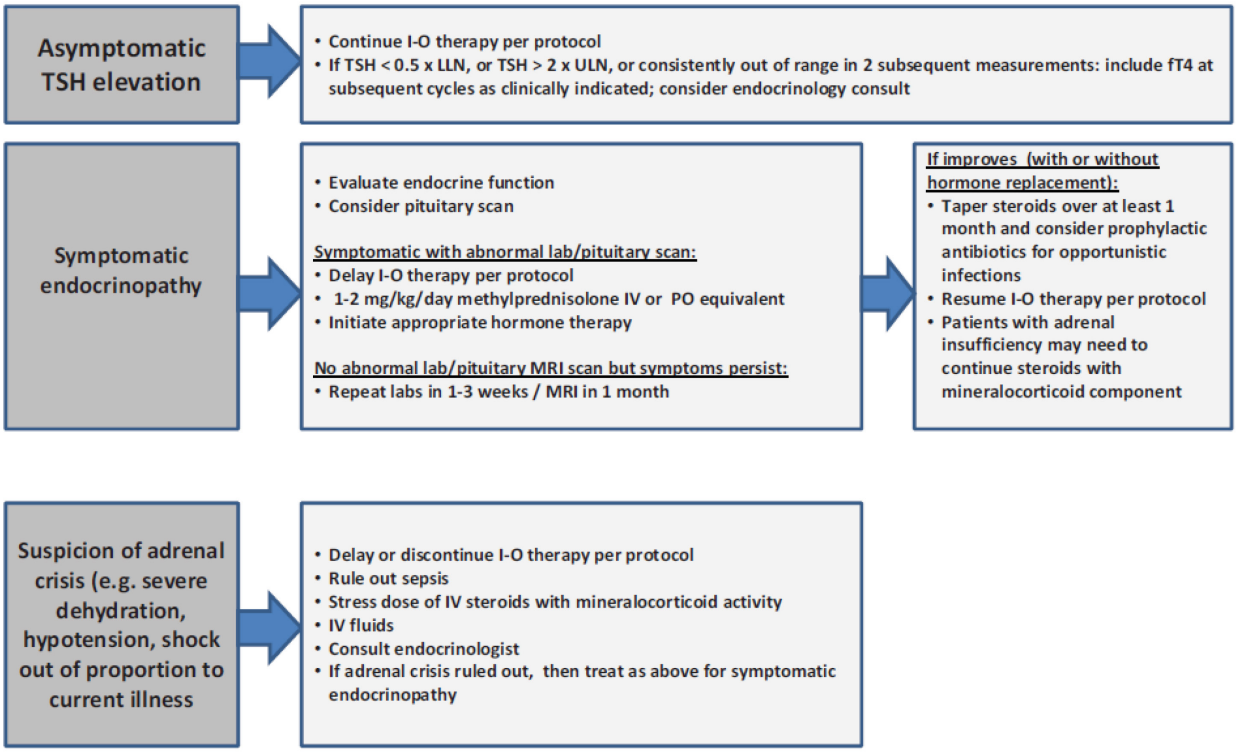
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

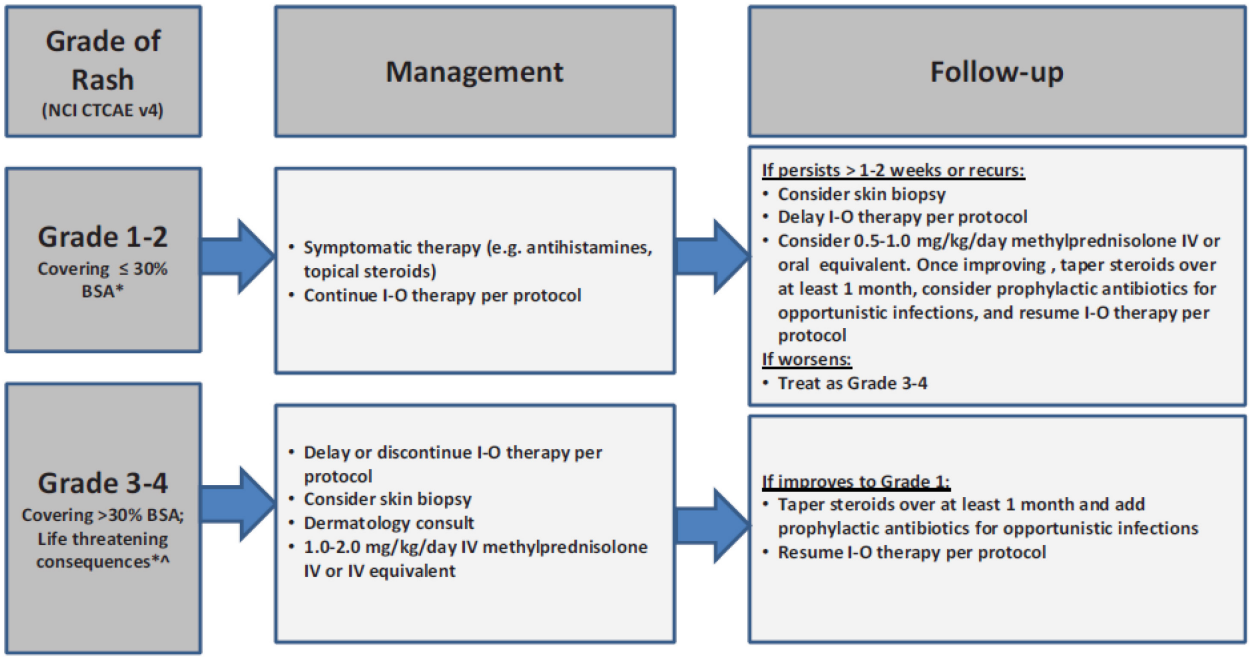
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

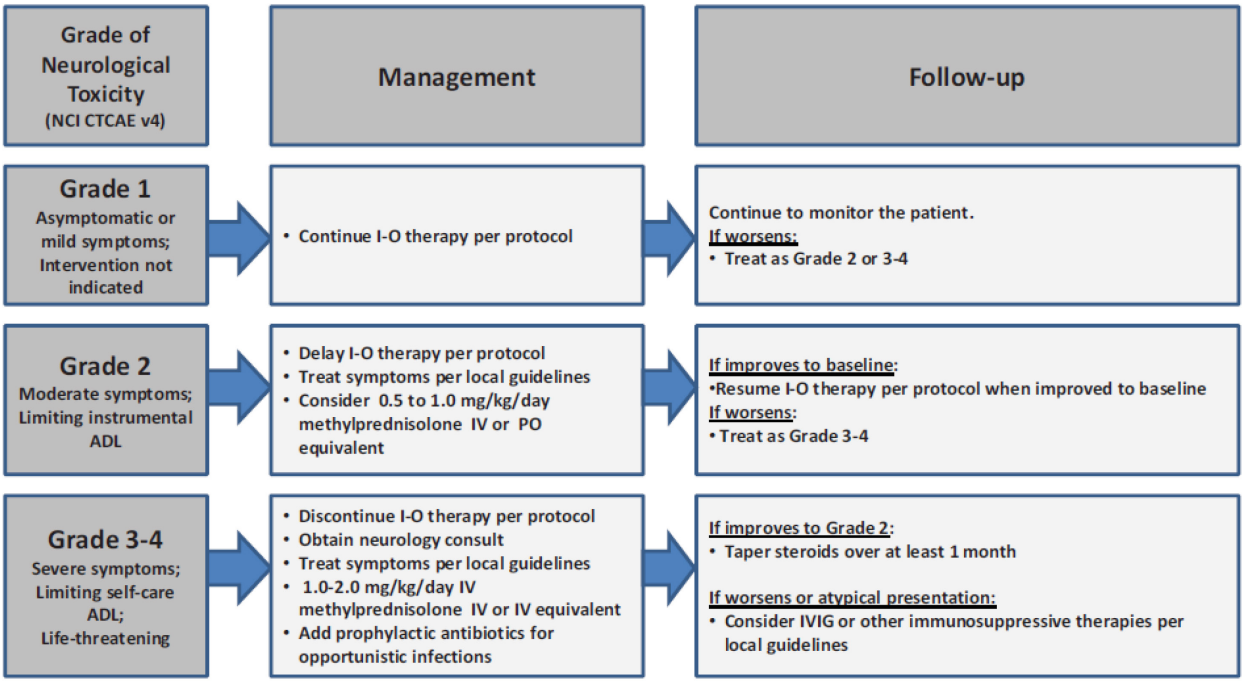
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Neurological Adverse Event Management Algorithm

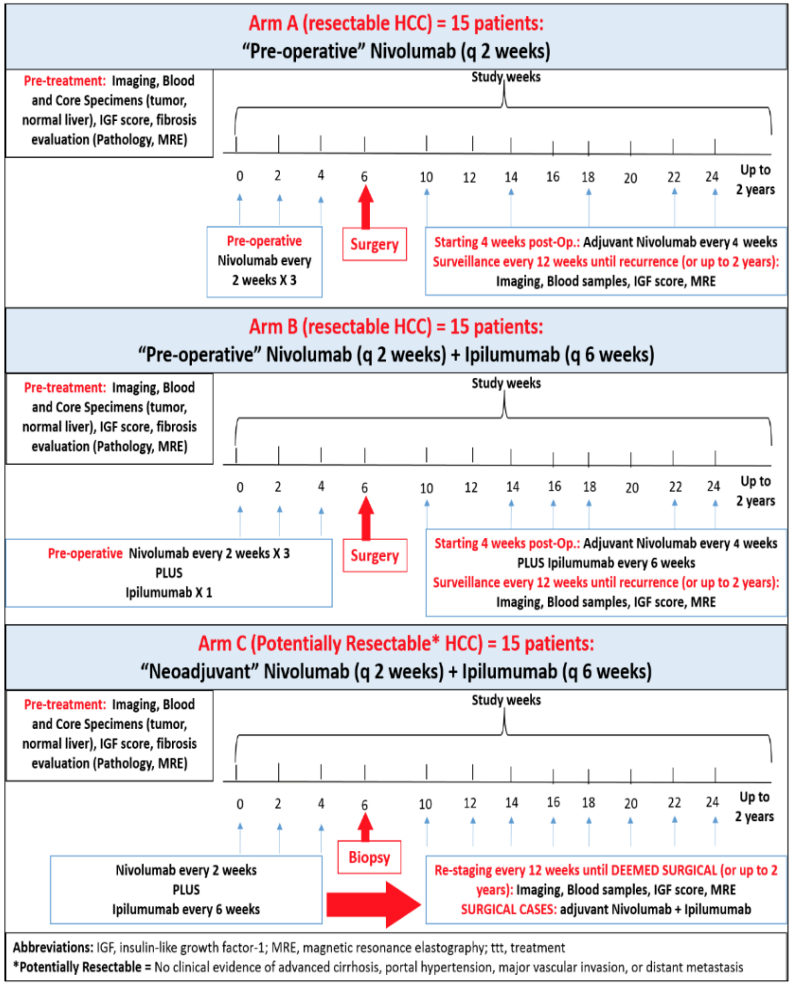
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Appendix II: Study Design Version Comparison

Protocol Version 1-8



Protocol Version 9