NU Study Number: *NU 16I01*
BMS Study Number: *CA 209-615*

Phase I/Ib study of nivolumab in combination with Therasphere® (yttrium-90) in patients with advanced hepatocellular carcinoma

Principal Investigator: Aparna Kalyan, MBBS, FRACP
Assistant Professor
Northwestern Medicine Developmental Therapeutics Program (NMDTP)
Division of Hematology and Oncology
Robert H. Lurie Comprehensive Cancer Center of Northwestern University (RHLCCC)
645 N. Michigan Ave, Suite 1006
Chicago, IL 60611
Aparna.kalyan@northwestern.edu

Sub-Investigator(s): Mary Mulcahy, MD
Al Benson, MD
Halla Nimeiri, MD
Sheetal Kircher, MD
Laura Kulik, MD
Robert Lewandowski, MD
Riad Salem, MD
Valerie Nelson, MD

Biostatistician: Denise Scholtens, PhD
Northwestern University
dscholtens@northwestern.edu

Study Intervention(s): Nivolumab and Theraspheres

IND Number: *Exempt*

IND Holder: *Exempt*

Funding Source: Bristol-Myers Squibb (BMS)

Version Date: April 10, 2019 (Amendment 6)

Coordinating Center: Clinical Trials Office
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
676 N. St. Clair, Suite 1200
Chicago, IL 60611
http://cancer.northwestern.edu/CRO/index.cfm

CONFIDENTIAL
This material is the property of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.
Do not disclose or use except as authorized in writing by the study sponsor.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS **5**

STUDY SCHEMA **6**

STUDY SUMMARY **6**

1.0 INTRODUCTION – BACKGROUND & RATIONALE **8**

1.1 Disease Background 8

1.2 Intervention Background & Overview 9

1.3 Rationale for combining y-90 with nivolumab: 12

1.4 Hypothesis 13

1.5 Exploratory Studies 13

2.0 OBJECTIVES & ENDPOINTS **14**

2.1 Primary Objectives & Endpoints 14

2.2 Secondary Objectives & Endpoints 14

2.3 Exploratory Objectives & Endpoints 14

3.0 PATIENT ELIGIBILITY **15**

3.1 Inclusion Criteria 15

3.2 Exclusion Criteria 17

4.0 TREATMENT PLAN **19**

4.1 Overview 19

4.2 Treatment Administration 19

4.3 Phase I Dose Escalation Scheme 20

4.4 Toxicity Management: Dose Delays and Discontinuation 22

4.5 Concomitant Medications/Treatments 26

4.6 Other Modalities or Procedures 27

4.7 Duration of Therapy 27

4.8 Duration of Follow Up 28

4.9 Removal of Subjects from Study Treatment and/or Study as a Whole 28

4.10 Patient Replacement 28

5.0 STUDY PROCEDURES 29

6.0 ENDPOINT ASSESSMENT 31

6.1 Definitions 31

6.2 Primary Endpoint 31

6.3 Secondary Endpoints 31

7.0 ADVERSE EVENTS 34

7.1 Adverse Event Monitoring 34

7.2 Definitions & Descriptions 35

7.3 Adverse Event Reporting 38

8.0 DRUG INFORMATION 39

8.1 Yttrium-90 (Theraspheres) 39

8.2 Nivolumab 44

9.0 CORRELATIVES/SPECIAL STUDIES 46

9.1 Sample Collection Guidelines 46

9.2 Sample Processing, Storage, and Shipment 46

9.3 Assay Methodology 47

9.4 Specimen Banking 47

10.0 STATISTICAL CONSIDERATIONS 48

10.1 Study Design/Study Endpoints 48

10.2 Data Analyses Plans 48

11.0 STUDY MANAGEMENT 48

11.1 Institutional Review Board (IRB) Approval and Consent 49

11.2 Subject Recruitment and Screening 49

11.3 Amendments 49

11.4 Registration Procedures 49

11.6 Instructions for Participating Sites 50

11.7 Data Management and Monitoring/Auditing 50

11.8 Adherence to the Protocol 50

11.9 Investigator Obligations 51

11.10 Publication Policy 51

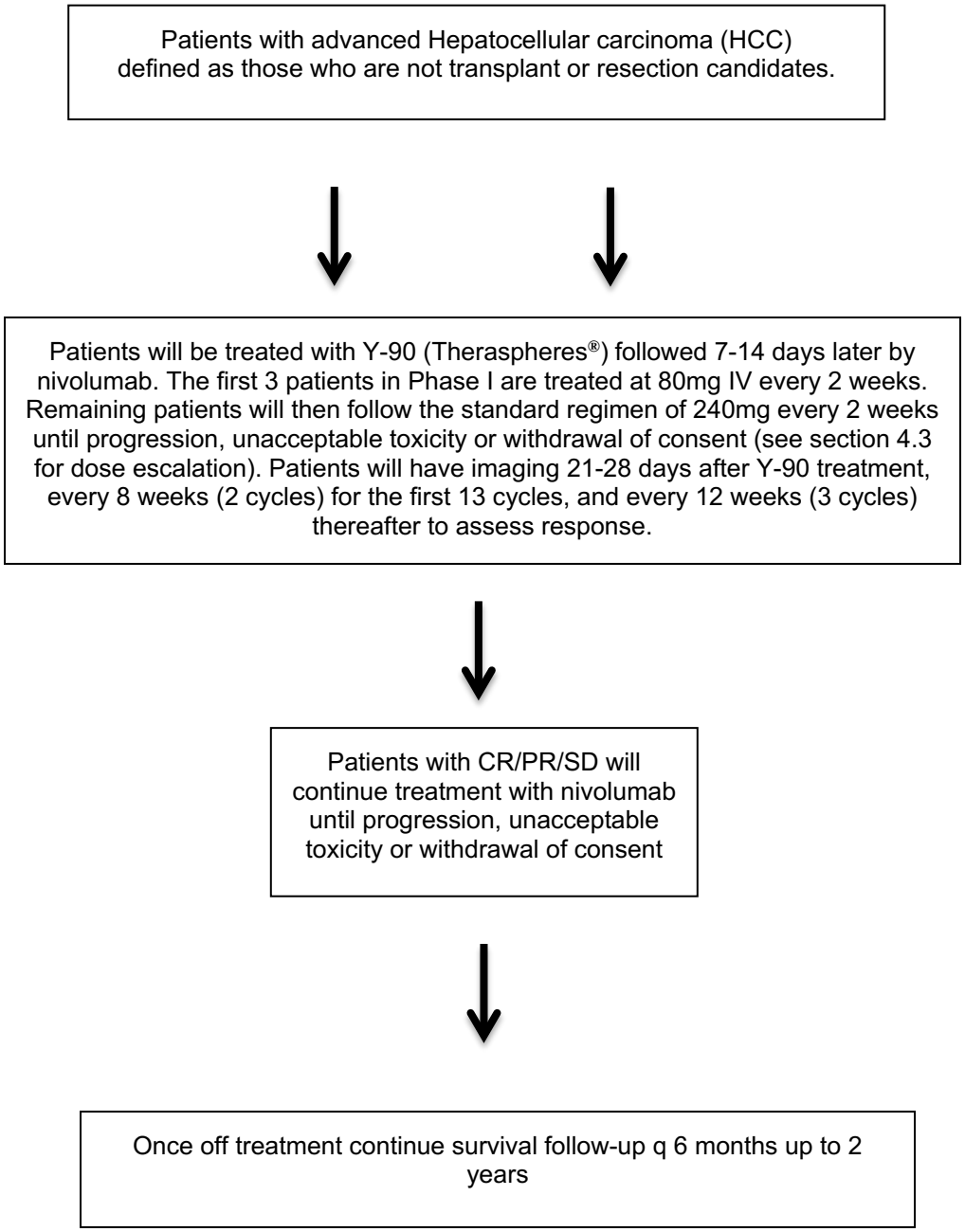
REFERENCES 53

Appendices 55

LIST OF ABBREVIATIONS

AASLD	American Association for the Study of Liver Diseases
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
H&PE	History & Physical Exam
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
OLT	Orthotopic liver transplant
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Phase I/Ib study of nivolumab in combination with yttrium-90 (Therasphere ®) in patients with advanced hepatocellular carcinoma
Version	04/10/2019 (Amendment 6)
Study Design	Phase 1/1b
Study Center(s)	Single-center, Northwestern: (Northwestern University, Northwestern Memorial Hospital and Northwestern Memorial Faculty Foundation)
Objectives	Primary Objective(s): • Phase I: To identify maximum tolerated dose (MTD) of nivolumab for combination treatment of nivolumab and Y-90 in patients with advanced hepatocellular carcinoma. • Phase Ib: To evaluate the proportion of patients with objective response rate (ORR) to the combination treatment of nivolumab with Y-90. Secondary Objective(s): • To evaluate the toxicities (according to the NCCN CTCAE v4.03) and tolerability of nivolumab and y-90 in patients with advanced hepatocellular carcinoma • To evaluate the proportion of patients alive and progression free at 24 weeks in the described population. • To evaluate the disease control rate for the combination of Y-90 and nivolumab at 24 weeks from starting nivolumab treatment. Exploratory Objective(s): • Intratumoral Assessment: Fresh biopsy or archived tissue will be used if available. PD-L1 protein on tumor cells and the expression levels of other markers of inflammatory/immune signature that may include but not be limited to PD-1, OX40, CD73, CD39, T cell immunoglobulin and TIM3, GITRL, CTLA-4, CD3, CD4, CD8, CD45RO, FOXP3, and granzyme by IHC and/or flow cytometry will be evaluated. Whole exome sequencing and computational analyses will be performed to assess mutanome and immunome (subpopulations of immune cells). • Circulating free DNA (cfDNA) mutation analyses: Blood will be drawn before treatment and every 8 weeks with imaging for the first 24 weeks then every 16 weeks until disease progression. Change in clonal burden landscape of various mutanome and immunome will be analyzed to investigate its correlation with treatment response or development of resistance to treatment.
Sample Size	Phase 1: 9-15 patients, Phase 1b requires 29 patients in a two-stage optimum Simon design. The 6 at the MTD in Phase 1 are counted as part of the 29. This would require up to 15 in Phase 1, 23 new patients in Phase 1b for a total of 38 patients. Target accrual is 40 patients to account for potentially unevaluable patients.
Diagnosis & Key Eligibility Criteria	Subjects with advanced hepatocellular carcinoma who are non-transplant candidates.

Treatment Plan	Y-90 will be administered once at a calculated dose based on the volume of liver tissue supplied by the artery to be infused (lobar, segmental, subsegmental) and the estimated lung shunt fraction. TheraSphere dosimetry is independent of the tumor burden. Nivolumab will be administered as an IV infusion 7-14 days after Y-90 administration. The first 3 patients in Phase I are treated at 80mg IV every 2 weeks until disease progression, intolerable toxicity, or withdrawal of consent. Remaining patients will then follow the standard regimen of 240mg every 2 weeks until disease progression, intolerable toxicity, or withdrawal of consent. See section 4.3 for dose escalation details.
Statistical Methodology	This is a Phase I/Ib study with dose identification in the initial phase and safety/tolerability in the phase Ib section. The expected number of patients on dose escalation will be in the range of 9-15 based on the 3+3 design. Six patients will be treated at the MTD in the dose escalation phase. The dose calculation for Yttrium-90 Therasphere will be done according to standard protocol at Northwestern Memorial Hospital. Please note - details of this are located in section 8.1. The Phase 1b expansion cohort will be a two-stage optimum Simon design with 29 patients. See Section 10.0 for details.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

The incidence of hepatocellular carcinoma (HCC) has risen over the last 3 decades.[1,2] Therapeutic options for HCC are complex. Treatment with ablative liver directed therapies or resection are often suboptimal due to cumulative local or de novo recurrence rates of 60 to 100% at 5 years.[3-5] Orthotopic liver transplant (OLT) offers the best chance for long term survival after the detection of early hepatocellular carcinoma (HCC) by removing the entire pre-neoplastic cirrhotic liver. However, with the growing number of patients who require OLT, prolonged waiting times can often lead to drop out from the transplant list due to tumor progression.[6] Patients with HCC within Milan criteria (a single lesion ≤ 5 cm or 3 lesions ≤ 3 cm, without gross vascular invasion) are granted an upgrade in order to expedite the access of patients with early HCC to transplantation before tumor progression.[7-9] With increasing Hepatitis C virus infection, HCC incidence and cancer death owing to this is becoming the third leading cause of cancer death worldwide. Furthermore, HCC arises on a background of chronic inflammation due to underlying viral infection, which in turn creates an ideal environment for tumor cells to accumulate mutations. These mutations have made HCC resistant to traditional chemotherapy and treatment with chemotherapies is further limited by impaired hepatic function (10). The only current systemic therapy approved for HCC is Sorafenib, based on the results of the SHARP trial (11). While, many agents have looked promising they have failed to demonstrate sufficient improvement for this difficult population.

HCC is a highly vascular tumor. Angiogenesis plays a pivotal role in the early stages of carcinogenesis, progression and development of metastasis in HCC. Vascular endothelial growth factor (VEGF) expression has been found to correlate with important clinicopathological factors and risk of recurrence post resection.[10] Environmental factors such as hypoxemia are known to upregulate the expression of VEGF via hypoxia induced factor -1α (HIF).

1.2 Intervention Background & Overview

1.2.1 Preclinical Evidence for the PD-1 pathway in HCC:

The role of immune surveillance in controlling growth and the oncogenic properties have been well established for several decades. There is now a plethora of evidence that describes the correlation between tumor-infiltrating lymphocytes (TILs) within tumor cells and favorable prognosis overall.
The PD-1 pathway is a major component of tumorigenesis by suppressing the immune system. The innate function of the PD-1, when expressed on activated T-cells is to down regulate unwanted / excessive immune responses thus controlling autoimmune conditions.

PD-1 is a T-cell co-inhibitory receptor with two well-recognized ligand PD-L1 (B7-H1) and PD-L2 (B7-DC)[12]. The binding of PD-1 to PD-L1 leads to T-cell activation and ultimately several immunosuppressive effects, which includes inhibition of cell survival factor Bcl-xL [(13,14)]. Within the HCC, a significant proportion of PD-L1 is expressed by Kupffer cells [(15)] and in turn this expression is driven by IL-10 in HCC. The expression of PD-1 is markedly higher in the tumor and peripheral blood of patients with HCC compared to controls with cirrhosis alone (16).

A study of 54 patients with HCC and HBV co-infection who underwent surgical resection, the levels of Pd-1 expression was evaluated. This study demonstrated that higher versus lower expression of intrahepatic PD-1 on T-cells was associated with lower disease free survival (13.6 mths vs. 28.7 mths; $p < 0.001$) (17). Similar results were mirrored when the expression of PD-1 in peripheral blood was measured. In addition, the levels of circulating PD-1 correlated directly with the stage of HCC. This small study clearly demonstrated that higher levels of PD-1 expression in the tumor microenvironment are associated with worse overall survival & prognosis. (17)

Chronic Inflammation is a key feature of hepatitis associated HCC. High rates of HCC recurrence after surgical resection is associated with chronic viral infection as well as its concomitant inflammatory features which lends itself to set up further de-novo mutations and tumor regrowth. Urbani and colleagues (27) have shown recently that the PD-1/PD-L1 pathway is a key contributor to viral persistence in HBV /HCV infections. Many studies have demonstrated that HBV circulating CD8+ t-cells in chronic HBV infection are in fact PD-1 positive – lending to thought that this is due to chronic antigenic stimulation (5). There is also up-regulation of the PD-1 system in chronic antigenic stimulation, which may be a mechanism of immune tolerance. Furthermore, in-vitro studies have shown that blockade of PD-1/PD-L1 increases HBV specific CD8+ T-cells, higher IL-2 and IFNγ by these cells, suggesting more potent effector activity.

1.2.2 Nivolumab as a PD-1 inhibitor

Nivolumab (also known by BMS-936558 or MDX1106) is a fully humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and PD-L1 and PD-L2. Both PD-1 and PD-1 ligands are upregulated following initiation of an immune response and help to limit that response to avoid tissue damage. Upregulation of PD-1 ligands also occurs in some tumors and is thought to contribute to inhibition of active T-cell immune surveillance of tumors.

Nivolumab has been extensively investigated in several large clinical trials thus establishing the safety, PK, and clinical activity of nivolumab. To date there are approximately 32 clinical trials in various phases (11 phase 1 studies, 13 phase 2 studies and 8 phase 3 studies) across several histologies (including NSCLC,

melanoma, RCC, mCRPC and hematologic malignancies) evaluating nivolumab either as monotherapy or in combination with cytotoxic chemotherapy or targeted therapies. Clinical activity has been shown both as monotherapy as well as in combination with other immunotherapy agents such as an anti-CTLA4 antibody (ipilimumab) with durable responses exceeding 6 months.

Currently, nivolumab is approved for treatment of unresectable or metastatic melanoma and disease progression on ipilimumab regardless of BRAF mutational status. It is also indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. It is currently approved at a dose of 3mg/kg every 2 weeks and for both melanoma and NSCLC. The side effect and safety profile seen to date are consistent across all histologies tested. There has been no maximum tolerated dose (MTD) reached at the monotherapy doses tested up to 10mg/kg. Additionally, there was no pattern in the incidence, severity or causality of AEs to nivolumab dose levels.

To-date the primary treatment-related AEs with nivolumab have included pulmonary toxicity, renal toxicity, endocrine abnormalities, GI toxicity, dermatologic toxicity and hepatotoxicity. The majority of the AEs encountered have been managed with supportive care and in severe cases a combination of dose delay, permanent cessation of the drug and/or addition of systemic corticosteroids.

There are now several more studies in the pipeline evaluating the combination of nivolumab with other agents. Recently, results from the phase II study of nivolumab for patients with advanced HCC were presented. Of 42 evaluable patients, 28 patients had a response (2 CR, 6 PR, 20 SD) corresponding to an objective response rate of 67% (28/42). Further, of the 8 patients with a response, 7 patients responded within 3 months of therapy and ongoing response was seen in 6/8 patients. This further provides evidence to the active role of PD-1 inhibitors in advanced HCC regardless of hepatitis status [1].

1.2.3 Role for Therasphere (yttrium-90) in HCC:

Treatments, such as TACE, attempt to take advantage of the vascular nature of HCC by impairing the blood supply of the tumor and inducing a hypoxic state. Higher baseline serum levels of VEGF have been demonstrated to predict a poor response to TACE.[(19)] Therasphere, a novel therapeutic approach, are composed of non-biodegradable glass microspheres coated with yttrium-90.[(20)] They are injected into the hepatic artery and are preferentially trapped in the tumor capillary bed relative to surrounding non-tumor parenchyma. The ability to concentrate radioactive microspheres within the tumor leads to an "inside-out" radiation, which in turn exerts a local tumoricidal effect. Unlike TACE, Therasphere do not induce hypoxemia, but rather, requires oxygen for the maximal radiation effect[20].

The mechanistic differences in TACE and Therasphere theoretically may have an impact on angiogenesis and therefore an effect on tumor progression as a patient awaits transplantation. Radioembolization of the hepatic artery with microspheres coated with yttrium-90, a source of beta energy, capitalizes on the hypervascular nature of HCC. The distribution of blood flow is three to seven times greater within the tumor than the surrounding noncancerous tissue (1). The preferential delivery of microspheres to the tumor capillary bed allows for higher doses of radiation to be delivered to the tumor relative to surrounding non-tumor parenchyma. The ability to concentrate radioactive microspheres within the tumor leads to an “inside-out” radiation, which in turn exerts a local tumoricidal effect. In 1999, the FDA

granted a humanitarian device exemption for the use of TheraSphere® (MDS Nordion, Ottawa, Ontario, Canada) for the treatment of unresectable HCC.

Phase 1 and 2 trials have demonstrated a positive safety profile for TheraSphere therapy in patients with a bilirubin < 2 rends in improved survival have been reported in patients who received > 104 Gy. Several additional publications have testified Y-90 to be a safe and efficacious therapy for unresectable HCC. While 1 year survival rates are comparable to the RCTs of trans-arterial chemoembolization (TACE) versus supportive care, no RCTs comparing Thera-Spheres to TACE have been performed.[30-35]

Radioembolization therapy is performed in a two-step process: a "trial run" followed by the treatment session which is generally performed a few days afterwards. Prior to the administration of Y-90, a mesenteric angiogram is performed to determine the tumor's blood supply, aberrant anatomy and to ensure proper catheter position. Coiling of extrahepatic arteries may be required to avoid inadvertent delivery of microspheres to surrounding organs (stomach, diaphragm and gallbladder). At the same time, Technetium-99 macroaggregated albumin (The^{99}Tc-MAA) is injected into the hepatic artery to estimate the degree of intratumoral arteriovenous shunting. The^{99}Tc-MAA particles are similar in size to the Y-90 microspheres (20-40 microns) and therefore will simulate the distribution of Y-90. A single photon emission CT is then used to calculate the dose of radiation that will be distributed to the lungs and/or viscera. A hepatopulmonary shunt greater than 20% of the injected dose, failure to prevent blood flow into the gastrointestinal organs by embolization or proper catheter placement will preclude therapy with Y-90. The dose of radiation delivered to the lungs is cumulative and should not exceed 50 Gy. A mesenteric angiogram and ^{99} Tc-MAA will be repeated before every treatment session with Y-90 to evaluate for the degree of shunting.

The calculated radiation dose for TheraSphere therapy is based on the volume of liver tissue supplied by the artery to be infused (lobar, segmental, subsegmental) and the estimated lung shunt fraction. TheraSphere dosimetry is independent of the tumor burden.

Side effects following Y-90 therapy are usually mild and temporary. Fatigue is the most common side effect. Fever, chills, and flu-like symptoms may also occur and generally require no specific intervention. More serious side effects relate to inadvertent migration of a microsphere(s) with radiation exposure to non-targets (cholecystitis, gastritis/ulceration, pancreatitis or pneumonitis). Lymphopenia presumed secondary to bone marrow suppression has been reported in patients treated with Y-90, however there have been no reports of opportunistic infections or clinical complication relating to Y-90 therapy. Cases of lymphopenia have been extremely rare and asymptomatic. Peak incidence while theoretically can occur up to 3 months after therapy, to date no clinical infections or clinical complications have been reported in the literature. Patients will have a 4 week break between receiving Y90 treatment and starting nivolumab to allow for recovery and to obtain repeat scans. A long-term complication of hepatic fibrosis and portal hypertension has been reported. All patients undergo esophagogastroduodenoscopy (EGD) as standard of care with banding of large esophageal varices. While pneumonitis has been reported, the number of cases from this remains very few and overall incidence is extremely rare; as such current standard of care does not require additional pulmonary testing prior to Y-90. All patients will undergo an angiogram prior to Y-90 administration to calculate the appropriate Y-90 dose, and presence of lung shunt will be ruled out at that time.

1.2.4 Measurement of disease response

Insight into the biological behavior of a tumor may be gained by the response to liver directed therapy. A lack of progression with liver directed therapy might lead to improved overall survival (OS). A recent study supported that radiographic response to TACE could serve as a biological marker of tumor behavior.(21) The ability to measure the effectiveness of therapy and/or need for additional treatment is restricted by reliance upon radiographic endpoints of tumor size and enhancement as opposed to a measurable biological response at the cellular level. The shortcomings of conventional imaging to assess treatment response are highlighted in studies demonstrating a discrepancy between radiographic response and explant pathology.(22,23) Ability to accurately determine efficacy of a therapy (radiographically) is vital to obtain the maximal benefit of locoregional therapy. The degree of necrosis on explant associated with liver directed therapy has shown conflicting results in terms of HCC recurrence post-transplant.(21,22,24) Diffusion-weighted magnetic resonance imaging (MRI) operates on the premise that the diffusion of water within a cell is dependent upon the integrity of the cellular membrane. Within viable cells, water movement is restricted by the boundaries of an intact cellular membrane, whereas in necrotic cells, water is able to freely diffuse. The distribution of water within a given area can be calculated as an apparent diffusion coefficient (ADC) and provide functional information for a given lesion. Increased diffusion of water within a targeted lesion has been shown to be a reliable early marker of treatment response to radiation and chemotherapy in brain and breast cancer.(25,26) More recently, diffusion weighted MRI has been reported to detect treatment response in HCC after chemoembolization and ^{90}Y radioembolization.(27-29) Detection of early treatment response with necrosis of the targeted tumor may act as a surrogate marker for selection of patients most likely to benefit from transplant. Such a tool could also prevent unnecessary repeated therapeutic sessions and the associated potential complications including treatment induced liver failure. Necrosis induced by systemic therapies such as nivolumab would also be expected to be detected with diffusion-weighted imaging.

1.3 Rationale for combining Y-90 with nivolumab:

As described above, there is evidence that manipulating the PD-1 pathway in HCC affects the balance between anti-tumor active and immune tolerance in advanced HCC. Nivolumab has recently been approved for the treatment of squamous non-small cell lung cancer and melanoma. The paucity of good treatment options in advanced HCC (apart from Sorafenib) creates an ideal environment to pursue immune-modulation in this population. Due to the complexity of hepato-carcinogenesis, including the heterozygosity of genetic alterations involved in the development and progression of HCC, it is likely that a combination approach with systemic immune therapy and liver directed therapy will be needed to obtain the most efficacious "kill" of tumor cells. A decrease in angiogenesis both locally within the treated tumor as well as in any clinically undetectable tumor cells would hopefully decrease the incidence of progression of HCC and might even allow for some patients to become transplant eligible.

It is for these reasons; we wish to proceed with this early phase study to evaluate the combination of Y-90 and nivolumab for treatment of advanced HCC. There is no data available that currently combines these two modalities in HCC.

1.3.1 Rationale for Nivolumab Dosing

The safety and efficacy of 240 mg (monotherapy) Q2W flat dose of nivolumab has recently received IRB approval and is expected to be similar to the 3 mg/kg Q2W dosing regimen. Using the population PK (PPK) model, exposure of nivolumab at 240 mg flat doses is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight in nivolumab clinical trials. Across the various tumor types in the clinical program, nivolumab

has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat doses compared to 1mg/kg and 3 mg/kg, it is expected that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab.

A phase I dose escalation of nivolumab starting at 80mg is included in this study given the lack of data combining nivolumab with Y-90.

1.4 Hypothesis

Subjects treated with nivolumab will have an overall improved response to liver directed therapy with Y-90 (Therasphere) as evidenced by markers of angiogenesis, radiographic response defined by RECIST criteria, immunological markers; leading to improved clinical outcome measurements, less recurrence and potentially meet criteria for liver transplantation.

1.5 Exploratory Studies

It has been shown in animal models, control human subjects as well as in oncology patients that, administration of nivolumab modifies the cytokine levels in plasma.

1.5.1 Exploration of the correlation between PD-1, PD-L1 and PD-L2 expression and CD4+ and CD8+ tumor infiltrating lymphocytes and PFS, OS and response to treatment.

PD-1 is a key immune checkpoint receptor expressed by activated T cells and mediates immunosuppression. PD-1 functions primarily in peripheral tissues, where T cells may encounter the immunosuppressive PD-1 ligands PD-L1 and PDL-2, which are expressed by tumor cells, stromal cells or both [1-3]. PD-L1 and PD-L2 are overexpressed in a variety of solid tumors however no data exists in ACC [1].

There are conflicting data on the predictive value of PD-L1 expression on PD-1 directed therapy in solid tumors [1, 4]. Herbst et al showed that patients with solid tumors including non-small cell lung cancer and melanoma treated with humanized PD-L1 antibody had higher ORR when immunohistochemistry showed intense staining for PD-L1 in the tumor [5]. The same correlation was not observed on stratified analysis according to tumor cell membrane PD-L1 expression of non-small cell lung cancer patients treated with nivolumab therapy in the second line setting [4].

Pathological slides from tumor archival tissue will be stained using a monoclonal antibody against PD-L1 and defined as PD-L1 positive if equal of greater than 5% of the tumor cells membrane analyzed. We hypothesize that tumor cell membrane expression of PD-L1 or PD-L2 can have an impact on treatment responses.

1.5.2 Peripheral blood lymphocyte phenotypes

Lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56) will be analyzed according to absolute cell numbers per microliter of whole blood, percent representation among all lymphocytes, and co-expression of the activation markers CD25, HLA-DR, and CD45RO using automated flow cytometric techniques at the Flow Cytometry Core Laboratory, Robert H Lurie Cancer Center of Northwestern University under the supervision of Suchitra Swaminathan, PhD.

1.5.3 Measurement of humoral and cellular responses to tumor antigens on serum samples by measuring the levels of cytokines (i.e., IL-2, IL-6, IL-8, IL-10, IL-18, IFNγ and TNF-α) and peripheral blood lymphocyte phenotype. Measures of immunologic response correlate with lack or presence of response to treatment with nivolumab.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objectives & Endpoints

2.1.1 **Phase I**: To identify maximum tolerated dose (MTD) of nivolumab for combination treatment of nivolumab and Y-90 in patients with advanced hepatocellular carcinoma. The MTD will be defined as the highest dose that causes dose limiting toxicities (DLTs) in <2 of 6 patients.

2.1.2 **Phase Ib**: To evaluate the proportion of patients with objective response rate (ORR, according to RECIST criteria version 1.1) to the combination treatment of nivolumab with Y-90.

2.2 Secondary Objectives & Endpoints

2.2.1 To evaluate the proportion of patients alive and progression free at 24 weeks in the described population.

2.2.2 To evaluate the toxicities (according to the NCCN CTCAE v4.03) and tolerability of nivolumab and y-90 in patients with advanced hepatocellular carcinoma

2.2.3 To determine the disease control rate (DCR) to the combination of nivolumab and Y-90 at 24 months from the start of nivolumab treatment. DCR is defined as the sum of Complete Response, Partial Response, and Stable Disease (DCR = CR + PR + SD).

2.3 Exploratory Objectives & Endpoints

2.3.1 Intratumoral Assessment:
Fresh biopsy or archived tissue will be used if available. PD-L1 protein on tumor cells and the expression levels of other markers of inflammatory/immune signature that may include but not be limited to PD-1, OX40, CD73, CD39, T cell immunoglobulin and TIM3, GITRL, CTLA-4, CD3, CD4, CD8, CD45RO, FOXP3, and granzyme by IHC and/or flow cytometry will be evaluated. Whole exome sequencing and computational analyses will be performed to assess mutanome and immunome (subpopulations of immune cells).

2.3.2 Circulating free DNA (cfDNA) mutation analyses:
Blood will be drawn before treatment and every 8 weeks with imaging for the first 24 weeks then every 16 weeks until disease progression. Change in clonal burden landscape of various mutanome and immunome will be analyzed to investigate its correlation with treatment response or development of resistance to treatment.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with hepatocellular carcinoma. This will be a single-center trial conducted at Robert H. Lurie Comprehensive Cancer Center (RHLCCC) of Northwestern University.

Up to 40 patients will be enrolled, up to 15 in Phase 1 and up to an additional 25 in Phase 1b. Approximately 3 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Aparna Kalyan, at 312-472-1234

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11.4 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 Patients must have a diagnosis of hepatocellular carcinoma (HCC) confirmed by American Association for Study of Liver Diseases (AASLD) guidelines with a Childs-Pugh score of A or B (but, ≤ Childs score B8).
NOTE: If the patient does not have histological confirmation of disease by biopsy, diagnosis of HCC must be documented with approval by a tumor board or other multidisciplinary conference. Please refer to the appropriate source document in NOTIS.

3.1.2 Patients must have at least 1 lesion that is measurable using RECIST guidelines.
NOTE: A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per RECIST, and has clearly progressed.
NOTE: For patients with infiltrative disease, evaluable disease needs to be confirmed by pathology if RECIST measurements cannot be made.

3.1.3 Patients must have advanced disease that is not amenable to transplant or resection.

3.1.4 Patients may be treatment naïve or have received any number of prior therapies.
NOTE: Prior immunotherapy is contraindicated and not permitted.

3.1.5 Patients with chronic Hepatitis B are eligible as long as they have evidence of ongoing viral replication (detectable HBsAg, HBeAg, or HBV DNA). They must have HBV DNA viral load <100 IU/mL at screening. In addition, they must be on antiviral therapy per regional standard of care guidelines prior to initiation of study therapy. If not on antiviral therapy at screening, then the subject must initiate treatment per regional standard of care guidelines at the time of consent. Both HBeAg positive and negative patients will be included.

3.1.6 Patients positive for Hepatitis C are permitted if controlled with medication, in the opinion of the investigator.

3.1.7 Adults ≥18 years old of either gender are eligible.

3.1.8 Patients must exhibit an ECOG performance status of 0, 1, or 2.

3.1.9 Patients must have adequate organ function within 14 days prior to registration as determined by:

- Hematological (without growth factor support)
  - Hemoglobin ≥ 8.5 g/dL (without the use of growth factors)
  - ANC ≥1000
  - Platelet count ≥ 50 x 10^9/L (without use of growth factors [i.e., IL-11 {Oprevilekin}])
  - Prothrombin time (PT)/ International normalized ratio (INR) ≤ 2.3 or PT ≤ 6 seconds above control.
    NOTE: Abnormal PT/INR may be considered, with documented PI approval, if it is due to the use of anticoagulants. For such patients, a normal PT/INR must be available from before the start of anticoagulation treatment.
    NOTE: Performed at time of screening angiogram; can be outside 14 days if applicable.
- Renal
  - Calculated creatinine clearance* (CrCl) or 24-hour urine CrCl > 30 mL/min (*Cockcroft-Gault formula will be used to calculate CrCl)
- Hepatic
  - Serum Bilirubin ≤ 3 times the upper limit of normal (ULN)
  - AST and ALT ≤ 5 times ULN
- Serum Electrolytes
  - Potassium, sodium, and calcium (corrected for serum albumin) ≤ Grade 1 or within the institutional ranges of normal. If clinically appropriate, electrolytes may be corrected and values re-assessed prior to enrollment

3.1.10 Females of childbearing potential (FOCBP), and non-sterilized males who are sexually active 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 in Appendix 2. They must also refrain from egg and/or sperm cell donation and breastfeeding for 90 days after the final dose of investigational product(s)

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause)
- WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab (19 weeks) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post-treatment completion.
- Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of the study drug (19 weeks) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion

3.1.11 FOCBP must have a negative pregnancy test within 7 days prior to registration
Note: FOCBP will have to have repeat pregnancy test within 24 hours of starting nivolumab, scheduled for Cycle 1 Day 1.

3.1.12 Subjects must provide archived tumor specimens for correlative biomarker studies if sufficient tissue is available. A fresh biopsy is not required.

3.1.13 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

3.2.1 Patients must not have had prior treatment with nivolumab or any other PDL1 or PD-1 antagonists

3.2.2 Patients must not have a history of severe allergic reactions (i.e., Grade 4 allergy, anaphylactic reaction from which the subject did not recover within 6 hours of institution of supportive care) to any unknown allergens or any components of the nivolumab formulations

3.2.3 Patients diagnosed or treated for malignancy other than HCC are not eligible unless they meet one of the following exceptions:
- Malignancy treated with curative intent and with no known active disease present for ≥3 years before registration and felt to be at low risk for recurrence by the treating physician.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated cervical carcinoma in situ without evidence of disease

3.2.4 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including chronic prolonged systemic corticosteroids (defined as corticosteroid use of duration one month or greater), should be excluded. These include but are not limited to patients with a history of:
- immune related neurologic disease
- multiple sclerosis
- autoimmune (demyelinating) neuropathy
- Guillain-Barre syndrome
- myasthenia gravis
- systemic autoimmune disease such as SLE
- connective tissue diseases
- scleroderma
- inflammatory bowel disease (IBD)
- Crohn's
- ulcerative colitis
- patients with a history of toxic epidermal necrolysis (TEN)
- Stevens-Johnson syndrome
- anti-phospholipid syndrome

NOTE: Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.5 Patients with renal failure currently requiring dialysis of any kind are not eligible.

3.2.6 Patients with untreated central nervous system (CNS) metastatic disease (including spinal cord and leptomeningeal disease) are excluded.
Note: Subjects with previously treated CNS metastases that are radiographically and neurologically stable for at least 6 weeks and do not require corticosteroids (of any dose) for symptomatic management are permitted to enroll

3.2.7 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study, is excluded.

3.2.8 Receipt of any investigational therapy is not permitted within 28 days prior to the first dose of nivolumab

3.2.9 Any concurrent chemotherapy, biologic or hormonal therapy for cancer treatment is not permitted within 28 days of registration.
Note: Prior immunotherapy is not permitted.
Note: Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

3.2.10 Patients with exposure to prior immunotherapy are not eligible.

3.2.11 Patients are ineligible if they have unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria.
Note: Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (e.g., hearing loss) after consultation with the PI and NU QAM.

3.2.12 Radiation therapy is not permitted within 14 days of registration.

3.2.13 Live vaccines are not permitted within 28 days of study registration.

3.2.14 No systemic glucocorticoids will be permitted within 48 hours prior to study registration.
Note: Topical steroids, bronchodilators and local steroid injections are permitted if clinically required.

3.2.15 Patients with cardiac disease defined as one of the following are not eligible:
- Congestive heart failure > class II NYHA.
- Unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months)
- Myocardial infarction within the past 6 months.

3.2.16 Patients with cardiac ventricular arrhythmias requiring anti-arrhythmic therapy are not eligible.

3.2.17 Patients with known human immunodeficiency virus (HIV) infection are not eligible.

3.2.18 Patients must not have elevated lung shunting precluding treatment with Y-90.

3.2.19 Patients who have had major surgery within 4 weeks prior to registration are not eligible.

3.2.20 Patients who have active clinically serious infection > CTCAE Grade 2 are not eligible.

3.2.21 Patients with a history of gastrointestinal bleeding (GIB) within 6 weeks prior to registration are not eligible.

3.2.22 Patients with prior transplant of any kind are not eligible.

3.2.23 Patients may not be pregnant or lactating at study registration.

3.2.24 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Hypertension that is not controlled on medication
- Ongoing or active infection requiring systemic treatment
- Psychiatric illness/social situations that would limit compliance with study requirements
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints
- Active alcohol use, drug use, or a psychiatric disease that would, in the opinion of the PI or a subinvestigator (sub-I), prevent the subject from complying with the study protocol and/or endanger the subject during their participation in the study

4.0 TREATMENT PLAN

4.1 Overview

Treatment will be administered on an outpatient basis. Patients will first be treated one time with liver directed therapy, Therasphere® (Y-90), following institutional procedures**. During screening, each patient will undergo an angiogram in interventional radiology to determine the appropriate Y-90 dose. Within 7-14 days, patients will begin treatment with intravenous nivolumab as maintenance either at 80mg (first 3 patients in Phase I) or 240mg (Phase Ib if MTD) over 30 minutes (-5 minutes / +15 minutes) every 2 weeks (Day 1 & 15 of each cycle; 1 cycle = 28 days).

After study registration, the patient will proceed to receiving Y-90 per the standard of care procedures listed in section 8.1. Y-90 administration is normally planned around 7 days from the angiogram, so registration should be planned accordingly. After completion of Y-90, patients will have 1-2 weeks recovery time prior to proceeding with nivolumab administration (4 weeks if necessary). This window allows for recovery from generalized fatigue. Study drug nivolumab will continue until disease progression or withdrawal of treatment by patient.

*** Repeat therapy to the treated lesion or additional untreated lesions may be warranted. If a patient requires additional Y-90 after starting nivolumab treatment, it may be given once approval from the interventional radiologist and treating physician has been confirmed. In such cases, nivolumab should be held for ≥7 days prior to administering Y-90. Nivolumab can be resumed at least 7 days after receiving additional Y-90, but can be delayed for up to 4 weeks if needed.*

4.2 Treatment Administration

4.2.1 Theraspheres® (Yttrium-90)

Institutional Standard of Care TheraSphere Treatment Procedure:

The calculated dose of radiation to be delivered to the targeted lesion will be calculated by a medical nuclear physicist in Interventional Radiology (Venessa Gates MS, DABR, DABSMM) during the screening angiogram. Once the required dose of Y-90 is determined, it is ordered from the manufacturer. It is recommended the time lapse between work up for Y-90 (angiogram) and the treatment session should not exceed 2-3 weeks.

Please see section 8.1.6 for specific details of Y-90 administration. Patients are observed for 2-6 hours post procedure prior to discharge. Patients will be evaluated within 14 days after y-90 therapy to assess for side effects, tolerability

of therapy and laboratory abnormalities. By 12 days post therapy (4 half-lives of Y-90), the radioactivity of Y-90 has significantly decayed. Tumor response is evaluated radiographically 21-28 days post therapy. Maximal therapeutic effect may only become apparent 3 months post therapy.

Based on follow-up imaging, repeat therapy to the treated lesion or additional untreated lesions may be warranted, barring minimal complications with the first session. Radiographic evidence of progression of disease following up to 2 treatments (to the same targeted lesion) of Y-90 may warrant alternative ablative or systemic therapies. These subjects would be considered treatment failures and would be terminated from the study. On the other hand, an incomplete response or recurrent disease may call for additional therapy.

4.2.2 Nivolumab

For the first 3 patients in Phase I, nivolumab will be administered at 80mg as an intravenous infusion over approximately 30 minutes (-5 minutes / +15 minutes) every 2 weeks (Day 1 & 15 of each cycle) until disease progression or intolerable toxicity.
Dose escalation to 240mg will be determined in the standard 3+3 fashion (detailed in section 4.3). All patients in Phase Ib will be treated at 240mg IV nivolumab if determined to be the MTD. Treatment will begin 7-14 days after Y-90 administration. Patients should have recovered from any side effects resulting from Y-90 treatment (to ≤G1 or baseline). If a patient is still experiencing side effects 14 days after Y-90 treatment, the patient's nivolumab treatment may be delayed by up to 14 additional days at the physician's discretion (maximum 4-week delay). Scans will need to be performed 21-28 days after Y-90 administration, and will fall during Cycle 1 of nivolumab. If a patient is not able to start nivolumab treatment within 4 weeks (28 days), the patient should come off study and be replaced.

Subjects may be dosed no less than 12 days from the previous dose. There are no pre-medications recommended for nivolumab on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.2.4.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described below. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

4.3 Phase I Dose Escalation Scheme

In this phase 1/1b pilot study, the dose escalation component will be for nivolumab, starting at a dose of 80mg. Please see the table in statistical section for dose adjustments.

Phase I Dose Escalation Plan based on 3+3 design:

Dose Level	Nivolumab
1	80mg IV every 2 weeks
2	240mg IV every 2 weeks

A standard "3+3" dose escalation design will be utilized. Initially, 3 patients will be enrolled at the starting dose (level 1), after which enrollment will be temporarily suspended until all

3 patients complete the DLT evaluation period (defined as cycle 1 or the first 28 days of treatment). Once all 3 patients complete the DLT period and toxicity data has been submitted, the Data and Safety Monitoring Committee (DSMC) will review the data and confirm the presence or absence of any DLTs (defined below). The following rules will be used at each dose level to determine whether or not to proceed to the next dose level:

- If 0 of 3 patients at a given dose level experience a DLT (defined below), then escalation will proceed to the next dose level.
- If 2 or 3 of 3 patients at a given dose level experience a DLT, then one of the following must occur:
    - If this happens at level 1, the PI will discuss with DSMC and BMS to determine the necessary outcome.
    - If this happens at level 2 or beyond, the previous level will be declared the maximum tolerated dose (MTD).
- If 1 of 3 patients at a given dose level experiences a DLT, then an additional 3 slots will be added (for a total of 6 patients at that level):
    - If 1 of 6 total experiences a DLT, then escalation will proceed to the next level.
    - If ≥ 2 of 6 total experience a DLT, the previous level will be declared the MTD.

NOTE: Whichever dose level is declared the MTD must have 6 total patients treated at that level. For example, if 3 patients are treated at level 2 and 0 patients experience DLT, escalation would then proceed to level 3. However, if ≥ 2 patients at level 3 experience DLT, enrollment to level 2 would need to be re-opened to enroll an additional 3 patients at that level (with 0 or 1 DLT observed in 6 total patients) in order to declare level 2 the MTD.

4.3.1 Definitions

DLT is defined as a significant adverse events (detailed below) occurring during the DLT period (first 28 days of nivolumab treatment) that is related to nivolumab. DLT will be evaluated according to CTCAE v 4.03 criteria. Delay in starting nivolumab therapy more than 2 weeks due to toxicity regardless of attribution or grade, is considered a DLT

4.3.1.1 Grade ≥ 3 non hematological toxicity

Grade ≥3 non-hematological toxicity felt to be related to study medication will be considered dose-limiting with the following clarifications:

- Diarrhea Grade 3 will only be considered dose limiting if it is refractory to treatment as outlined in the supportive care guidelines (section 4.4.3)
- Bloody or grade 4 diarrhea will be considered dose limiting
- Nausea or vomiting grade 3 will only be considered dose limiting if it is refractory to anti-emetic therapy and unable to be corrected to ≤ Grade 1 within 24 hours
- Rise in serum creatinine to grade 3, not corrected to ≤ grade 1 within 24hrs with IV fluids will be considered dose limiting
- Grade 3 metabolic toxicities unable to be corrected ≤grade 2 within 24 hours (like glucose changes, hypokalemia, hypomagnesaemia, hypophosphatemia, and hyponatraemia) will be considered dose limiting, unless patient had metabolic abnormalities at baseline. Grade 4 metabolic toxicities that are symptomatic will be considered dose-limiting regardless of duration or ability to correct.
- Other Grade 3 lab abnormalities will only be considered a DLT if they do not resolve within 2 weeks.
- Elevated bilirubin will not be considered a DLT unless >3.5 mg/dL

4.3.1.2 Hematological Toxicity

The following hematological toxicity will be considered dose-limiting:

- Grade 4 thrombocytopenia (<25,000/μL)
- Grade 4 (<500/μL) neutropenia
- Grade 3 (<1000/μL) neutropenia associated with fever (Febrile neutropenia) will be considered dose-limiting

4.4 Toxicity Management: Dose Delays and Discontinuation

Dosing with Yttrium-90 will follow standard of care procedures, and there will be no dose modifications.

Any patient who receives at least one dose of nivolumab will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity by laboratory results and physical exam at each study visit, according to CTCAE 4.03.

Nivolumab may be delayed or discontinued following the instructions detailed in section 4.4.1.

In addition, nivolumab should be discontinued for toxicities as outlined in section 4.4.2.

4.4.1 Dosing delays

There will be no dose modifications allowed for management of toxicities.

Patients will be allowed to delay nivolumab treatment by up to 6 weeks. Nivolumab administration should be delayed for the following until resolution to ≤ Grade 1 or baseline:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 or 2 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
  - During Cycle 1, a delay in dosing is not required for Grade 3 total bilirubin ≤3.5mg/dL
    NOTE: If bilirubin worsens after the first dose of nivolumab, a delay in dosing may be warranted per physician discretion.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

- Gastrointestinal
- Renal

- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure and appendix 3 of this protocol.

4.4.2 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, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All grade 3 or 4 infusion reactions should be reported within 24 hours to the study QAM and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.03) guidelines.

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

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 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/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations
Grade 2 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/paracetamol 325 to 1000 mg; Remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/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 (please follow stability instructions in section 8.2.4) ; if no further complications ensue after 30 minutes, the rate	For future infusions, the following prophylactic pre-medications are recommended: • Diphenhydramine 50 mg (or equivalent) and/or • Acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 100 mg of SoluCortef or equivalent) may be used.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.	
<u>Grades 3 or 4</u> 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 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms In 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	No subsequent dosing

4.4.3 Treatment Discontinuation Criteria:

Tumor assessments for all subjects should continue every 8 weeks or 12 weeks once beyond 13 months of therapy, as per protocol, even if dosing is held or delayed.

Nivolumab treatment should be permanently 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 uveitis,

pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction **of any duration** requires discontinuation
- Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
  - Any 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 > 5-10 x ULN for > 2 weeks
  - AST or ALT > 10 xULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 xULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The PI and DSMC should be consulted for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation.

- Any event that leads to interruption in dosing lasting > 6 weeks from the previous dose requires discontinuation, 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 interruptions lasting > 6 weeks from the previous dose, the PI and DSMC must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing interruptions.
  - Dosing interruptions lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the PI and DSMC. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI and DSMC must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing interrupted.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.4.4 Treatment with nivolumab beyond progression

In the event of an initial assessment of PD (based on RECIST Version 1.1), a subject may continue to receive the assigned study treatment as long as none of the criteria listed below are met. Criteria for discontinuation of investigational product include:

- Confirmed PD without clinical benefit: An initial assessment of PD by RECIST Version 1.1 will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later (see Section 6.3.3 for disease evaluation). Patients with confirmed PD at this time should be discontinued. However, if a patient with confirmed PD is still receiving clinical benefit in the investigator's opinion, study drug may be continued after discussion and agreement between the treating physician and PI.
- Meets any of the other investigational product discontinuation criteria (Section 4.4.3)
- Clinical symptoms or signs indicating significant PD such as the benefit-risk ratio of continuing therapy is no longer justified.
- Decline in ECOG performance status.
- Threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention, and continuation of study therapy would prevent institution of such intervention.

If the lesions included in the tumor burden subsequently regress to the extent that the criteria for PD are no longer met, then treatment may continue according to the treatment schedule.

4.5 Concomitant Medications/Treatments

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from the trial may be required. The investigator should discuss any questions regarding this with the PI. The final decision on any supportive therapy or vaccination rests with the investigator and /or the subject's primary oncologist. However the decision to continue the patient on trial therapy or vaccination schedule requires the mutual agreement of the Investigator, the study Quality Assurance Monitor (QAM) and the subject.

4.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare, with the exception of those listed in section 4.5.2, may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency route and date may also be included on the CRF. All concomitant medications received from the time of informed consent until 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered past 30 days after the last dose of trial treatment should be recorded if given in relation to SAEs.

Patients who are on treatment for hepatitis B and C will be allowed to continue their medications while on study with close monitoring from their treating hepatologists.

4.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy within 28 days of registration.
- Investigational agents within 28 days of study registration.
- Radiation therapy within 14 days of registration
- Live vaccines within 28 days prior to study registration and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed at any time during the study.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. However, patients are allowed to use bronchodilators or local steroid injections if clinically necessary.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications, which are prohibited in this trial. There are no prohibited therapies during the follow-up phase

4.6 Other Modalities or Procedures

Radioembolization therapy is performed in a two-step process: a diagnostic angiogram and Technetium-99 macroaggregated albumin (^{99}Tc-MAA) scan, followed by the treatment session. Y90-specific informed consent will be obtained. Prior to the administration of Y90, a mesenteric angiogram is performed to determine the tumor's blood supply, aberrant anatomy and to ensure proper catheter position. Using a unilateral femoral approach, selective catheterization of the hepatic artery will be performed. Vascular access is obtained via the common femoral artery and a guidewire advanced under fluoroscopic guidance. A 5-F sheath is then inserted over the guidewire. The superior mesenteric artery is selected and an angiogram performed.

4.7 Duration of Therapy

Y-90 will be administered at the start of the study. A single Y-90 treatment will be performed, and nivolumab treatment will start 7-14 days later to allow for full recovery. Additional Y-90 treatments may be allowed after discussion with the principal investigator**.

Subjects will receive study treatment (nivolumab) until disease progression (see section 4.4.3 for details on treatment beyond initial progression), intolerance due to toxicity or withdrawal from the study either by the patient or at the recommendation of the treating oncologist. The study may be stopped sooner, for, toxicity, IRB stopping the study, FDA stopping the study, sponsor stopping the study, principal investigator stopping the study, subject has a positive pregnancy test, use of illicit drugs, non-compliance, deterioration to ECOG level 4, progression of HCC, withdrawal of consent (regardless of reason), variceal bleeding, or death. Patients will be assessed for response by CT scan or MRI every 8 weeks (2 cycles) for the first 13 months, and every 12 weeks (3 cycles) thereafter.

***Repeat therapy to the treated lesion or additional untreated lesions may be warranted. If a patient requires additional Y-90 after starting nivolumab treatment, it may be given once approval from the interventional radiologist and treating physician has been confirmed. In such cases, nivolumab should be held for ≥7 days prior to administering Y-90. Nivolumab can be resumed at least 7 days after receiving additional Y-90, and can be delayed for up to 4 weeks if needed.*

4.8 Duration of Follow Up

Once a patient comes off study treatment for any reason other than death, an End of Treatment visit should occur 30 days (+/- 7 days) after the last dose of nivolumab.

Patients will be followed for survival for up to 2 years after treatment discontinuation. If a patient discontinues treatment prior to 24 weeks (6 cycles), they should undergo follow-up (either by routine clinic visit or by phone call) every 2 weeks until the end of the 24-week period from start of study treatment to document survival and disease progression. After this period, patients should be followed for survival every 6 months for 2 years (by routine clinic visit or phone call). Patients should also be followed for SAE's for 100 days after discontinuing study drug.

4.9 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Any event which, in the opinion of the investigator/sub-I's opinion, requires termination of the study/study medications (including non-compliance)
- At the request of the subject (Withdrawal of consent)
- At the request of a regulatory body (FDA, NU IRB)
- Patients with a positive beta-HCG test (consistent with pregnancy)
- Use of illicit drugs or other substances that may contribute to toxicity
- Deterioration of PS to ECOG 4
- Progression of disease, as evidenced by radiologic progression and/or clinical status is worsening, subject not benefiting from the study drug.
- Development of a second cancer
- Subject is lost to follow-up
- More than two Y-90 treatments
- Grade 4 hyperbilirubinemia (high bilirubin) defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 of bilirubin more than 10 times the upper limit of normal,
- The Northwestern University Institutional Review Board/Office for the Protection of Research Subjects (offices at Northwestern that protects study patients) stops the study.
- Death

  The study will be stopped if 2 of the first 5 patients receiving (Y-90 + nivolumab) develop grade 4 hyperbilirubememia (>10) OR a death occurs believed to be related to therapy and not due to the natural progression of liver disease and liver cancer.

4.10 Patient Replacement

Any patient who signs consent but does not receive study treatment may be replaced. In addition, any study patient who receives Y-90 but discontinues prior to treatment with nivolumab can be replaced. This includes patients who cannot start nivolumab within 4 weeks of Y-90 treatment, who must come off study.

5.0 STUDY PROCEDURES

	Screening[1]	On Treatment (1 cycle = 28 days)					Off Treatment	
Time Period	Baseline	Induction Treatment[9]	Cycle 1[10] (± 3 days)		Cycle 2+ (± 3 days)		End of Treatment[13]	Follow-up[14]
			D1	D15	D1	D15		
Assessment or Activity								
Informed Consent	X							
Medical history	X							
Physical exam[2]	X		X		X			
ECOG status	X		X		X			
Adverse Events & ConMeds	X	X	X		X		X	X
Tumor Measurement [3]	X		X[3]		X[3]			
Coagulation studies (INR, PT, PTT)[4]	X[4]							
Child-Pugh Class	X		X					
CBC with diff[5]	X[5]		X	X	X	X	X	
Chemistry panel[6]	X[6]		X	X	X	X	X	
AFP	X		X		X			
TSH with reflex T3, T4			X		X			
Hepatitis Panel[7]	X						X	
Urinalysis	X						X	
Pregnancy Test[8]	X	X	X				X	
ECG	X							
Angiogram[9]	X							
Y-90 [9]		X						
Nivolumab [10]			X	X	X	X		
Correlative studies[11]	X		X		X[11]			
Archival tissue collection[12]	X							
Survival status[14]								X

1 All screening procedures should take place within 28 days of registration unless noted otherwise.
2 Includes vital signs (pulse, respirations, blood pressure), height (baseline only) and weight.
3 Imaging will be performed at screening, 21-28 days after Y-90 administration (during Cycle 1), and every 2 cycles (starting with Cycle 3 Day 1, ±7 days) for the first 13 months. Imaging will then occur every 3 cycles (±7 days) until disease progression or treatment discontinuation. Imaging will include either CT of Chest/Abdomen/Pelvis or MRI as indicated. Contrast should be used to the greatest extent possible (see section 6.1 for details).
4 Coagulation studies will be performed at the time of the screening angiogram. Patients who are on Coumadin will require their INR to be checked every cycle or according to the treating oncologist. If patient is on low molecular weight heparin, an Anti-Xa level should be tested to ensure it is within therapeutic range
5 CBC with differential will include WBC, ANC, ALC, Platelets, and Hemoglobin. CBC should be collected within 14 days prior to registration and reviewed prior to each nivolumab treatment.
6 Chemistry panel will be drawn at screening (within 14 days prior to registration) and pre-dose at all treatment visits. Chemistry panel will include glucose, calcium, albumin, ALT, AST, sodium, potassium, total bilirubin, alk phos, and creatinine.
7 Full hepatitis panel at screening including HBsAg, HBeAg, and HBV DNA. If active hepatitis will need to see hepatologist and begin treatment prior to starting on study. Patient should have viral load < 100 IU/mLprior to nivolumab infusion. See inclusion criteria 3.1.5 for hepatitis B requirements for eligibility.
8 FOCBP can have either a serum or urine pregnancy test within 7 days prior to registration (note: this may be completed as part of the angiogram), prior to Y-90 treatment (pregnancy testing is a standard procedure before Y-90), and within 24 hours prior to starting nivolumab treatment (scheduled for C1D1).
9 Prior to registration, patients will undergo a planning angiogram in IR to determine doses of Y-90. Since Y-90 administration is usually planned around 7 days from the angiogram, screening procedures and registration should be planned accordingly.
10 Patients will receive IV nivolumab starting with Cycle 1 Day 1, which is planned 7-14 days after the induction Y-90 procedure to allow for count recovery (Note: Patients can be treated with nivolumab up to 4 weeks after Y-90 in the case of TB or continuing side effects). During this break, patient will be evaluated by a medical oncologist as part of standard procedures. Starting with Cycle 1 Day 1, patients will begin treatment with intravenous nivolumab as maintenance either at 80mg or 240mg over 30 minutes (-5 minutes / +15 minutes) every 2 weeks (Day 1 & 15 of each cycle). Treatment will continue until disease progression, intolerable side effects, or patient withdraws consent or is removed from the study for any other reason.
11 Correlative blood work will be collected for all patients in a 10mL NaHep tube at baseline, post Y-90 treatment (pre-dose on Cycle 1 Day 1) and during nivolumab treatment as follows: pre-dose every 8 weeks for the first 24 weeks (C3D1, C5D1, and C7D1), and every 16 weeks thereafter (every 4 cycles starting with C11D1). This will be used for peripheral lymphocyte analysis and correlative studies as detailed in the protocol.
12 If patient has archival tissue present, it will be collected after registration for next-generation sequencing (NGS) and immunohistochemistry as described in section 9.0 and the separate lab manual.
13 An End of Treatment visit should occur 30 days (+/- 7 days) after the last dose of nivolumab.
14 Patients will be followed for survival for up to 2 years after treatment discontinuation. If a patient discontinues treatment prior to 24 weeks (6 cycles), they should undergo follow-up (either by routine clinic visit or by phone call) every 2 weeks until the end of the 24-week period from start of study treatment to document survival and disease progression. After this period, patients should be followed for survival every 6 months for 2 years (by routine clinic visit or phone call). Patients should also be followed for SAE's for 100 days after discontinuing study drug.

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [6]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

High resolution CT with oral/intravenous contrast or contrast-enhanced MRI is the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of start of study treatment. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments.

Radiographic tumor assessments will be conducted at screening, 21-28 days after Y-90 administration (during Cycle 1 of nivolumab), Cycle 3 Day 1 (±7 days, 1 cycle = 28 days) and every 2 cycles (±7 days) thereafter for the first 13 months. Imaging will then occur every 3 cycles (±7 days) until disease progression or treatment discontinuation. Imaging will include either CT of Chest/Abdomen/Pelvis or MRI as indicated. Contrast should be used to the greatest extent possible. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST.

6.2 Primary Endpoint

The primary endpoint of this study is establishing the maximum tolerated dose for the combination therapy of nivolumab and Y-90. Patients who received at least one dose of nivolumab will be considered for evaluation.

6.3 Secondary Endpoints

- For the purposes of this study, patients who have received at least one dose of nivolumab will be considered for evaluation of the safety and toxicity profile of the combination therapy. Safety and tolerability will be measured by the incidence of all adverse events, serious adverse events, deaths and laboratory abnormalities. Adverse event assessments and laboratory tests will be performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.
- All patients should be re-evaluated for response 21-28 days after Y-90 then every 8 weeks (every 12 weeks after 13 months) using RECIST criteria. Overall response will be calculated by sum of the complete and partial response rates according to measurement of target and non-target lesions as described below.
- Disease control rate will be determined at 24 months from the start of nivolumab treatment by the sum of complete response, partial response and stable response according to measurement of target and non-target lesions as described below.
- Patients who have a response sufficient enough where by shrinkage of the tumors allows them to be considered for transplant will be determined by established BCLC transplant guidelines for individual tumor sizes.
- PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Progression assessment will be performed by

investigator each time the patients has a radiologic evaluation after 8 weeks of treatment. OS is defined as the duration of time from start of treatment to time of death.

6.3.1 Definitions:

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with nivolumab.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. RECIST measurements should be used when available. When RECIST measurements cannot be made due to infiltrative disease, evaluable disease needs to be confirmed by pathology.

Evaluable non-target disease response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one dose of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.3.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non- cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 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 (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend

themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non- nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

6.3.3 Response criteria

6.3.3.1 Evaluation of target lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

6.3.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

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

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.
Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.3.3.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Responses will be assessed using CT scans or magnetic resonance imaging according to standard RECIST 1.1 criteria in order to assess disease progression. These criteria will also allow for patients who experience an initial disease flare, and as some patients who will have a delayed response may experience an initial disease flare, we will allow patients to continue receiving nivolumab beyond progression (see section 4.2.5)

6.3.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met
category when no lesions can be measured is not advised for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to NOTIS for additional information). The level of risk attributed to this study requires High Intensity Monitoring as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 and 7.2.5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

7.2 Definitions & Descriptions

7.2.1 Adverse Event

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

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

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, “hepatitis” and not “elevated liver function tests” should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Event

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 100 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**

If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- **Is life-threatening.**

The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- **Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event.**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.2.5 Adverse Event Reporting Period

For this study, adverse events will be followed from the time of informed consent until 30 days following the last administration of study treatment. SAE's will also be collected from the time of consent until 100 days following the last administration of study treatment. For patients registered and never treated with study drug, SAE's should be collected for 30 days from the date of consent.

7.2.6 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

7.2.7 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

7.2.8 Post-study Adverse Event

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

7.2.9 Abnormal Laboratory Values

All clinical laboratory abnormalities should be documented as adverse events.

7.2.10 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

7.2.11 Reporting of Serious Adverse Events

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

7.2.12 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. 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 AST/ALT 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.

7.2.13 Pregnancy
If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

The investigator must immediately notify Worldwide Safety @BMS of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

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

7.2.14 Overdose
An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data and Safety Monitoring Committee (DSMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current protocol
- the drug package insert
- the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DSMC

All SAEs must be reported to the assigned QAM **(as well as BMS – see section 7.3.3.3)** within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DSMC at their next meeting.

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any <u>death of an NU subject</u> that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB <u>within 24 hours of notification</u>.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any <u>death of a non-NU subject</u> that is unanticipated and at least possibly related and <u>any other UPIRSOs</u> will be reported to the NU IRB <u>within 5 working days of notification</u>.
- All <u>other deaths of NU subjects</u> not previously reported, <u>other non-NU subject deaths</u> that were unanticipated and unrelated, and <u>any other SAEs</u> that were not previously reported as UPIRSOs will be reported to the NU IRB <u>at the time of annual continuing review.</u>

7.3.3.3 Reporting to Bristol Myers Squibb

All SAE reports (including death by any cause), regardless of attribution, will be reported within 24 hours to BMS Global Safety (using the NU CRO SAE Form and referencing the BMS study number, CA 209-615). The assigned study coordinator will facilitate all reporting to the BMS.Global Safety and email QA a copy of the report upon completion. BMS Global Safety can be notified at:

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

8.0 DRUG INFORMATION

8.1 Yttrium-90 (Theraspheres)

8.1.1 Other names

TheraSphere®-MDS Nordion

8.1.2 Classification - type of agent

Insoluble glass microspheres where yttrium-90 is an integral constituent of the glass.

8.1.3 Mode of action

Yttrium-90, a pure beta emitter, decays to stable zirconium-90 with a physical half-life of 64.2 hours (2.67 days). The average energy of the beta emissions from yttrium-90 is 0.9367 MeV. Following embolization of the yttrium-90 glass microspheres in tumorous liver tissue, the beta radiation emitted provides a therapeutic effect. The microspheres are delivered into the liver tumor through a catheter placed into the hepatic artery that supplies blood to the tumor. The microspheres, being unable to pass through the vasculature of the liver due to arteriolar capillary blockade, are trapped in the tumor and exert a local radiotherapeutic effect with some concurrent damage to surrounding normal liver tissue.

8.1.4 Storage and stability

Each TheraSphere dose vial contains one of six available dose sizes of yttrium-90, a high-energy beta emitter. Even with low-density materials such as the acrylic vial shield, the attenuation of beta particles gives rise to Brehmsstrahlung radiation that requires lead shielding. Users should avoid exposure by leaving the vial in the acrylic product container, and by leaving the acrylic container in the lead shield as much as possible. The use of additional shielding is recommended. Finger-ring dosimeters should be worn in the orientation most likely to record the highest exposure to the fingers. The TheraSphere dose vial should not be removed from its acrylic vial shield. It should be stored in the lead pot and acrylic shield in which it is packaged. The TheraSphere dose vial, TheraSphere Administration Set and TheraSphere Administration Accessory Kit should be stored at room temperature. The requirements of the applicable regulatory agency for safe handling and storage of radioactive materials should be consulted and must be followed.

8.1.5 Protocol dose specifics

According to Treatment Plan. The amount of radioactivity required to deliver the desired dose to the liver may be calculated using the following formula:

$$Activity\ \mathrm{Re}quired\ (GBq) = \frac{[Desired\ \ Dose\ (Gy)]\,[Liver\ \ Mass\ (kg)]}{50}$$

The liver volume and corresponding liver mass may be determined using CT or ultrasound scans.

For the purpose of ordering TheraSphere, use the Yttrium-90 Physical Decay Table (according to appendix 4 Table 3) to determine the appropriate time of injection. For determining the actual liver dose (Gy) delivered to the liver after injection, the following formula is used:

$$Dose\ (Gy) = \frac{50\,[Injected\ \ Activity\ (GBq)]\,[1-F]}{Liver\ \ Mass\ (kg)},$$

where F is the fraction of injected radioactivity localizing in the lungs, as measured by Tc-99m MAA scintigraphy. The upper limit of injected activity shunted to the lungs is F x A = 0.61 GBq.

8.1.6 Preparation and Route of Administration

The entire contents of the TheraSphere dose vial are administered to the patient. The administration instructions must be followed to optimize delivery of the calculated dose.

1. Place the Accessory Kit on an appropriate platform, remove the top shield and place the TheraSphere dose vial in its lead pot into the pot holder in the acrylic box base. Adjust the catheter extension arm to the desired position by pulling out the spring lock. Place the hook in its holder on the side of the kit.

2. Turn the radiation dosimeter 'ON', set it to the 'dose rate - mR/h' setting, and then secure the dosimeter to the holder located on the acrylic box. Record the stabilized dose rate reading as the initial reading.

3. Remove the sterile Administration Set and empty vial from the packaging and place them next to the acrylic box on a sterile surface such as a sterile towel or drape.

4. Insert the piercing bag spike into the flushing fluid bag, and hang the bag on the hook provided on the kit.

5. Insert the vented vial spike into the sterile empty vial and place the vial in its stand on the exterior of the kit. Snap the relief valve line within the gripper clip A.

6. Remove the red shield cap from the plunger assembly and place sterile absorbent material under plunger assembly.

7. Fill and discharge the syringe to remove air from the Administration Set inlet and outlet lines. Visually determine that there are no air bubbles in the lines. Verify that there are two steady streams of sterile solution flowing from the plunger assembly.

8. Remove the lead pot lid from the TheraSphere dose vial. Remove the tamper-evident seal from the top of the acrylic vial shield using a remote handling tool. Then remove the acrylic plug. The acrylic plug may be removed by placing surgical tape onto the plug and lifting upward.

9. Swab the exposed top of the dose vial septum with disinfectant using a remote handling tool such as a Kelly clamp

10. Push the plunger assembly into the top of acrylic TheraSphere vial shield until a "click" or "snap" is heard or felt.

11. Place the tubing set through the appropriate openings in the acrylic box. The inlet line B goes through opening B on the near side of the box and the outlet line D goes through the U-shaped opening D on the catheter side of the box. Loop the line around the side of the acrylic box so that connection C rests in the priming valve holder C.

12. Insert the inlet and outlet needles into the vial by pushing the plunger tabs down with sufficient force until a "click" or "snap" is heard or felt.13. Disconnect the outlet line luer fitting E from the priming extension line and firmly connect the outlet line luer E to the patient catheter luer fitting. Place this luer connection firmly into the holder E on the end of the extension arm on the Accessory Kit. Ensure a vertical orientation of the lines and fittings with the outlet line luer connection above the patient catheter fitting.

14. Place the top shield lid on the Accessory Kit. Ensure that none of the lines (including the infusion catheter) are pinched or have a visible kink. Replace a kinked catheter before proceeding.

15. Flush the TheraSphere microspheres into the patient by pushing approximately 20 mL of sterile solution with the syringe. For subsequent flushes pull back on the syringe plunger to the back stop of the syringe and then push the plunger again. Repeat dose vial flushing until electronic dosimeter reading indicates that an appropriate proportion of TheraSphere microspheres have been delivered to the patient catheter. A minimum of 3 flushes for a total of 60 mL is recommended. The dose vial (still in lead pot) can be gently shaken or tapped to release microspheres that may have become trapped on the top of the product vial during shipping.Note: Excessive force on the syringe will result in fluid being transferred through the pressure relief valve into the attached empty vial. If this occurs, reduce the infusion syringe force until there is no fluid flow into the empty vial.

16. Once the infusion is complete, cut the inlet line at the indicated position upstream of the check valve. Monitor the radiation fields along the lines and use remote handling tools to handle areas where radiation fields may be present. Do not disconnect the catheter inlet luer fitting from the outlet line. Remove the catheter from the patient, and place it into the Nalgene waste container (within the acrylic shielding container) with all potentially contaminated materials including the acrylic vial shield with the needle plunger assembly still attached, as well as outer gloves. Seal the Nalgene container cap in place and place the top lid on the acrylic shielding container. Remove the waste for disposal.

17. Appropriate radiation protection measures must be employed to remove draping materials. The room, equipment and personnel must be monitored for any potential radioactive contamination.

8.1.7 Incompatibilities

The use of TheraSphere is contraindicated in patients:

- whose Tc-99m macroaggregated albumin (MAA) hepatic arterial perfusion scintigraphy shows any deposition to the gastrointestinal tract that may not be corrected by angiographic techniques (see package insert);
- who show shunting of blood to the lungs that could result in delivery of greater than 16.5 mCi of yttrium-90 to the lungs. Radiation pneumonitis has been seen in patients receiving doses to the lungs greater than 30 Gy in a single treatment (see package insert);
- in whom hepatic artery catheterization is contraindicated; such as patients with vascular abnormalities or bleeding diathesis;
- who have severe liver dysfunction or pulmonary insufficiency; and
- who present with complete occlusion of the main portal vein (see package insert).

8.1.8 Availability & Supply

Commercially available

8.1.9 Side effects

Yttrium-90 (Theraspheres) – expected adverse events

Based on clinical and preclinical animal experience with TheraSphere and other yttrium-90 microspheres, certain adverse reactions have been identified [4-6, 15, 16, 17, 18]. Serious adverse events that occurred under clinical studies and that

were definitely, probably or possibly related to TheraSphere, or if the relationship was unknown, are summarized in Table 1. In addition to these serious adverse events, lymphocyte depression, which may be graded as moderate to severe but with no clinical sequellae, is expected to occur in some patients.

The introduction of microspheres into the vasculature of the stomach, duodenum or other organs of the gastrointestinal tract may cause chronic pain, ulceration and bleeding. Microsphere shunting to the lungs may cause edema and fibrosis that may not be reversible.

Extrahepatic shunting may be identified through the injection of Tc-99m MAA into the hepatic artery [19,20]. Flow of radioactivity to the gastrointestinal tract may be avoided by the use of balloon catheterization or other angiographic techniques to block such flow [21]. In addition, placement of the delivery catheter in the hepatic branch distal to collateral vessels provides a safety margin with respect to inadvertentdeposition of microspheres.

Some adverse events observed may be explained by the effect of attenuated radiation from the treated liver. Pleural effusion may be caused by attenuated radiation when the treated tumor is positioned proximal to the base of the lung. Similarly, treatment of tumors in the left lobe of the liver, in proximity to the gut, may explain some of the gastrointestinal events observed. Putative attenuated radiation effects to extrahepatic structures have generally been found to resolve over time.

The use of this product leads to irradiation of both tumorous and normal liver tissue. As a result, patients with diseases that compromise the functioning of their normal liver tissue or patients with either diffuse tumors or a high tumor burden may be at greater risk of liver function impairment.

A number of patient baseline characteristics, indicative of either impaired normal liver function or tumor status, correlated with a higher incidence of liver-related serious adverse events in clinical trials.

A retrospective study of 121 patients from 5 clinical trials has shown that the following 5 Pre-treatment High Risk Factors have been associated with at least 48% of all serious adverse events that were possibly related to use of the device and with 11 of the 12 deaths that were possibly related to use of the device:

• infiltrative tumor type
• “Bulk disease” (tumor volume > 70% of the target liver volume, or tumor nodules too numerous to count)
• AST or ALT > 5 times ULN
• bilirubin > 2 mg/dL
• tumor volume > 50% combined with an albumin < 3 g/dL

8.1.10 Nursing implications

Radioactive products should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to license the use of radionuclides. Adequate shielding and precautions for handling radioactive material must be maintained. As in the use of any radioactive material, care should be taken to ensure minimum radiation exposure to the patient extraneous to the therapeutic objective and to ensure minimum radiation exposure to workers and others in contact with the patient. Since adequate studies have not been performed in animals to determine whether

this device affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus, this product should not be administered to pregnant or nursing women unless it is considered that the benefits to be gained outweigh the potential hazards. Ideally the use of this radioactive device in women of childbearing capability should be performed during the first few (approximately 10) days following the onset of menses. Dose rate to personnel should be monitored during administration. Any spills or leaks must be cleaned up immediately and the area monitored for contamination at the end of the procedure. The TheraSphere dose vial is supplied secured within a clear acrylic vial shield to limit radiation exposure to personnel. The dose rate at the vial shield surface is still high enough to require caution including the use of tongs and a lead shielded container when possible. The TheraSphere dose vial should always be stored in a shielded location away from personnel.

8.2 Nivolumab

8.2.1 Other names

ONO-4538, BMS-936558, or MDX1106, Opdivo

8.2.2 Classification - type of agent

Human IgG4 anti-PD-1 monoclonal antibody

8.2.3 Mode of action

Nivolumab acts as an immunomodulator by blocking ligand activation of the programmed cell death 1 (PD-1) receptor on activated T cells anti-PD1.

8.2.4 Storage and stability

Nivolumab solution for infusion (100mg/vial) is a sterile non-pyrogenic single-use, isotonic aqueous solution formulated at 10mg/mL. Vials must be stored in a secure, limited-access location at 2 to 8 degrees C (36 to 46 degrees F) and protected from light, freezing, and shaking. The product is a clear to opalescent solution, which may contain proteinaceous and extraneous particulates. The product is intended for IV administration. The DP can be further diluted with normal saline or 5% Dextrose solution in IV containers made of polyvinyl chloride (PVC) or non-PVC material. Opened or accessed vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

After preparation, store the Nivolumab infusion either:

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

8.2.5 Protocol dose specifics

The first 3 patients in Phase I will be dosed at 80mg q2weeks. Patients will then be dosed at 240mg q2weeks, and the study will continue into Phase Ib provided 240mg is the MTD.

Nivolumab is to be administered as an approximately 30-minute IV infusion, using a volumetric pump with a 0.2 - 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% Sodium Chloride or 5% Dextrose for delivery with minimum allowable concentration of 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.

8.2.6 Preparation

Refer to most recent investigator's brochure for nivolumab preparation instructions.

8.2.7 Route of administration for this study

Nivolumab will be given as an intravenous infusion. Do not administer as an IV push or bolus injection. Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding in-line filter. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

8.2.8 Potential Drug Interactions:

No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

No formal pharmacokinetic drug-drug interaction studies have been conducted with nivolumab.

8.2.9 Availability & Supply

The supply for this study will be investigational – not commercially available. Supply will be provided by BMS free of charge. Nivolumab will be supplied as 100 mg/vial (10mg/mL). Drug is protocol specific, but not patient specific.

A supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS. The first request may take place upon screening of the first patient. The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is imperative that only drug product designated for this protocol number be used for this study.

Drug re-supply request form should be submitted electronically 10 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
When assessing need for resupply, keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific.

8.2.10 Side effects

Below are safety data from 268 subjects with unresectable or metastatic melanoma and 117 patients with metastatic squamous NSCLC who received nivolumab alone. Related side effects reported in subjects receiving nivolumab alone were:

Very Frequent – Expected to occur in more than 20% of people (more than 20 out of 100 people): Fatigue (50%), Dyspnea (38%), Musculoskeletal pain (36%), Rash (21%), Increased AST (28%), Increase alkaline phosphatase (22%), Hyponatremia (25-38%)

Frequent - Expected to occur in 10% to 20% of people (10 to 20 out of 100 people): Pruritus (19%), Cough (17%), URI (11%), Peripheral edema (10%), Increased ALT (16%), Hyperkalemia (15%)

Not Frequent – Expected to occur in less than 10% of people (less than 10 out of 100 people): ventricular arrhythmia, iridocyclitis, infusion-related reactions,

increased amylase, increased lipase, dizziness, peripheral and sensory neuropathy, exfoliative dermatitis, erythema multiforme, vitiligo, psoriasis

Deaths thought to be related to nivolumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people).

For the most recent safety update, please refer to the current Investigator's Brochure or Study Agent Prescribing Information.

8.2.11 Return and Retention of Study Drug

The clinical study team will be responsible for keeping accurate records of the clinical supplies received from BMS or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. 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.

Table 8.1 – Nivolumab Product Information

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Appearance	Storage Conditions (per label)
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/vial)	10 mL vial	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8ºC. Protect form light and freezing

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to identify biomarkers that help predict benefit and/or toxicities from the study drug. A separate Laboratory Manual will be developed and maintained with detailed sample collection and procurement guidelines, processing instructions, and additional assay descriptions. The Laboratory Manual will also include all contact information for key personnel and departments involved with correlative studies for this protocol.

9.1 Sample Collection Guidelines

Peripheral blood samples will be collected for all patients pre-dose on Cycle 1 Day 1 as well as every 8 weeks for the first 24 weeks, and every 16 weeks thereafter.

If patient has archival tissue available, it will be collected for next-generation sequencing (NGS) and immunohistochemistry (IHC). See lab manual for collection details.

9.2 Sample Processing, Storage, and Shipment

All samples will be processed by PCF-CTU according to instructions in the lab manual. Samples will be labeled with the subject's de-identified study number and collection date.

9.3 Assay Methodology

9.3.1 Tumor biopsy immunohistochemical (IHC) staining and analysis for PD-L1, PD-1, CD8+ and CD4+ tumor infiltrating lymphocytes

Detection of the selected markers for this study will be performed using immunohistochemistry. After the staining, the slides will be digitally scanned in an Aperio AT system (AperioTM, Leica BiosystemsTM) to convert the IHC slides into digital pathology files for posterior analysis. IHC expression analyses of markers consider a thorough staining pattern evaluation including distribution (percentage of positive cells) and intensity in the form of H-score, and evaluating the IHC expression in the proper subcellular location (i.e. membrane, cytoplasm or nucleus). IHC analysis and scoring will be performed by a certified pathologist using an image analysis software (Image Toolbox, AperioTM).

Outcome from the analysis will be calculated according to the H-score. The H-score ranges from 0 to 300, and it considers both intensity of the IHC (from 0 to 3) and distribution (percentage of the target cells positive, from 0 to 100). The scoring is the addition of the percentages of cells with intensity 0 + intensity 2 + intensity 3, thus the addition of the final percentage is 100% and the scoring will range from 0 to 300. Hence, the H score will incorporate both percentage of positive cells and intensity of marker expression. Hematoxylin/eosin and PD-1, PD-L1 and PD-L2-stained sections will be reviewed by a pathologist. Criteria to be evaluated include histologic subtype and grade, TNM 2002 pathologic tumor stage, the presence and type of intratumoral lymphocytic infiltration, and the quantity and location of PD-L1 staining. The tumor will be considered positive for PD-1, PD- L1, PD-L2 if >5% of tumor cells had histologic evidence of plasma membrane staining.

9.3.2 Peripheral blood lymphocyte phenotypes

Lymphocyte subsets (CD3, CD4, CD8, CD19, and CD56) will be analyzed according to absolute cell numbers per microliter of whole blood, percent representation among all lymphocytes, and co-expression of the activation markers CD25, HLA-DR, and CD45RO using automated flow cytometric techniques at the Flow Cytometry Core Laboratory, Robert H Lurie Cancer Center of Northwestern University under the supervision of Suchitra Swaminathan, PhD.

9.4 Specimen Banking

Patient samples collected for this study will be retained at the Northwestern University Biorepository. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Dr. Aparna Kalyan will be responsible for reviewing and approving requests for clinical specimen from potential research collaborators outside of Northwestern University. Collaborators will be required to complete an agreement (a Material Transfer Agreement or recharge agreement) that states specimens will only be released for use in disclosed research. Any data obtained from the use of clinical specimen will be the property of Northwestern University for publication and any licensing agreement will be strictly adhered to.

The following information obtained from the subject's medical record may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome – if available
- Demographic data

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a single-center Phase I/Ib study aiming to evaluate the safety, efficacy, and tolerability of nivolumab combined with therasphere, Y-90, in patients with advanced hepatocellular carcinoma.

The expected number of patients on dose escalation will be in the range of 9-15 based on the 3+3 design. Six patients will be treated at the MTD in the dose escalation phase. The dose calculation for Yttrium-90 Therasphere will be done according to standard protocol at Northwestern Memorial Hospital. Please note - details of this are located in section 8.1.

Phase Ib Expansion Cohort:
A Simon two stage optimum Phase II design (1989) will be used to test the null hypothesis that the response rate is 10% versus an alternative hypothesis of 30 [36]. Up to 29 evaluable patients will be entered into Phase 1b. The 6 patients at the MTD in Phase 1 will be counted as part of the 29 in Phase 1b. In the first stage, 10 patients will be entered. If none or 1 show a response, then consideration will be given to trial termination due to inactivity of the treatment. If 2 or more of 10 show a response, then an additional 19 patients will be added. If 5 or fewer of 29 show a response, then the trial will conclude that the response rate could be as low as 10%. If 6 or more respond, then the trial will conclude that the response rate is greater than 10%. This design has a 20% chance of falsely concluding the rate is 10% (Type II error = 20%), and a 5% chance of falsely concluding that the rate is greater than 10% (Type I error = 5%). There is a 74% chance that the trial will show 0 or 1 responses in the first stage if the true response rate is 10%.

For the total sample size, Phase 1 requires 9-15 patients, Phase 1b requires 29 patients in a two-stage optimum Simon design. The 6 at the MTD in Phase 1 are counted as part of the 29. This would require up to 15 in Phase 1, 23 new patients in Phase 1b for a total of 38 patients. Target accrual is 40 patients to account for potentially unevaluable patients.

Treatment duration:
Treatment will continue until disease progression (imaging done every 8 weeks), intolerable side effects, or patient withdraws consent or is removed from the study for any other reason.

10.2 Data Analyses Plans

Any subject who has received the investigational combination will be analyzed in an intention to treat format. The MTD will be determined as described in Section 4.3. Objective response rate (ORR = CR + PR) as defined in Section 6.3.3.1 and disease control rate (CR+PR+SD) will be calculated and a 95% confidence interval for response will be obtained using the methods of Porcher and Desseaux (2012) [37]. Progression-free survival will be summarized using the Kaplan-Meier product limit curve. Besides the required reporting of adverse events, adverse events will be summarized for all patients in the trial by type, duration, severity, timing and attribution (probable cause of adverse event). Whole exome sequencing and computational analyses will be performed to assess mutanome and immunome (subpopulations of immune cells). Change in clonal burden landscape of various mutanome and immunome will be analyzed to investigate its correlation with treatment response or development of resistance to treatment.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Subject Recruitment and Screening

Subjects will be recruited through hepatology clinic, hepatocellular carcinoma clinic, pre-transplant clinic and medical oncology clinics. They will be identified by the PI, or referred to the PI from other hepatologists, transplant surgeons or medical oncologists. The PI or sub-investigator will discuss the protocol with potential subjects (patients from one of the above clinics) that may qualify for the study based on the inclusion/exclusion criteria in this protocol. If the patient is interested they will discuss the study in depth and if they prefer, they can take home information (combination consent/HIPAA form) on the study to discuss with their family/significant other/primary care provider.

Once a potential subject decides they'd like to participate in the study they will come in to meet with the research coordinator/PI and/or sub-I to sign the consent after any other questions are answered. It is only after the informed consent is signed that any study-related procedures can be performed. The subject will be given a signed copy of the informed consent and the consent process will be documented in the subject's medical record.

11.3 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Bristol-Meyers Squibb. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.4 Registration Procedures

For potential patients, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

The QAM will review all source documentation required to confirm eligibility that is readily available in the patient's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.5 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, all data for phase I patients during the time period patients are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis.

11.6 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Office at Northwestern University:

- Signed and completed Letter of Invitation to participate in the study.
- Signed copy of Northwestern University's Data Monitoring Committee policy pertaining to data submission.
- Draft informed consent form should for review/approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent.
- CVs and medical licensure for the local PI and any sub-investigators who will be involved in the study at the site.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training). Full requirements will be outlined in a memo upon receipt of the signed Letter of Invitation.

11.7 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires High Intensity Monitoring as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to study-specific data submission guidelines.

11.8 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.8.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.8.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non-Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.9 Investigator Obligations

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

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.10 Publication Policy

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor (Dr. Aparna Kalyan) for the purposes of performing the study, will be published or passed on to any third party without the consent of Dr. Aparna Kalyan. Results of this study may be used for teaching, research, publications, or presentations at scientific meetings.

All potential publications and/or data for potential publications (e.g. manuscripts, articles, data, text, diagrams, abstracts, posters, charts, slides, pictures, or clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. For trials that require high intensity monitoring, the assigned QAM will prepare a preliminary data summary (to be approved by the DSMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DSMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DSMC at their next available meeting, and a final, DSMC-approved dataset will be released along with any DSMC decisions regarding publication. The investigators are expected to use only DSMC-approved data in future publications.

The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DSMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

NU shall provide BMS with a copy of each Publication at the earliest practicable time, but in any event not less than thirty (30) days prior to its submission to a journal, publisher or meeting or fifteen (15) days prior to any public disclosure of any manuscript or other public disclosure (e.g., presentations). To the extent applicable, BMS personnel shall be acknowledged (including authorship where applicable) in accordance with customary scientific practice.

REFERENCES

1. Altekruse, S. F., McGlynn, K. A. & Reichman, M. E. Hepatocellular carcinoma incidence, mortality, and survival trends in the United States from 1975 to 2005. *J. Clin. Oncol.* **27,** 1485–91 (2009).
2. El-Serag, H. B. & Mason, A. C. Rising incidence of hepatocellular carcinoma in the United States. *N. Engl. J. Med.* **340,** 745–50 (1999).
3. Lin, S.-M. & Chu, C.-M. Secondary prevention of hepatitis C virus-related hepatocellular carcinoma. *J. Gastroenterol. Hepatol.* **20,** 1475–7 (2005).
4. Beaugrand, M., N'kontchou, G., Seror, O., Ganne, N. & Trinchet, J.-C. Local/regional and systemic treatments of hepatocellular carcinoma. *Semin. Liver Dis.* **25,** 201–11 (2005).
5. Bruix, J., Gores, G. J. & Mazzaferro, V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* **63,** 844–55 (2014).
6. Yao, F. Y. *et al.* Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl.* **8,** 873–83 (2002).
7. Mazzaferro, V. *et al.* Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N. Engl. J. Med.* **334,** 693–9 (1996).
8. Regalia, E. *et al.* Liver transplantation for small hepatocellular carcinoma in cirrhosis: analysis of our experience. *Transplant. Proc.* **33,** 1442–4
9. Duffy, J. P. *et al.* Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann. Surg.* **246,** 502–9; discussion 509–11 (2007).
10. Pang, R. & Poon, R. T. P. Angiogenesis and antiangiogenic therapy in hepatocellular carcinoma. *Cancer Lett.* **242,** 151–67 (2006).
11. Llovet, J. M. *et al.* Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* **359,** 378–90 (2008).
12. Agata, Y. *et al.* Expression of the PD-1 antigen on the surface of stimulated mouse T and B lymphocytes. *Int. Immunol.* **8,** 765–72 (1996).
13. Ingham, M. & Wu, J. Immunotherapy and Hepatocellular Carcinoma. *J Liver* e108, doi:10.4172/2167–0889.1000e108 (2013). at <http://www.omicsgroup.org/journals/Immunotherapy-and-Hepatocellular-Carcinoma-2167-0889.1000e108.pdf>
14. Urbani, S. *et al.* PD-1 expression in acute hepatitis C virus (HCV) infection is associated with HCV-specific CD8 exhaustion. *J. Virol.* **80,** 11398–403 (2006).
15. Wenjin, Z., Chuanhui, P., Yunle, W., Lateef, S. A. & Shusen, Z. Longitudinal fluctuations in PD1 and PD-L1 expression in association with changes in anti-viral immune response in chronic hepatitis B. *BMC Gastroenterol.* **12,** 109 (2012).
16. Zeng, Z. *et al.* Upregulation of circulating PD-L1/PD-1 is associated with poor post-cryoablation prognosis in patients with HBV-related hepatocellular carcinoma. *PLoS One* **6,** e23621 (2011).
17. Boni, C. *et al.* Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic HBV infection. *J. Virol.* **81,** 4215–25 (2007).
18. Urbani, S. *et al.* Restoration of HCV-specific T cell functions by PD-1/PD-L1 blockade in HCV infection: effect of viremia levels and antiviral treatment. *J. Hepatol.* **48,** 548–58 (2008).
19. Poon, R. T.-P., Lau, C., Yu, W.-C., Fan, S.-T. & Wong, J. High serum levels of vascular endothelial growth factor predict poor response to transarterial chemoembolization in hepatocellular carcinoma: a prospective study. *Oncol. Rep.* **11,** 1077–84 (2004).
20. SIR-Spheres Yttrium-90 Microspheres Package Insert, SIRTeX Medical. Lane Cove. at <http://www.sirtex.com/media/29845/ssl-us-10.pdf>
21. Otto, G. *et al.* Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma. *Liver Transpl.* **12,** 1260–7 (2006).
22. Porrett, P. M. *et al.* Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. *Liver Transpl.* **12,** 665–73 (2006).
23. Mejia, G. A. *et al.* Correlation between the radiologic and histologic size of hepatocellular carcinoma in patients eligible for liver transplantation. *Transplant. Proc.* **38,** 1394–5 (2006).
24. Ho, M.-H. *et al.* Locoregional therapy-induced tumor necrosis as a predictor of recurrence after liver transplant in patients with hepatocellular carcinoma. *Ann. Surg. Oncol.* **18,** 3632–9 (2011).
25. Mardor, Y. *et al.* Early detection of response to radiation therapy in patients with brain

malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. *J. Clin. Oncol.* **21,** 1094–100 (2003).

26. Hall, D. E. *et al.* Therapeutic efficacy of DTI-015 using diffusion magnetic resonance imaging as an early surrogate marker. *Clin. Cancer Res.* **10,** 7852–9 (2004).
27. Kamel, I. R. *et al.* Role of diffusion-weighted imaging in estimating tumor necrosis after chemoembolization of hepatocellular carcinoma. *AJR. Am. J. Roentgenol.* **181,** 708–10 (2003).
28. Kamel, I. R. *et al.* The role of functional MR imaging in the assessment of tumor response after chemoembolization in patients with hepatocellular carcinoma. *J. Vasc. Interv. Radiol.* **17,** 505–12 (2006).
29. Deng, J. *et al.* Diffusion-weighted MR imaging for determination of hepatocellular carcinoma response to yttrium-90 radioembolization. *J. Vasc. Interv. Radiol.* **17,** 1195–200 (2006).
30. Goin JE, Dancey JE, Roberts CA, et al. Comparison of Post-embolization Syndrome in the Treatment of Patients with Unresectable Hepatocellular Carcinoma: Trans-catheter Arterial Chemo-embolization versus Yttrium-90 Glass Microspheres. ***World J of Nuc Med*** 3:49-56, 2004
31. Goin JE, Salem R, Carr BI, et al. Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium-90 microspheres: factors associated with liver toxicities. ***J Vasc Interv Radiol*** 16:205-13, 2005
32. Goin JE, Salem R, Carr BI, et al. Treatment of unresectable hepatocelllular carcinoma with intrahepatic yttrium-90 microspheres: a risk-stratification analysis. ***J Vasc Interv Radiol*** 16:195-203, 2005
33. Salem R, Lewandowski RJ, Atassi B, et al. Treatment of unresectable hepatocellular carcinoma with the use of 90-Yttrium microspheres (TheraSphere): safety, tumor response, and survival. ***J Vasc Interv Radiol*** 16:1627-39, 2005
34. Dancy JE, Shepherd FA, Paul K, et al. Treatment of nonresectable hepatocellular carcinoma with intrahepatic 90-Yttrium- microspheres. ***J Nucl Med*** 41:1673-81, 2000
35. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. ***Lancet*** 359:1734-9, 2002
36. Simon R. Optimal Two-Stage Designs for Phase II Clinical Trials. ***Controlled Clinical Trials*** 10:1-10, 1989).
37. Porcher R, Desseaux K. What inference for two-stage phase II trials. ***BMC Medical Research Methodolog***y 12:117, 2012.

APPENDICES

APPENDIX 1:

Treatment-Emergent Serious Adverse Events from 5 Clinical Studies (N=121) for Patients Undergoing TheraSphere® Treatment Therapy

Expected Adverse Device Effects	
Adverse Device Effect	**Expected Frequency (%)**
TheraSphere	
Elevated alkaline phosphatase	75
Elevated SGOT	75
Elevated SGPT	75
Lymphocyte depression (asymptomatic)	35
Fatigue	29
Fever	25
Nausea	15
Heartburn	14
Vomiting	15
Pain	15
Decreased albumin	10
Ascites	10
Elevated bilirubin	10
Pleural effusion	10
Ulcer, GI	10
Anorexia	10
Constipation	5
Dizziness	5
Muscle pain	5
Renal Failure	5
Cholecystitis	< 5
Pneumonitis	<1
Death	< 1
Angiographic Procedure	
Allergic reaction (e.g. contrast media)	< 5
Medication reaction (e.g nausea from narcotics)	< 5
Vascular spasm	< 1
Vessel dissection	< 1
Vessel rupture	< 1
Thrombosis / embolism (vascular access)	< 1
Bleeding / Hematoma	< 1
Infection	< 1
Venipuncture	
Discomfort/pain	5
Fainting	< 1
Bleeding at site	< 1
Infection	< 1

APPENDIX 2:
Pregnancy and Contraception Requirements

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 from the time of treatment initiation to 5 months (for FOCBP) or 7 months (for males with FOCBP partners) after the last dose of nivolumab. 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

a) 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. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
b) Nonhormonal IUDs, such as ParaGard®
c) Tubal ligation
d) Vasectomy.
e) Complete Abstinence*

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

LESS EFFECTIVE METHODS OF CONTRACEPTION

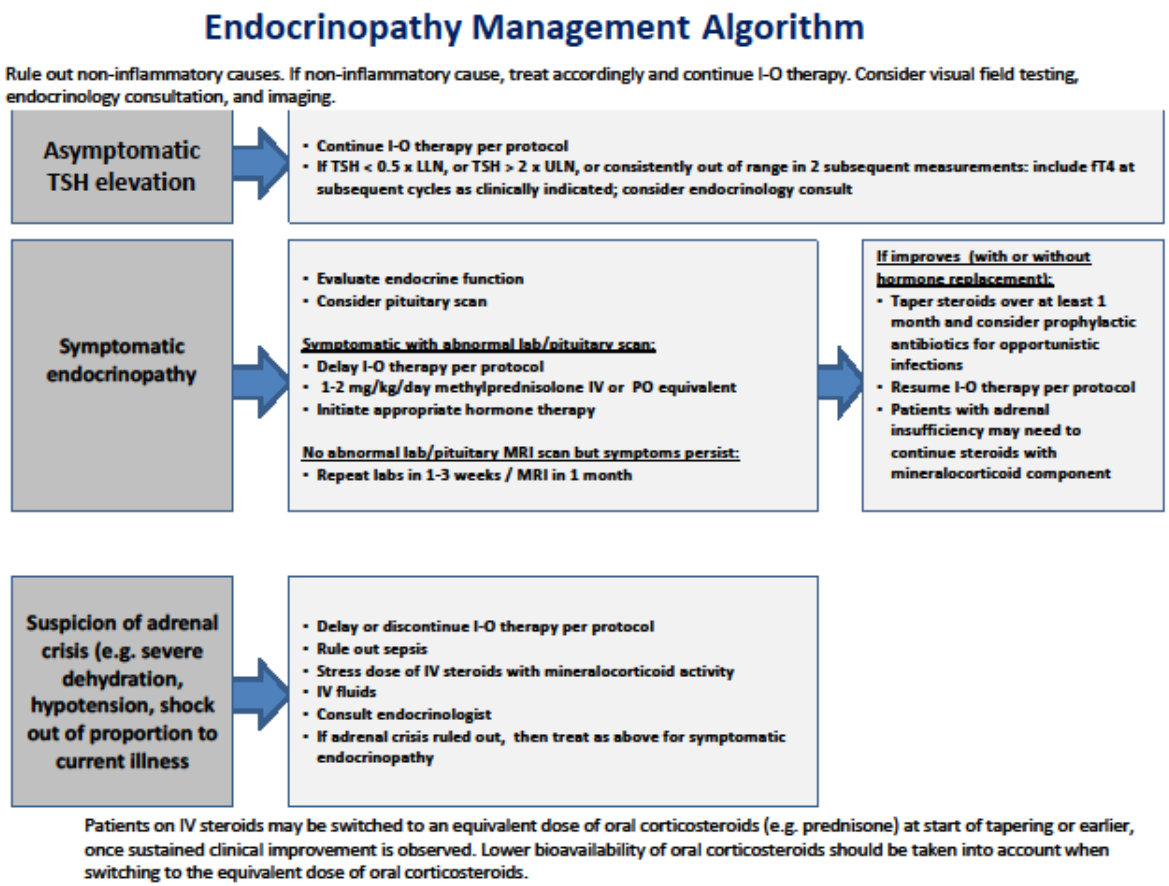
a) Diaphragm with spermicide
b) Cervical cap with spermicide
c) Vaginal sponge
d) Male Condom without spermicide*
e) Progestin only pills by WOCBP subject or male subject's WOCBP partner
f) Female Condom*

*A male and female condom must not be used together

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

APPENDIX 3:

Recommended management algorithms for suspected nivolumab related endocrinopathy, gastrointestinal toxicity, hepatotoxicity, neurologic toxicity, pulmonary toxicity, renal toxicity and skin toxicity



GI Adverse Event Management Algorithm

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

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

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

Hepatic Adverse Event Management Algorithm

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

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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.

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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.

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

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

Renal Adverse Event Management Algorithm

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

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

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

Skin Adverse Event Management Algorithm

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

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering ≤ 30% BSA*	• Symptomatic therapy (e.g. antihistamines, topical steroids) • Continue I-O therapy per protocol	<u>If persists > 1-2 weeks or recurs:</u> • Consider skin biopsy • Delay I-O therapy per protocol • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving , taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol <u>If worsens:</u> • Treat as Grade 3-4
Grade 3-4 Covering >30% BSA; Life threatening consequences*^	• Delay or discontinue I-O therapy per protocol • Consider skin biopsy • Dermatology consult • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent	<u>If improves to Grade 1:</u> • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol

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-Otherapy.

APPENDIX 4:
Yttrium-90 Dosage and Administration

To correct for the physical decay of yttrium-90, the fractions that remain at selected time intervals from calibration are shown in Table 3.

Table 3: Yttrium-90 Physical Decay Table

Half-Life 64.2 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining	Hours	Fraction Remaining
-4	1.044	26	0.755	56	0.546
-2	1.022	28	0.739	58	0.534
0*	1.000	30	0.723	60	0.523
2	0.979	32	0.708	62	0.511
4	0.958	34	0.692	64	0.500
6	0.937	36	0.677	66	0.489
8	0.917	38	0.663	68	0.479
10	0.897	40	0.649	70	0.469
12	0.878	42	0.635	72 (Day 3)	0.459
14	0.859	44	0.622	96 (Day 4)	0.354
16	0.841	46	0.609	120 (Day 5)	0.273
18	0.823	48 (Day 2)	0.596	144 (Day 6)	0.210
20	0.806	50	0.583	168 (Day 7)	0.162
22	0.789	52	0.570		
24 (Day 1)	0.772	54	0.558		

*Calibration Time

APPENDIX 5:
Summary of Changes

Original Version Approved by the Northwestern University IRB – July 22, 2016			
Amendment 1 – July 27, 2016 *Approved by Scientific Review Committee 8-12-2016*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
4.2.2 (Nivolumab Treatment Administration); 8.2.5 (Protocol Dose Specifics)	Nivolumab infusion duration listed as 60 minutes	Changes infusion duration to 30 minutes	Updated, as requested by BMS, to reflect new dosing strategy for nivolumab
4.3 (Phase I Dose Escalation Scheme)	If a DLT occurred at dose level 1, de-escalation to level -1 was to occur	If a DLT occurs at dose level 1, "the PI will discuss with DMC and BMS to determine the necessary outcome"	The protocol was originally written with a dose level -1, and this language was mistakenly left in the protocol when dose level -1 was removed. The likelihood of a DLT occurring at level 1 is low, so further discussion will be warranted in this case.
4.4.1 (Dosing Delays); Appendix 3	n/a	Adds recommended algorithms for investigators to reference related to immuno-oncology specific AE's	Additional information provided by BMS
5.0 (Study Procedures)	• #7: • n/a	• #7: Removes specific language about hepatitis eligibility and refers to inclusion criteria 3.1.5. Previously stated that patients with active hepatitis B would see a hepatologist and begin hepatitis treatment before study treatment • Adds note in table "1 cycle = 28 days" • Adds specific time points for treatment (C3, 5, 7, 11 etc.) in footnote 11	• To clarify prior discrepancy from eligibility criteria (3.1.5) • Clarifications
7.3.3.1 (Reporting to the Northwestern	n/a	Adds language that SAE's must be reported to BMS, regardless of attribution and	Clarifications

University QAM/DMC); 7.3.3.3 (Reporting to Bristol Myers Squibb)		adds the BMS study reference number (CA209-615)	
8.1.5 (Protocol Dose Specifics)	Referred to Appendix F, Table 3 for the Physical Decay Table to order TheraSphere based on the appropriate time of injection.	Replaces references to Appendix F with Appendix 4 and adds Appendix 4 with the relevant table.	Adds previously missing information related to Y-90 dosing.
8.2 (Nivolumab)	n/a	Adds "Product Information Table" for nivolumab	Additional information provided by BMS
9.3.1 (Tumor Biopsy IHC)	Included instructions for IHC analysis involving Dako kits and pathology analysis at MD Anderson	Removes references to Dako kits and MD Anderson	Dako kits are not being provided. Pathology analysis will take place at Northwestern.
11.3 (Amendments)	Amendments were listed as needing to be approved by Janssen Scientific Affairs	Removes reference to Janssen – amendments must be approved by Bristol-Myers Squibb	Correction of typographical error
11.10 (Publication Policy)	n/a	Includes language specific to NU's publication agreements with BMS	Updated to reflect contract

Amendment 2 – March 2nd, 2017 *Approved by Scientific Review Committee: 1/31/2017*			
Section(s) Affected	***Prior Version***	***Amendment 2 Changes***	***Rationale***
Cover Page	Northwestern Medicine Developmental Therapeutics **Institute** (NMDTI)	Northwestern Medicine Developmental Therapeutics **Program** (NMDTP)	Administrative; department underwent name change
Cover Page	n/a	Adds Valerie Nelson as sub-investigator. Removes Jason Kaplan, Frank Giles, Benedito Carneiro, Young Chae and Sunandana Chandra as sub-Is	Administrative; new faculty. Not all DTP faculty are listed as sub-I's in newest protocol template.
Cover Page	IND Number/Holder: **Pending**	IND Number/Holder: **Exempt**	Clarification; we are not waiting on information about the IND
Cover Page	"Bristol Meyers Squibb"	"Bristol-Myers Squibb"	Typographical error
Study Schema	Listed eligibility criteria related to autoimmune disease to describe study population	Removes autoimmune requirement, only listing diagnosis details to describe study population	Simplification

Study Schema; Study Summary; 4.1 (Overview); 4.2.2 (Nivolumab); 4.3 (Phase I Dose Escalation Scheme); 5.0 (Study Procedures #10); 8.2.5 (Protocol dose specifics)	Nivolumab was to be given at a starting dose of 80mg with a dose escalation to 240mg and then 480mg IV.	"The first 3 patients in Phase I are treated at 80mg IV every 2 weeks. Patients will then follow the standard regimen of 240mg every 2 weeks until progression, unacceptable toxicity or withdrawal of consent (see section 4.3 for dose escalation)."	The study will no longer include an escalation to 480mg IV nivolumab q2weeks given that the drug is approved at 240mg IV q2weeks.
Study Schema; 5.0 (Study Procedures #3)	Imaging is required "every 8 weeks"	Expands on imaging requirements: "every 8 weeks (2 cycles) for the first 13 cycles, and every 12 weeks (3 cycles) thereafter"	Clarification to incorporate cycles
Study Summary	Included a short title: "Y-90 + nivolumab in advanced HCC"	Removes short title	To align with current NU protocol template; short title is not required
Study Summary; 2.1 (Primary Objectives & Endpoints); 2.2 (Secondary Objectives & Endpoints)	One primary objective: "To identify MTD of nivolumab for combination treatment of nivolumab and Y-90 in this population." Secondary objectives include: "To evaluate the proportion of patients with ORR to the combination treatment nivolumab with Y-90	Changes MTD to the Phase I primary objective, and moves ORR from a secondary objective to the Phase Ib primary objective. Expands "this population" to state "patients with advanced hepatocellular carcinoma".	Given that nivolumab is FDA-approved at 240mg IV, it is important to look at efficacy as a more prominent study objective. It is also appropriate to have a primary objective for each study phase.
Study Summary; 3.0 (Patient Eligibility)	"Phase 1: 9-15 patients, Phase 1b: 20 patients"	"Phase 1: 9-15 patients, Phase 1b: requires 29 patients in a two-stage optimum Simon design. The 6 at the MTD in Phase 1 are counted as part of the 29. This would require up to 15 in Phase 1, 23 new patients in Phase 1b for a total of 38 patients. Target accrual is 40 patients to account for potentially unevaluable patients."	Statistical clarification to account for removal of the 480mg dose level.
Study Summary; 10.1 (Study Design / Study Endpoints)	Phase Ib Expansion Cohort: Twenty patients will be enrolled with the maximum tolerated dose (MTD). The 6 patients at the MTD in the dose escalation phase will be included in this expansion cohort. A one sample Bayesian design for the dichotomous primary endpoint of ORR will be	The Phase 1b expansion cohort will be a two-stage optimum Simon design with 29 patients. See Section 10.0 for details.	Statistical clarification to account for the need for a two-stage Simon design rather than a one-sample Bayesian design.

	used for the Phase Ib portion of the trial.		
1.3.1 (Rationale for Nivolumab Dosing)	n/a	Adds justification for the dose escalation from 80mg to 240mg IV nivolumab, indicating that nivolumab is now FDA-approved at 240mg	Additional information provided to justify stopping escalation at 240mg nivolumab.
3.1.9 (Inclusion Criteria)	• n/a • Included screening requirements for lipase, amylase, and magnesium	• Adds note to PT/INR requirement: "Performed at time of screening angiogram; can be outside 14 days if applicable." • Removes screening requirements for lipase, amylase, and magnesium	• Clarification requested by study team. • Clarification to fix discrepancy – screening chemistry panel does not include lipase, amylase, or magnesium
3.2.24 (Exclusion Criteria)	Excluded patients with hypertension (>150/90) and cardiac arrhythmia	No longer excludes cardiac arrhythmia and removes numerical value for hypertension.	PI determined that these exclusion criteria were not clinically relevant or necessary.
4.1 (Overview); 4.2.2 (Nivolumab); 5.0 (Study Procedures #10)	Nivolumab was to be given over 30 minutes with a window of ±5 minutes	The window for nivolumab infusion has been extended to -5 minutes / +15 minutes	BMS approved this extension in order to allow greater flexibility in infusion times.
4.3.1.1 (Grade ≥3 non-hematological toxicity)	Grade ≥ 3 metabolic toxicities unable to be corrected within 24 hours were considered dose-limiting	Adds an exception if patient had metabolic abnormalities at baseline. Also adds: "Other Grade 3 lab abnormalities will only be considered a DLT if they do not resolve within 2 weeks"	Clarifications. Patients with metabolic abnormalities at baseline are allowed more flexibility. Grade 3 lab abnormalities were not previously accounted for outside of metabolic abnormalities
4.3.1.1 (Grade ≥3 non-hematological toxicity); 4.4.1 (Dosing delays)	Dose delays and DLT's were to take place for any bilirubin abnormality ≥Grade 3	Grade 3 bilirubin ≤3.5mg/dL is not considered dose limiting and does not require delay during Cycle 1. However, if bilirubin worsens after the first dose of nivolumab a delay in dosing may be warranted per physician discretion.	Patients often experience elevated bilirubin as a result of Y-90; a cut-off of 3.5mg/dL is felt to be appropriate during cycle 1, with criteria being more strict thereafter (Grade 3: >3.0mg/dL requires delay)
4.4.1 (Dosing delays)	Patients were allowed to delay nivolumab by up to 14 days.	Adds an exception for patients who undergo prolonged steroid tapers to manage drug-related AE's, who can be delayed up to 6 weeks	Clarification of discrepancy in section 4.4.3
4.4.1 (Dosing delays)	Nivolumab should be delayed until resolution to ≤Grade 1 If baseline AST, ALT, or bilirubin is within Grade 1	Nivolumab should be delayed until resolution to ≤Grade 1 **<u>or baseline</u>** If baseline AST, ALT, or bilirubin is within Grade 1 **<u>or 2</u>**	To account for discrepancies in protocol eligibility and patients with baseline abnormalities.

	toxicity range, delay dosing for drug-related Grade 3 toxicity	toxicity range, delay dosing for drug-related Grade 3 toxicity	
4.4.4 (Treatment with nivolumab beyond progression)	"Subjects must provide separate consent to continue treatment despite radiological scans indicating PD. Separate consent must be provided when progression is first detected."	Removes statement for treatment beyond progression requiring a separate consent	To fix discrepancy. Separate consent is not necessary, and there is no such consent available.
5.0 (Study Procedures #11, #12)	n/a	Expands on correlative details: to be collected in a 10mL NaHep tube every 16 weeks (**4 cycles**) starting with C11D1, and references lab manual	Clarifications for easier referencing
7.2.9 (Abnormal Laboratory Values)	Listed conditions for documenting abnormal labs as adverse events.	Removes conditions and specifies that **all** lab abnormalities should documented as AE's.	To align with Northwestern University policies to record all lab abnormalities.
10.2 (Data Analyses Plans); References	n/a	Adds specific plans and references for analyzing response (ORR, CBR), PFS, adverse events, and exploratory objectives.	Elaboration of statistical plans for clarity.
Amendment 3 – February 6th, 2018			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Study Schema; 4.8 (Duration of Follow Up); 5.0 (Study Procedures #14)	Discrepancies in follow-up timing: Schema says to follow up every 6 months for 2 years from treatment discontinuation. Other sections only require follow-up for 24 weeks from start of treatment.	Updates protocol to require both. If a patient discontinues treatment prior to 24 weeks (6 cycles), patient will be followed for survival every 2 weeks up to 24 weeks from starting treatment. Patients will then be followed for survival every 6 months for 2 years.	Clarification for consistency.
3.1.2 (Inclusion Criteria); 6.3.1 (Definitions)	n/a	Adds note: "For patients with infiltrative disease, evaluable disease needs to be confirmed by pathology if RECIST measurements cannot be made."	Clarification to allow for patients with infiltrative disease where lesions are not measurable but still evaluable as HCC.
4.1 (Overview of Treatment Plan); 4.7 (Duration of Therapy)	Patients were to receive nivolumab 4 weeks after Y-90 administration	Clarifies that 4-6 weeks are allowed between Y-90 and nivolumab administration	Clarification to address discrepancy
4.1 (Overview of Treatment Plan); 4.7 (Duration of Therapy)	Y-90 was to be given one time with a brief note stating it could be repeated if needed.	Adds clarifying note: "Repeat therapy to the treated lesion or additional untreated lesions may be warranted. If a patient	Clarification – p

		requires additional Y-90 after starting nivolumab treatment, it may be given once approval from the interventional radiologist and treating physician has been confirmed. In such cases, nivolumab should be held for 14 days prior to administering Y-90. Nivolumab can be resumed within 14 days after receiving additional Y-90, but can be delayed for up to 6 weeks if needed."	
4.3 (Phase I Dose Escalation); 4.4.3 (Treatment Discontinuation Criteria); 7.3 (Adverse Event Reporting)	Referenced DMC (Data Monitoring Committee)	Updates to DSMC (Data and Safety Monitoring Committee)	Updated to reflect new internal policies
4.4.1 (Dosing Delays)	Nivolumab dosing delays up to 14 days were permitted with a 6 week exception in the case of prolonged steroid tapers	Updated to state that nivolumab dosing may be delayed up to 6 weeks in general.	Clarification to address discrepancy throughout protocol.
4.4.4 (Treatment with nivolumab beyond progression)	Nivolumab treatment was to be discontinued in the case of confirmed PD (confirmed by repeat evaluation 4 weeks after initial suspicion)	Treatment should be discontinued in the case of confirmed PD **without clinical benefit**. Adds a stipulation that if a patient with confirmed PD is still receiving clinical benefit in the investigator's opinion, study drug may be continued after discussion and agreement between the treating physician and PI.	
4.7 (Duration of Therapy); 6.3 (Secondary Endpoints)	Patients were to have scans every 8 weeks	Patients will have scans every 8 weeks (2 cycles) for the first 13 months, and every 12 weeks (3 cycles) thereafter.	To address discrepancy throughout protocol. Scans will move to q3months after one year of treatment.
5.0 (Study Procedures)	Imaging will occur every 3 cycles with no window listed	Adds a window of ±7 days	Clarification
6.1 (Definitions)	Listed scan frequency in terms of weeks (every 8 weeks for 13 months, then every 12 weeks thereafter), and did not list screening or prior to nivolumab	Lists scan frequency in terms of cycles. Adds the scan at screening and within 7 days prior to starting nivolumab.	Clarifications for consistency.
8.2.4 (Storage and Stability);	n/a	Replaces language with internal nivolumab template language (same content)	For consistency with other protocols involving nivolumab

8.2.6 (Preparation)			
8.2.9 (Availability & Supply)	Did not specify timing for drug re-supply requests	Replaces language with internal nivolumab template language. Drug re-supply should be submitted 10 business days before the delivery date	Updated for accuracy per BMS
8.2.12 (Return & Retention of Study Drug)	n/a	Updates table to reflect accurate packaging of nivolumab product	Clarification
Appendix 2	n/a	Adds timeframe of contraception requirements for both females (5 months) and males (7 months) after the last dose of nivolumab	To align with BMS template and requirements
Appendix 3	Contained outdated AE Management Algorithms. Specific outdated parameters include: Hepatic: • Discontinue for AST/ALT >5xULN **and/or** Tbili >3xULN Pulmonary (G3-4): • Includes example immunosuppression Renal (G2-3): • "Consider renal biopsy" Skin (G3-4): • n/a	Updates AE Management Algorithms to align with nivolumab IB v16. Specific changes to AE management include: Hepatic: • Discontinue for AST/ALT > 5xULN **or** Tbili > 3xULN Pulmonary (G3-4): • Removes examples of immunosuppression Renal (G2-3): • "Consider renal biopsy with nephrology consult" Skin (G3-4): • Adds footnote: "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."	Updated per BMS for consistency with new nivolumab IB v16 and additional or clarified safety measures.

Amendment 4 – September 26th, 2018
Approved by Scientific Review Committee: 10/31/2018

Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Cover Page	Listed Northwestern's Clinical **Research** Office as coordinating center	Updates to Clinical **Trials** Office	To align with internal administrative changes
Study Schema; Study Summary; 4.1 (Overview); 4.2 (Treatment Administration); 4.7 (Duration of Therapy); 5.0	Nivolumab treatment was planned to start **4 weeks** after Y-90 administration. A delay of **6 weeks** will be permitted in case of toxicity.	Nivolumab treatment will now start **7-14 days** after Y-90 administration. A delay of **4 weeks** will be permitted in case of toxicity. Also applies to cases where Y-90 is	Shortening the window allows for patients to be treated sooner in a setting where treatment is needed somewhat urgently. In patients treated so far, lymphopenia has not been an issue which was the initial reason for the 4-week treatment delay. The new of window of 7-14

(Study Procedures, #10)		repeated during the study.	days is sufficient to account for generalized fatigue that may occur with Y-90 and given the short half-life of Y-90, it is out of the system.
Study Schema; 4.2 (Treatment Administration); 5.0 (Study Procedures, #3); 6.1 (Definitions); 6.3 (Secondary Endpoints);	Scans were to take place "**within 7 days prior to starting nivolumab**"	Scans will take place "**21-28 days after Y-90 administration**"	To align with new, shorter window between Y-90 and nivolumab. Scans will still occur the same amount of time after Y-90, which falls after starting nivolumab
5.0 (Study Procedures, #6)	Chemistry panel required within 14 day of registration	Required within 14 days prior to registration	Clarification of ambiguous language
6.1 (Definitions)	Includes scan timing of every 8 weeks	Removes first paragraph with scan timing	Language was redundant and inaccurate
Amendment 5 – February 8, 2019 *Approved by Scientific Review Committee: 02/08/2019*			
Section(s) Affected	***Prior Version***	***Amendment 5 Changes***	***Rationale***
8.2.6 (Preparation)	Listed detailed instructions for preparing nivolumab	Removes specific instructions and instead refers to most recent nivolumab investigator's brochure	BMS request; removing specific details allows for variance if needed and ensures the most recent IB is always followed
8.2.9 (Availability and Supply)	Specified that nivolumab comes cartons of 5 or 10 mL	Removes details about carton sizes	BMS request; removed unnecessary details in case of variance
8.2.11 (Return & Retention of Study Drug)	Included a column for secondary packaging details (5-10 vails per carton)_	Removes details about secondary packaging	BMS request; removed unnecessary details in case of variance
Amendment 6 – April 10, 2019			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
4.1.0 (Patient Replacement)	Stated that patients who cannot start nivolumab within 6 weeks of Y-90 treatment may be replaced.	States that patients who cannot start nivolumab within 4 weeks of Y-90 treatment may be replaced.	To correct discrepancy; language now aligns with other sections of the protocol which state that patients must start nivolumab within 4 weeks of Y-90 treatment.
Cover Page	Listed Alfred Rademaker as the biostatistician	Replaces Alfred Rademaker with Denise Scholtens	Administrative change to account for new biostatistician
Table of Contents	Listed incorrect page numbers	Corrects page numbers	Administrative update