Document Coversheet

Study Title:

A Phase Ib/ II Study of Sorafenib and Pembrolizumab in Advanced Hepatocellular Cancer (HCC)

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Confidentiality Statement

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1.0 Objectives

1.1 Primary Objective

- To assess the overall response rate (ORR) related to the combination of sorafenib + pembrolizumab in advanced hepatocellular carcinoma patients.

1.2 Secondary Objective

- To assess time to tumor progression in patients who received the combination therapy of sorafenib + pembrolizumab compared to historical data on sorafenib only treatment in patients with advanced hepatocellular carcinoma.

1.3 Exploratory Objectives

- To obtain data on changes in immune cell function and in the tumor microenvironment pre- and post-treatment to screen for potential biomarkers that may be able to predict clinical benefit.
- All patients will be followed for survival.

2.0 Background

Hepatocellular cancer (HCC) is a lethal malignancy and an increasing global health problem. With an estimated global incidence of 782,451 cases in 2012, it is the fifth-most common cancer and the sixth-most fatal.(1) HCC is a complex and heterogeneous tumor driven by angiogenesis and several genomic alterations including aberrant activation of signal transduction pathways such as EGFR, Ras/Erk, PI3K/mTOR and apoptotic signaling.(2)

2.1 Hepatocellular Carcinoma and Sorafenib

Sorafenib is a synthetic compound targeting growth signaling and angiogenesis. Sorafenib blocks the enzyme RAF kinase, a critical component of the RAF/MEK/ERK signaling pathway that controls cell division and proliferation. Sorafenib has an antiangiogenic effect by targeting vascular endothelial growth factor receptor-2/-3 (VEGFR-2/-3) and platelet derived growth factor receptor-beta (PDGRF-beta) tyrosine kinases, FLT3 Ret and c-Kit.

Targeting angiogenesis with agents such as the tyrosine kinase inhibitor sorafenib is now the standard of first line therapy for advanced HCC, but treatment is not curative and survival of these patients remains less than one year. Agents with a similar mechanism of action have not proven to be superior or more tolerable than sorafenib. There is a clear unmet urgent need for tolerable, effective therapies for advanced HCC.

2.2 Hepatocellular Carcinoma and Immune Dysfunction

Presently there are no validated biomarkers that predict response to sorafenib in HCC or other malignancies where the drug is approved for use.(3) As trial eligible patients are few, rationally designed, biomarker driven studies are urgently needed.

Since immune dysfunction from advanced cancer and hepatitis are hallmarks of HCC, new agents that target immune suppression are a major focus of HCC research. Studies from our laboratory on peripheral blood samples from HCC patients show that: (1) programmed cell death-1 (PD-1)+ T cell numbers and T cell PD-1 expression levels are elevated; (2) frequency of PD-1+ T cells and T cell PD-1 expression levels decreased in a patient with spontaneous HCC regression; (3) depletion of Tregs, MDSCs, and PD-1+ cells results in complete restoration of

HCC patient effector T cell granzyme B production in vitro.(4, 5) Others have shown that elevated cognate inhibitory molecule PD-1-ligand 1 (PD-L1) expression in HCC is associated with tumor aggressiveness and enhanced risk for postoperative recurrence.(6) Collectively, these observations support the rationale that immunotherapy may have therapeutic benefit in HCC.

Our laboratory has also studied whether sorafenib may impact the systemic immunological function in addition to its mechanism of action in the tumor and vasculature. Sorafenib targets multiple tyrosine kinase receptors, including Flt3 which is present on MDSC and Tregs.(7, 8) Multiple avenues for tumor-induced immunosuppression exist in HCC, including accumulation of MDSC and Tregs. Depletion or inhibition of these cells is considered an important clinical feature for successful immunotherapeutic treatment and we have determined that depletion of these immunosuppressive cells in vitro can restore important T cell effector functions. Importantly and relevant to the current application, our preliminary studies show evidence of decreased frequency of several immunosuppressive cells in vivo (including PD-1+ T cells) 4-6 weeks after sorafenib treatment in some but not all HCC patients. The decrease in PD-1+ T cell frequency following sorafenib therapy correlated strongly with longer patient survival.

Preliminary in vitro data indicate that the immunomodulatory effects of sorafenib are dose-dependent. Specifically, sorafenib at 10μM induced activation of nuclear factor of activated T cells (NFAT) NFAT1 and NFAT2 in CD4 and CD8 T cells. Of note, clinically achievable concentrations of sorafenib exceed 15μM. NFAT activation was associated with the gain of an anergic phenotype (gain of PD-1 expression, loss of CD25 expression in CD4 and CD8 T cells and loss of CD8 expression in effector cells). NFAT activation was irreversible upon SOR removal and occurred within a narrow window of activation (between 5 and 10μM), demonstrating the threshold of the immunosuppressive action is well above the reported IC50 of sorafenib. In addition to our work, other studies have shown that elevated programmed cell death 1 ligand 1 (PD-L1) expression in HCC is significantly associated with tumor aggressiveness and enhanced risk for postoperative recurrence.(6) Targeted blockade of the PD-L1/PD-1 pathway could facilitate hepatitis virus clearance.(9)

In a Phase 1/2 trial (LBA101) nivolumab another anti-PD-1 antibody showed safety in 47 patients and a response rate of 19%. Although 68% of those patients had received prior sorafenib, no difference was seen in benefit from anti-PD-1 therapy. Based on our work, prior SOR may influence immunosuppressive phenotype and impact patient outcomes.(10)

2.3 Pembrolizumab

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is approved in the US for the treatment of patients with advanced/ metastatic melanoma, NSCLC, and HNSCC.

To-date, pembrolizumab is being used as both a monotherapy, and in combination with other therapies, in more than 30 tumor types.

Preclinical Studies with Pembrolizumab

A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of pembrolizumab can be found in the Investigator's Brochure v11.

2.4 Correlative Studies

- **PD-L1/-L2 Expression**

The current understanding on whether PD-L1 and PD-L2 status is a biomarker of response is limited, as there are no published data on frequency of PD-L1/-L2 expression in western populations and there is no uniformly accepted readily available validated assay. To test the hypothesis that PDL-1/-L2 status correlates with outcome, pre-and post-treatment formalin-fixed, paraffin-embedded (FFPE) tissue will be evaluated using the validated assay by Merck. As ligand status was not tested in all patients in prior trials and, some PD-L1 / L2 + patients failed to respond, we as yet do not know if this should be an exclusion criterion. In patients whose tumors are PD-L1 / L2 positive before therapy commences and they do NOT respond to combination treatment, then an optional second biopsy will be performed to test our hypothesis that there may be a change in their PD-L1 / -L2 expression status.

- **Immune Biomarkers**

Determining immune marker changes that can predict clinical benefit and toxicities (as some of them may have an immune basis) would be valuable to the clinician. To this end we propose to address our hypothesis that sorafenib+anti-PD-1 treatment will diminish checkpoint blockade and the accumulation of immunosuppressive networks in advanced stage HCC patients and thereby restore beneficial cytotoxic anti-tumor function in effector T cells. We will assess the alteration in the frequency and phenotype of immunosuppressive cells prior to treatment and, importantly, at three additional time points after commencement of the combination. In addition, the activity of the NFAT transcription factor which regulates PD-1 expression in these cells will be assessed. A longitudinal study of this nature is ideal to determine the kinetics and maintenance of sorafenib and anti-PD1 mediated immunomodulation.

Baseline levels of immunosuppressive cells and the functional activity of effector T cells as measured by NFAT activity, proliferative capacity and IFN-gamma and granzyme B production will be correlated with OS to determine whether these could serve as biomarkers and identify patients most likely to benefit from the combination therapy.

- **Immune-Mediated Adverse Events**:

A number of serious AEs observed with pembrolizumab are immune-mediated pneumonitis, thyroiditis, renal insufficiency and transaminitis, and many of these are also seen with sorafenib therapy, although the mechanism for these effects remains unknown. We propose to assess TSH and anti-thyroid antibodies at baseline and while patients are on therapy and correlate them with immune suppression.

- **Immunomodulatory Effects of Sorafenib/Pembrolizumab:**

Chronic hepatitis B and C virus infection are known risk factors for the development of cirrhosis and HCC. Since immune modulation could affect viral replication; resulting in potential liver function abnormalities or radiographic changes in the liver, viral titers for Hepatitis B and Hepatitis C (Hepatitis B Surface Antigen (HBsAg) and/or detectable HBV DNA and, Hepatitis C Antibody anti-HCV Ab) and detectable HCV RNA) will be measured at baseline (and as clinically indicated in patients who have elevated baseline titers) and at every 12 weeks from the start of combination therapy (C1D1) to assess possible effects on outcome.

- **Pharmacodynamic Markers**

In our studies we have seen PK/PD modelling of a pharmacodynamics marker solubleVEGFR2 along with drug exposure to predict clinical response in HCC patients receiving sunitinib and propose to test the hypothesis that this model could be used to predict response to this sorafenib combination.

2.5 Rationale

Inflammation and immune dysfunction are hallmarks of HCC. Our studies show that HCC is associated with increased levels of PD-1+ cells. Immunomodulation can partially restore effector function, suggesting that targeted blockade of PD-1 may be of clinical benefit in HCC. Importantly, the preliminary evidence that sorafenib dose-dependently affects PD-1 expression in T cells supports the concept of combining sorafenib with a PD-1 targeting drug. There remains a great need for rationally selected, noninvasive, prospectively validated biomarkers with the potential to provide mechanistic information on how the drug/combination worked or why it did not work. The studies we propose meet all these needs.

Pembrolizumab is a humanized IgG4 monoclonal antibody (mAb) which binds PD-1, and thus, inhibits cognate interaction with PD-L1 and PD-L2. PD-1 is an immune-checkpoint receptor expressed on T cells and high levels of PD-L1 expression are correlated with poor prognosis and survival in HCC. There is an urgent unmet need for novel therapies for patients with HCC that build on the backbone of the approved agent sorafenib.

Successful completion of this study will significantly impact the development of pembrolizumab, the field of HCC research and biomarker development in oncology as a whole. In addition to the much-needed clinical impact this combination will have, new knowledge on the immunomodulatory effects of sorafenib alone, and how anti-PD-1 therapy augments efficacy will be gained from the biomarker work. In oncology biomarker research, the paradigm has always been prediction of response to the therapy being studied: having a marker that would allow for rational selection or prediction of benefit of a combination therapy, would be a major paradigm shift.

3.0 Inclusion and Exclusion Criteria

To be included in this study, participants must meet the criteria listed in Section 3.1.

Participants will be excluded from this study following the criteria listed in Section 3.2.

3.1 Inclusion Criteria

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA

Participant Name: (Multi-site use participant initials): _____

Medical Record No.: (Multi-site use participant ID): _____

Title: A Phase Ib/ II Study of Sorafenib and Pembrolizumab in Advanced Hepatocellular Cancer (HCC).

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Age ≥ 18 years.	
☐	☐	☐	2. Participant must have histologically or radiographically confirmed HCC that is advanced or metastatic ***and if archival tissue is available***, have archival tissue submitted for PD-L1, PD-L2 testing.	
☐	☐	☐	3. Participants with measurable disease that has progressed are eligible if prior surgery or locoregional therapy occurred > 28 days prior to enrollment.	
☐	☐	☐	4. Have an ECOG Performance Status of 0-1 (Karnofsky ≥ 60%). Refer to Appendix B.	
☐	☐	☐	5. Child-Pugh Class-A liver function. Refer to Appendix C.	
☐	☐	☐	6. Have the following clinical laboratory values: • ANC ≥ 1,500/ mcL • Hemoglobin ≥ 8.5 g/dL • Platelets ≥ 75,000/ mcL • total bilirubin ≤ 2.0 mg/dL • AST and ALT ≤ 5 X ULN • Serum Creatinine ≤ 1.5 X ULN or Creatinine clearance > 50 mL/ minute if serum creatinine is elevated above 1.5 X ULN	
☐	☐	☐	7. Have measurable disease per RECIST 1.1 criteria present.	
☐	☐	☐	8. Ability to swallow and retain oral medication.	
☐	☐	☐	9. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	10. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	11. Participants with past or ongoing hepatitis C virus (HCV) infection will be eligible for the study. The treated participants must have completed their treatment at least 1 month prior to starting study intervention.	
☐	☐	☐	12. Participants with controlled hepatitis B will be eligible as long as they meet the following criteria: • Antiviral therapy for HBV must be given for at least 12 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Participants on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment. • Participants who are anti-HBc (+), negative for Hepatitis B surface antigen (HBsAg), and negative or positive for anti-HBs, and who have an HBV viral load under 100 IU/mL, do not require HBV anti-viral prophylaxis.	

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

3.2 Exclusion Criteria

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA

Participant Name: (Multi-site use participant initials): _____

Medical Record No.: (Multi-site use participant ID): _____

Title: A Phase Ib/ II Study of Sorafenib and Pembrolizumab in Advanced Hepatocellular Cancer (HCC).

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. One prior line of therapy that may include a PDL1 blocker allowed, no prior sorafenib or PD1 blocker allowed.	
☐	☐	☐	2. Participants who have had radiotherapy or chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.	
☐	☐	☐	3. Any evidence of bleeding diathesis (patients on therapeutic warfarin or heparin will be excluded).	
☐	☐	☐	4. Participants with a history of variceal bleed within 6 months prior to enrollment.	
☐	☐	☐	5. Known HIV-positive participants (even if on combination retrovirals, participant will be excluded because of the expected pharmacokinetic drug interactions and unknown safety of anti PD-1 therapy in that patient population).	
☐	☐	☐	6. Participants with chronic autoimmune disease.	
☐	☐	☐	7. Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.	
☐	☐	☐	8. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	9. Has known history of, or any evidence of active, non-infectious pneumonitis.	
☐	☐	☐	10. Pregnant or nursing female participants.	
☐	☐	☐	11. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	12. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	
☐	☐	☐	13. Received a live vaccine within 30 days prior to start of study treatment.	

Participant meets all entry criteria: ☐ Yes ☐ No

If "NO", do not enroll participant in study.

Investigator Signature: _____ Date: _____

Printed Name of Investigator: _____

3.3 Special Populations

The following special populations are excluded from this study:

- Cognitively impaired adults/adults with impaired decision-making capacity
- Individuals who are not yet adults (infants, children, teenagers)
- Prisoners
- Pregnant women

3.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this study

4.0 Local and Study-Wide Number of Subjects

A total of 41 participants will be accrued (with a maximum of n=27 evaluable for the primary endpoint) from multiple sites, including RPCI, will be enrolled. RPCI is expected to enroll 38 participants over a period of 5 years.

5.0 Local and Study-Wide Recruitment Methods

Participants will be identified/recruited/screened from patients at the GI clinic at RPCI and participating sites and from multi-disciplinary conference discussion.

6.0 Multi-Site Research

It is the responsibility of the principal Investigator to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
- All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Refer to Appendix A: Instructions for Multi-Site Studies

7.0 Study Timelines

A maximum of 41 participants at multiple sites, including RPCI will be enrolled. Accrual is expected to take 5 years, with follow-up for 12 months from the start of combination therapy. Upon completion of the 12-month follow-up period, patient survival status will be monitored every 6 months.

8.0 Study Endpoints

- The primary endpoint is the Overall Response Rate (ORR), defined as partial or complete response (per irRECIST) within 6 months of initiating combination therapy.
- The secondary endpoint is time to tumor progression (TTP), measured from the date of

study enrollment to the first observation of progressive disease.

- Exploratory endpoints: Pre-treatment levels of immunosuppressive cells and the functional activity of effector T cells will be compared to post-treatment blood and tumor samples and will be correlated with overall survival.

9.0 Design

This is an open-label, single arm, non-randomized, multi-center Phase Ib/II study of sorafenib when administered with pembrolizumab in patients with advanced hepatocellular carcinoma. The study will include an initial Phase Ib safety lead-in cohort of 6 patients.

Prior to starting on the combination therapy of sorafenib + pembrolizumab, patients will have completed initial treatment with sorafenib alone and must be stable on sorafenib (at least 200 mg BID for a minimum of 1 week) before the introduction of pembrolizumab. The sorafenib starting dose will be at the discretion of the treating physician based on clinical assessment of the patient.

All participants will sign an informed consent prior to any study-related tests. All participants will meet the inclusion and exclusion criteria summarized in Section 3.1 and 3.2.

9.1 Phase Ib/II

The first 6 patients who have completed at least 4 weeks of sorafenib-only treatment and begin the combination therapy (addition of pembrolizumab at a fixed dose of 200 mg Q3W) will comprise the Phase 1b safety lead-in. Patients who withdraw from the study prior to initiation of combination therapy (for reasons other than DLT) will be replaced.

Definition of Dose-Limiting Toxicity: A dose-limiting toxicity will be defined as any ≥ grade 3 clinically significant toxicity which is deemed possibly treatment related and occurs within the first cycle of combination therapy. Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE v4.0).

Patient data for the safety lead-in portion of the study will be discussed and monitored by The Early Phase Clinical Trials committee, which meets on a regular basis per the RPCI Data Safety Monitoring Plan.

After a minimum of 6 have completed at least one cycle of sorafenib + pembrolizumab, the study will be suspended, and the safety/tolerability of the combination will be examined. At that time, the study team will decide what action to take, e.g., continue the study as is, make changes to the study with regard to treatment or dose modifications, or discontinue the study.

- If ≥ 2 of these patients experience an unexpected, treatment related toxicity of grade ≥3 during the first cycle of combination therapy, the study will be stopped to reevaluate dosing. We anticipate that such limiting toxicities will be observed in ≤1 of the first 6 patients. All evaluable patients who receive the Phase 2 dose of pembrolizumab (200 mg Q3W) will be included in the Phase 2 study.

Once analysis is complete and a safe treatment plan has been established, the Phase II study will commence.

Patients who have toxicity during the first 3 weeks of combination therapy that appears to be attributed to sorafenib will have sorafenib dose reduced to 2 x 200 mg every other day, as was done in the SHARP study(11). We anticipate such dose modifications to be infrequent. Patients will be considered evaluable if they receive more than 75% of prescribed sorafenib dosing during

the first 3 weeks of combination therapy (a medication diary will be provided during this time to monitor participant compliance: see Appendix F). All toxicities will be assessed upon completion of the first 6 evaluable patients to see if any higher than anticipated occurrence of sorafenib toxicity is seen due to the addition of pembrolizumab.

The goal of the study is to evaluate efficacy of the combination therapy, therefore patients who are removed from the study prior to receiving the soraf+pembro combination treatment will be replaced. This includes replacing patients who do not tolerate sorafanib alone, as administered in the 1st 4 - 6 weeks of the treatment regimen. In addition, the following patients will be replaced:

- Patient withdraws consent
- Withdrawal from study due to toxicity,
- Withdrawal from study due to liver failure
- Patients who withdraw before the Week 12 (±1 week) response assessment (for reasons other than progression)

Patients who withdraw due to disease progression prior to the Week 12 (±1 week) response assessment of the combination therapy will not be replaced and will be counted as non-responders in the response rate calculations.

Patients who complete the 4-6 week initial treatment with sorafenib alone, and withdraw from the study after being treated with the combination therapy will not be replaced and will be counted as non-responders in the response rate calculations.

Patients will receive sorafenib + pembrolizumab until progression. If a patient discontinues either agent due to toxicity, they will still be able to stay on study until progression. Clinical benefit will be considered when making decision to stop therapy as radiographic reflection of true failure of this combination is still unknown.

Disease assessment (imaging) will be done every 6 weeks from the start of C1D1 combination therapy, with a confirmatory assessment no less than 6 weeks after an irPR or irCR or irPD. Therapy will be continued until the confirmatory scan, even if progression is noted on the Week 12 scan. After the 12-week scan disease assessment will be done every 9 weeks (±1 week). Note: Timing for assessing ORR in patients on immunotherapies is not clear. Disease stability is the commonly seen response to sorafenib alone. Allowing continuation until the confirmatory scan at Week 18, even if progression is seen, allows us to assess the true response to this novel combination.

10.0 Treatment

Dosing and Administration

1 cycle = 3 weeks of combination therapy

10.1 Sorafenib

During the first 4-6 weeks following enrollment (Days -28 to -1 or Days -42 to -1) patient will be on sorafenib alone.

The recommended daily dose of sorafenib is 800mg (2 x 200mg tablets taken twice daily) without food (at least 1 hour before or 2 hours after a meal.) However, the starting dose may be adjusted at the discretion of the treating physician based on clinical assessment of the patient

during screening with a minimum dose of sorafenib at 200mg BID.

All patients should report to clinic for toxicity evaluation 2 weeks after starting sorafenib.

NOTE: Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of sorafenib therapy. However, the sorafenib lead-in phase should not extend to greater than 6 weeks from the start of sorafenib to the start of pembrolizumab (For example: Patient develops toxicity 2 weeks after starting sorafenib, which requires a dose hold for 1 week, then re-starts sorafenib with a dose reduction. That patient must be stable on the new dose for at least 1 week before starting pembrolizumab. In this case, the sorafenib lead-in phase is 5 weeks which is in the acceptable window of 6 weeks from start of sorafenib to start of pembrolizumab). Patients will continue to take sorafenib (po), BID, during each 3-week cycle.

10.1.1 Dose Modifications for Suspected Adverse Drug Reactions

- Temporary interruption of sorafenib is recommended in patients undergoing major surgical procedures (refer to package insert).

10.1.2 Dose Modifications for Hepatic Impairment at Baseline

- Mild to moderate (Child-Pugh class A and B) impairment: No dosage adjustment is necessary.

***The following adjustments have also been reported*:**

Safety and pharmacokinetics were studied in varying degrees of hepatic dysfunction with the following empiric dose levels recommended based on patient tolerance (Miller, 2009) (12):

- *Mild hepatic dysfunction* (bilirubin >1 to ≤1.5 times ULN and/or AST >ULN):
    - 400 mg twice daily
- *Moderate hepatic dysfunction* (bilirubin >1.5 to ≤3 times ULN; any AST):
    - 200 mg twice daily
- *Severe hepatic dysfunction:*
    - Bilirubin >3 to 10 x ULN (any AST): 200 mg every 3 days was not tolerated
    - Albumin <2.5 g/dL (any bilirubin and any AST): 200 mg once daily

Drug-induced liver injury during treatment:

- Unexplained (e.g., not due to viral hepatitis or progressive underlying malignancy) significantly increased transaminases:
    - Discontinue treatment

10.1.3 Suggested Dose Modifications for Dermatologic Toxicities

- If Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, discontinue therapy.

Refer to Appendix I for suggested dose modifications for dermatologic toxicities in patients with hepatocellular carcinoma.

10.2 Pembrolizumab

Starting with Cycle 1, treatment with pembrolizumab will be administered on Day 1 of each 3-week treatment cycle, after all procedures and assessments have been completed (as detailed on the Schedule of Procedures: Appendix E).

Pembrolizumab will be administered at a fixed dose of 200 mg, using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and + 10 minutes is permitted (i.e., infusion time is 30 minutes -5 min and + 10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

Toxicities will be assessed upon completion of the first 6 evaluable patients to see if any higher than anticipated occurrence of sorafenib toxicity is seen due to the addition of pembrolizumab.

Reported adverse events (AEs) and potential risks are described in Section 13. Appropriate dose modifications are described in Table 1 (see **Appendix F**).

Pembrolizumab Dose Modifications

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 1 (**Appendix F**).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Participants should be placed back on study therapy within 3 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

Management and dose modifications associated with the above AEs are outlined in **Appendix F**.

10.3 General Concomitant Medications

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 trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the primary investigator and/or the subject's primary physician.

Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a patient’s welfare 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 all 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 within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications

administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 17.0.

Prohibited Concomitant Medications

Patients are prohibited from receiving the following therapies during the Baseline and Treatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - *Note*: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Anti-viral medications for treatment of hepatitis C while receiving combination therapy
    - *Note*: Patients may continue on anti-viral medication for hepatitis C during the 4-week sorafenib-only therapy.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved.

Patients 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. Patients may receive other medications that the investigator deems to be medically necessary.

10.4 Rescue Medications & Supportive Care

10.4.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not

need to follow the treatment guidance (as outlined below). Refer to **Appendix F** for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Pneumonitis:

- For Grade 2 events, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For Grade 3-4 events, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

Diarrhea/Colitis:

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For Grade 2 diarrhea/colitis, administer oral corticosteroids.
- For Grade 3 or 4 diarrhea/ colitis, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

Hypophysitis:

- For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones

may be required as the steroid dose is tapered.

Hyperthyroidism or Hypothyroidism:

Thyroid disorders can occur at any time during treatment: Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

Hepatic:

In addition to overdose (see Section 32.1.6), hepatic events of clinical interest will include any of the following events (see Appendix J: Guidance for Diagnosis and Management of Hepatic Events of Clinical Interest). All of these events will require holding study treatment and, notification to Merck within 2 days.

Refer to Section 17.4 for reporting guidelines and the definition of hepatic events of clinical interest.

Renal Failure or Nephritis:

- For Grade 2 events, treat with corticosteroids.
- For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

Management of Infusion Reactions: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 2 (Appendix G) shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

10.5 Diet/ Activity/ Other Considerations

10.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

10.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if

pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) Post-menopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR,

(2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) Has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- Intrauterine device (IUD)
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the participant's preferred and usual lifestyle and if considered

acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for participants participating at sites in this country/region.

Participants should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study participants of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

10.5.3 Use in Pregnancy

If a participant inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Roswell Park Compliance and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Roswell Park Compliance and to Merck and followed as described above and in Section 17.4.

10.6 Duration of Treatment

Participants may remain on study and continue to receive treatment in the absence of disease progression, unacceptable toxicity and withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime, participant withdraws from study or, death; whichever occurs first.

If patients have been on pembrolizumab for over 24 months the PI can decide if the patient can come off pembrolizumab and continue on with sorafenib treatment.

11.0 Procedures Involved

Eligibility of each participant will be established prior to enrollment.

Informed consent MUST be completed prior to receiving any study related procedures.

The schedule of procedures and observations for this study is summarized in Appendix E: Schedule of Procedures.

11.1 Pharmacokinetic Blood Sample Collection and Processing

Blood samples for Pharmacokinetic analysis (plasma) of sorafenib levels will be collected via venipuncture using 1, 10 mL green-top tube.

*Note: Patients to be advised to hold morning dose of sorafenib until after PK blood draw.

The time of two doses of Sorafenib prior to the draw will need to be entered on the specimen requisition form for PK analysis, e.g., Cycle 3 Day 21, enter the time. Sorafenib was taken in the am and pm prior to the Cycle 4 Day 1 PK draw.

Pharmacokinetic sample collection will be obtained on:

- Cycle 1-Day 1 (for sorafenib steady state PK), prior to sorafenib and IV pembrolizumab
- Cycle 4-Day 1 prior to sorafenib and IV pembrolizumab and Day 1 of every subsequent 4 cycles (prior to sorafenib and IV pembrolizumab) until end of study
- End of study treatment

The whole blood samples should be maintained on ice and sent to the Hematological Procurement Facility for processing for plasma: Centrifuge whole blood as soon as possible, or within 30 minutes, at 4°C using a refrigerated centrifuge at approximately 3000 rpm for 10 minutes.

Plasma will be aliquoted into (2) cryovials per time-point. The screw cap polypropylene cryogenic tube will be labeled with the participant's clinical study number and patient study ID, protocol time point, dose, and protocol day and time. The label for each participant's sample will be supplied by each site. The samples will immediately be frozen at -80ºC or below. At the completion of the study, all samples will be shipped on dry ice to the BMPK core facility at Roswell Park for analysis:

Roswell Park Cancer Institute
Bioanalytics, Metabolomics & Pharmacokinetics (BMPK) Core Facility
Center for Genetics and Pharmacology, Room L1-140
Refer to Study Number– I 35316
Elm & Carlton Streets
Buffalo, New York 14263
PKPDCore@RoswellPark.org

For additional information regarding the handling of pharmacokinetic samples please contact RPCI's Bioanalytics, Metabolomics & Pharmacokinetics Core Facility laboratory at 716-845-3313 (Tel) or 716-845-1579 (Fax). Or email Katherine.Enderle@RoswellPark.org and Krystin.Mantione@RoswellPark.org.

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), the clinical study number, protocol time point, dose, and protocol day and time. The samples will immediately be frozen at -80ºC or below. Samples are to be stored and batch shipped to the RPCI BMPK Core Facility, on dry ice, at the completion of the study.

Note: Samples cannot be frozen in glass tubes – cryogenic vials must be used.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri.

NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

11.2 Correlative Studies Blood Sample Collection

11.2.1 Immune Biomarker Blood Samples:

Blood samples for immune biomarker analysis (phenotyping ELISA, CYTOF) will be collected via venipuncture using 3, 10 mL green-top tubes and 2, 10 mL lavender -top tube. Samples will be processed and analyzed at RPCI's Immune Analysis Facility.

In addition, 1, 10 mL STRECK Cell-Free DNA BCT® tube for plasma for future CT-DNA studies will also be collected at the same time points as for immune biomarker samples.

***Note*: ALL blood samples will be sent at ambient temperature to the RPCI Immune Analysis Facility (IAF).** Samples for CT-DNA analysis (STRECK tube) will be sent (immediately after sample log-in) from RPCI's IAF to RPCI's Genomics Shared Resource facility (c/o Prashant Singh PhD, Assistant Director Genomics Shared Resource, CGP & COE L1-210, 716-845-3869 (office),email: Prashant.Singh@RoswellPark.org) for processing, storage and analysis upon study termination.

Note: Roswell Park Patients- notification of sample collection must be noted on public calendar for Immune Analysis prior to date of collection.

Whole blood sample collection will be obtained at:

- Baseline
- Cycle 1-Day 1 (prior to start of sorafenib and IV pembrolizumab)
- Cycle 4-Day 1 prior to sorafenib and IV pembrolizumab ***and*** Day 1 of every subsequent 4 cycles (prior to sorafenib and IV pembrolizumab) until end of study
- End of Study (or at time of progression; or any other reason that requires study termination, whichever occurs sooner)

All of the above blood samples will be sent at ambient temperature to the Center for Immunotherapy at Roswell Park Cancer Institute:

Roswell Park Cancer Institute
Immune Analysis Facility Shared Resource
Cancer Cell Center, 4th Floor, Room 416
Attn: Study# I 35316
Elm and Carlton Streets
Buffalo, NY 14263
Telephone #: (716) 845-1300, ext. 6555
Courtney.Ryan@RoswellPark.org

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection and processing. The tubes will be labeled with the Subject ID # (unique to Network patients), clinical study number, protocol time point, dose, and protocol day and time***. Samples are to be shipped for OVERNIGHT delivery, at ambient temperature to:***

Roswell Park Cancer Institute
Immune Analysis Facility Shared Resource
Cancer Cell Center, 4th Floor, Room 416
Attn: Study# I 35316
Elm and Carlton Streets
Buffalo, NY 14263
Telephone #: (716) 845-1300, ext. 6555
Courtney.Ryan@RoswellPark.org

Please send an email, once a sample has been shipped, that includes the tracking number to Courtney.Ryan@RoswellPark.org.

Samples will be shipped via Fed Express Overnight with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

11.2.2 NFAT Analysis Blood Samples:

Blood samples for NFAT analysis will be collected via venipuncture using 1, 10 mL green-top tube.

Whole blood sample collection will be obtained at:

- Baseline
- Cycle 1-Day 1 (prior to start of sorafenib and IV pembrolizumab)
- Cycle 4-Day 1 prior to sorafenib and IV pembrolizumab ***and*** Day 1 of every subsequent 4 cycles (prior to sorafenib and IV pembrolizumab) until end of study
- End of Study (or at time of progression; or any other reason that requires study termination, whichever occurs sooner)

Samples will be sent at ambient temperature to RPCI's Flow Cytometry Department (pneumatic tube station #621) for processing and analysis:

Note: Include specimen tracking form with protocol kit and notify receiving lab.

Roswell Park Cancer Center
Cancer Cell Center, Room C308 & C312
Attn: Dr. Hans Minderman
Attn: Study #: I 35316
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845-3528

Hans.Minderman@RoswellPark.org and Orla.Maguire@RoswellPark.org.

For additional information regarding the handling of samples please contact Dr. Hans Minderman, Assistant Director Flow Cytometry Research Services at 716-845-1162 (office) or 716-845-3470 (lab) or by email: Hans.Minderman@RoswellPark.org

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection and processing. The tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. ***Samples are to be shipped, packed with cold packs, for OVERNIGHT delivery to:***

Roswell Park Cancer Center
Cancer Cell Center, Room C308 & C312
Attn: Dr. Hans Minderman, Study #: I 35316
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845-3528

Please send an email, once a sample has been shipped, that includes the tracking number to Hans.Minderman@RoswellPark.org

Samples will be shipped via Fed Express Overnight with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

11.3 Pathology

11.3.1 Pre-treatment Formalin-Fixed Paraffin-Embedded (FFPE) Biopsy Samples

The following sections of tissue from the most recent (or available) liver biopsy (neoplastic tissue) that exists in the Paraffin Archive in the Department of Pathology (or outside institution) will be collected if available:

1. Eight unstained sections cut at 4 microns on plus glass slides:
    a. Four (4) for PD-L1/-L2 testing (RPCI Pathology Resource Network for analysis)
    b. Four (4) for Nanostring analysis (RPCI Genomics Shared Resource for analysis).
2. One H&E stained section (RPCI Pathology Resource Network).

3. Five (5) unstained sections cut at 4-micron thickness on Fisher ProbeOn Plus slides for PD-L1 testing (QualTek). Refer to *QualTek MISP Sample Handling Manual* for detailed processing and shipping instructions. **NOTE**: **ALL SITES will send these samples DIRECTLY to QualTek.**

NOTE: If a fresh pre-treatment liver biopsy is obtained as a part of standard of care:

- *1 core*: Fixed in formalin for 8 to 24 hours and processed as paraffin embedded block (FFPE block)

- Section as per Section 11.3.1 prior to shipment

For **External (Network) Sites**, the de-identified tissue samples should be labeled using study-specific subject ID number and tissue accession#. All of the above slides and/or block (*except the slides to QualTek)* are to be sent to RPCI Correlative Science Pathology Office (Attn: Protocol Lab Team). Please ship slides ambient (or with a refrigerated gel pack when temperatures will exceed 24°C). The **shipping label** should read as follows:

Roswell Park Cancer Institute
Elm & Carlton Streets
Correlative Science Pathology Office
Gratwick Basic Science Building, S-636
Attn: Protocol Lab Team, I 35316 Samples
Buffalo, NY 14263
(716) 845-8917

Email: CRSLabPathTeam@RoswellPark.org

Samples for NanoString analysis (4 unstained slides) will be batched and sent from the CSPO to Dr. Prashant Singh, Assistant Director Genomics Shared Resource, CGP & COE L1-210, for analysis. For additional information regarding the handling of samples please contact Dr. Prashant Singh at 716-845-3869 (office) or email Prashant.Singh@RoswellPark.org.

Samples for PL-L1/-L2 testing (4 unstained slides and 1 H&E) will be batched and sent from the CSPO to Cassandra Whalen, GBSB-S608, for analysis. For additional information regarding the handling of samples please contact Cassandra Whalen at 716-845-1515 (office) or email Cassandra.Whalen@RoswellPark.org.

NOTE: Samples for PD-L1 only testing (5 unstained sections cut at 4-micron thickness on Fisher ProbeOn Plus slides) should be sent DIRECTLY to QualTek Molecular Laboratories if available:

QualTek Molecular Laboratories
300 Pheasant Run
Newtown, PA 18940
Phone: 215-504-7402
Fax: 805-830-6379
Email: MISPsamples@qmlabs.com

11.3.2 Post-treatment Liver Biopsy Samples

PD-L1,-L2 positive patients will be asked to undergo an ***optional***, post-treatment biopsy for PD-L1,-L2 at the end of treatment, to assess any change in ligand status (6 responders to treatment and 6 non-responders).

Optional Post-Treatment Biopsy Tissue Requirements

Four (4) cores each from tumor and adjacent normal liver tissue:

- *3 cores each of tumor and adjacent normal liver tissue* (each core to be stored separately): Snap frozen in cryovials in liquid nitrogen for subsequent RNA/DNA analysis (2 cores each) and future biomarker studies (1 core each).
- *1 core each of tumor and adjacent normal liver tissue*: Fixed in formalin for 8 to 24 hours and processed into separate paraffin embedded blocks (FFPE blocks) for subsequent CYTOF and PD-L1/L2 analysis

All of the above tissue samples will be sent to RPCI Correlative Science Pathology Office (Attn: Protocol Lab Team). The shipping label should read as follows:

Roswell Park Cancer Institute
Elm & Carlton Streets
Correlative Science Pathology Office
Gratwick Basic Science Building, S-636
Attn: Protocol Lab Team, I 35316 Samples
Buffalo, NY 14263
(716) 845-8917

Email: CRSLabPathTeam@RoswellPark.org

For External (Network) Sites: Follow directions above for sample collection, processing and, shipping. The cryogenic tubes FFPE blocks are to be labeled with the clinical study number and patient study ID, collection date/study cycle and day and, "Tumor" or "Adjacent Normal Liver". Snap-frozen samples are to be batch-shipped frozen, on dry ice. FFPE blocks may be batch-shipped at ambient temperature (please include refrigerated gel pack when temperatures will exceed 24°C).

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

11.3.3 PD-L1/L2 and CYTOF analysis of Post-treatment Formalin-Fixed Paraffin-Embedded (FFPE) Biopsy Samples

At RPCI, the following sections will be prepared from the post-treatment biopsy FFPE blocks:

1. Eight unstained sections of each sample (tumor and adjacent normal liver) cut at 4 microns on plus glass slides (4 of each sample for PD-L1/-L2 testing to RPCI Pathology Resource Network for analysis, 4 of each sample for Nanostring analysis).
2. Two H&E stained sections (1 from each block).

3. Five (5) unstained sections (tumor tissue only) cut at 4-micron thickness on Fisher ProbeOn Plus slides for PD-L1 testing (QualTek). Refer to *QualTek MISP Sample Handling Manual* for detailed processing and shipping instructions.

Once all sections from the FFPE core have been taken, the remainder of the blocks will be sent to RPCI Immune Analysis facility (c/o Courtney Ryan) for CYTOF analysis.

Samples for NanoString analysis (FFPE sections) and the snap-frozen samples for RNA/DNA analysis and biomarker analysis will be sent from the CSPO to Dr. Prashant Singh, Assistant Director Genomics Shared Resource, CGP & COE L1-210, for analysis. For additional information regarding the handling of samples please contact Dr. Prashant Singh at 716-845-3869 (office) or email Prashant.Singh@RoswellPark.org

Samples for PL-L1/-L2 testing (4 unstained slides of each sample and 1 H&E of each sample) will be sent to RPCI's Core Pathology Laboratory for analysis.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

12.0 Withdrawal of Subjects

12.1 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
- The Investigator may discontinue a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal

13.0 Risks to Subjects

13.1 Pembrolizumab

The most frequently reported adverse events in patients treated with pembrolizumab (reported in

≥ 20% of patients) are: fatigue (37.3%), nausea (24.5%), decreased appetite (22.5%), cough (22%) and, pruritis (20.1%).

The following AEs were reported in 10% - 20% of patients: dyspnea, arthralgia, rash, constipation, headache, vomiting, asthenia, pyrexia, back pain, anemia, and peripheral edema.

The most frequently reported SAEs were pneumonia (3%), pleural effusion (1.7%), pneumonitis (1.6%), dyspnea (1.6%), and pulmonary embolism (1.5%).

In addition, the following serious, life-threatening adverse effects have been reported:

- Myocarditis: a complication of therapy reported to lead to death in less than 3 patients out of 1000 who receive the drug.
- Stevens-Johnson Syndrome
- Toxic Epidermal Necrolysis (TEN)

13.2 Sorafenib

The most common adverse reactions (≥ 20%) related to sorafenib in patients with HCC are diarrhea, fatigue, infection, alopecia, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains, hypertension, and hemorrhage.

14.0 Potential Benefits to Subjects

Studies of novel therapies for HCC which have been based on preclinical studies in mouse models have not translated into meaningful clinical benefit in patients. The strength of this study is the high translational value of studies performed in human T cells from advanced HCC patients.

In our laboratory, we are currently testing the hypothesis that sorafenib treatment in patients with advanced HCC decreases immunosuppressive networks and thus increases the cytotoxic activity of the patient's own effector T cells. This may be very important, as it is poorly studied and its mechanism of action is unknown. Results from our laboratory show that PD-1 levels are high in all advanced HCC patients, compared to normals.(4) In recently completed work (unpublished data) in HCC patients receiving sorafenib therapy, when the percentage of PD-1+ cells and the PD-1 expression levels remain unchanged patients do poorly (mean survival 4.7 months). In striking contrast, HCC patients with a statistically significant decline in the percentage of PD-1+ cells and the PD-1 levels following sorafenib therapy had the highest mean survival of 18.3 months. A decrease in PD-1 levels was also seen in one patient with spontaneous regression of HCC, which is a rare but well described occurrence in the literature and, further supports the hypothesis that targeting PD-1 may have therapeutic benefit.

Thus, our results demonstrate that in a subset of patients, sorafenib therapy alone results in decreased numbers and level of expression of PD-1 and results in clinical benefit. These highly novel findings support our hypothesis that combining SOR with anti-PD-1 therapy may result in additional (additive or synergistic) significant clinical benefit in patients with advanced HCC.

15.0 Data and Specimen Banking

NA

16.0 Measurement of Effect

16.1 Solid Tumors

Tumor response will be assessed at Week 6 (± 1 week) and Week 12 (±1 week) of combination therapy, and every subsequent 9 weeks (± 1 week) thereafter by immune-related response criteria (irRECIST) (13, 14). Conventional RECIST 1.1 (15) will also be documented during the trial, however RECIST 1.1 will not be used to determine disease progression, as it has been shown in prior clinical trials using pembrolizumab in large number of patients, that conventional RECIST might underestimate the benefit of pembrolizumab in approximately 15% of patients; thus using irRECIST could permit treatment beyond initial progression per RECIST v1.1 and prevent premature cessation of treatment.(14, 16, 17)

The irRECIST will be used for tumor response assessment at time of continuing review and will be used for IRB reporting and formal analysis.

Refer to Appendix H for a summary of tumor response assessment using irRECIST criteria.

17.0 Safety Evaluation

17.1 Adverse Events

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

- **Diagnosis Versus Signs and Symptoms**
  If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.
- **Adverse Events Occurring Secondary to Other Events**
  In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.
  However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

- **Abnormal Laboratory Values**
  Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

  If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

  If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia".

  Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.
- **Preexisting Medical Conditions (Baseline Conditions)**
  A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2 Grading and Reporting Adverse Events

Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot

be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

Reporting Adverse Events: Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Guidelines for Routine Adverse Event Reporting for Pilot, Phase 2, and Phase 3 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

17.3 Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of the investigator results in ANY of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

Reporting Serious Adverse Events

- The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.
- SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229, use Merck provided Global Safety Intake Form and Merck Fax Cover Sheet.
- SAEs occurring after the 90 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.
- SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to **Section 17.8** for details on reporting Unanticipated Problems.
- External (Network) Sites: see Appendix A for reporting requirement Section 7.

17.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to Roswell Park and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229).

For the time period beginning with the start of therapy until the safety follow-up visit, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to Roswell Park and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 32.1.6, that is not associated with clinical symptoms or abnormal laboratory results.

2. Hepatic Events of Clinical Interest include any of the following events. All of these events will require holding study treatment until the patient no longer meets the criteria listed below. Notification of the event(s) to Roswell Park within 24 hours via electronic media or paper is required:

a) ALT:
   a. Among subjects with Baseline ALT <2×ULN: ALT ≥5×ULN
   b. Among subjects with Baseline ALT ≥2×ULN: ALT >3× the Baseline level
   c. ALT >500 U/L regardless of baseline level

b) AST
   a. 2×ULN: AST ≥5×ULN

b. Among subjects with Baseline AST ≥2×ULN: AST >3× the Baseline level

c. AST >500 U/L regardless of baseline level

c) Total Bilirubin

a. Among subjects with Baseline levels <1.5 mg/dL: a value of >2 mg/dL

b. Among subjects with Baseline levels that are ≥1.5mg/dL: a value ≥2× the Baseline level

c. Total bilirubin >3.0 mg/dL regardless of baseline level

d) Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:

a. New onset clinically detectable ascites

b. Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)

c. Hepatic Encephalopathy

Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before initiation of study treatment must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of initiation of study treatment through 120 days following cessation of pembrolizumab, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Roswell Park and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 661-6229)

17.5 Protocol-Specific Exceptions to Serious Adverse Event Reporting

For trials capturing Disease Progression as primary or secondary endpoint (PFS or ORR):

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 10, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Roswell Park within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is

disease progression of the cancer under study.

Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g., transportation issues etc.) will not be considered a SAE.

17.6 Investigator Reporting:

Investigators MUST report within 1 business day upon becoming aware, ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

EXTERNAL (NETWORK) SITES: see Appendix A Sections 7 & 8 for reporting requirements.

17.7 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.8 Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
    - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
    - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is deemed **Serious** per **Section 17.3.**

Reporting Unanticipated Problems:

Unanticipated problem reporting will begin at the time of participant consent. An Unanticipated Problem shall be submitted to the CRS Quality Assurance (QA) Office as "Reportable New Information" in the Click system within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems to the IRB in accordance with their local institutional guidelines.

18.0 Data Management and Confidentiality

18.1 Data Collection

Full build studies are managed by RPCI CRS Data Management for analysis by RPCI Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

18.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

18.3 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or Merck, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant

19.0 Statistical Plan

Primary interest is in the Overall Response Rate (ORR) related to sorafenib + pembrolizumab combination therapy in advanced stage HCC patients. The ORR is defined as the proportion of evaluable patients who attain either complete or partial response (by irRECIST) within 6 months of initiating combination therapy. Our working hypothesis is that sorafenib + pembrolizumab will increase the ORR by at least 15 percentage points over the standard of care (where responses are rare ~2-3%).

19.1 Sample Size Determination

Proposed is a one-stage, single arm, unblinded Phase II trial. ORR for patients receiving the standard of care therapy is around 0.05. An exact one-stage design proposed by Kepner and Chang tests the null hypothesis that the proposed treatment has an ORR that is equal to the

standard of care, against an alternative that it is greater. The design has 80% power to detect an ORR of 0.20 or greater with the study treatment, while controlling to 5% the nominal probability of erroneously finding a truly ineffective treatment as worthy of further research (21, 22).

The first 6 patients will comprise the Phase 1b safety lead-in. If ≥ 2 of these patients experience an unexpected, treatment related toxicity of grade ≥3 during the first cycle of therapy, the study will be stopped to reevaluate dosing. We anticipate that such limiting toxicities will be observed in ≤1 of the first 6 patients. All evaluable patients who receive the Phase 2 dose will be included in the Phase 2 study.

We expect 27 evaluable patients will be enrolled on the trial. If 4 or more of the 27 evaluable patients achieve complete or partial response, the treatment will be deemed effective and considered for further study.

19.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.3 Efficacy Analysis

The response rate will be estimated as the binomial proportion of responders among evaluable patients and supported by Jeffreys' 95% confidence interval.

Time to tumor progression (TTP) will be measured from the date of study enrollment to the first observation of progressive disease. Overall survival (OS) will be measured from the date of study enrollment to the time of death from any cause. These variables will be estimated using the Kaplan-Meier method. Statistics describing the time to event distributions will be obtained from Kaplan-Meier methods and Proportional Hazards models. Continuous variables will be summarized with commonly used statistics (mean, standard deviation, median, etc.), with sub-group associations tested using the Wilcoxon Rank Sum test. Categorical variables will be summarized in contingency tables, with associations of interest assessed using Fisher's Exact Test. Given the exploratory nature of this study, all p-values less than 0.05 will be deemed statistically significant. No adjustment will be made to the significance threshold to control for the effects of multiple testing on the overall Type I error rate.

19.4 Correlative Data Analysis

Measurements for several immune parameters will be obtained before and after treatment. The effect of treatment will quantified as the post/pre-treatment mean ratio of the (potentially log transformed) expression measurements. Primary and derived immune marker expression measurements will be summarized with common descriptive statistics (mean / standard deviation). Associations between the paired pre- and post-measurements will be described with scatterplots and dot plots. The null hypothesis of no difference in the paired pre- and post-treatment measurements was assessed using permutation paired t-tests.

In previous experiments, immune marker expression measurements varied widely, with means between 8.0 and 1,200; the coefficient of variation has been between 0.5 and 1.0. For power calculations, the (original scale) expressions are assumed to have mean (standard deviation) of 100 (100), and within-patient correlation = 0.20. Comparing measurements at two time points, the within-patient effect of therapy on an immune marker can be assessed using a permutation paired t-test. A paired t-test with a two-sided significance threshold of 0.05 has 80% power to

detect a fold-change of at least 1.76 in the post/pre geometric means.

All data analyses were generated using SAS/STAT software, Version 9.4. Copyright 2012, SAS Institute Inc. SAS is a registered trademark of SAS Institute Inc., Cary, NC, USA.

20.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Phase 1 studies will be reviewed at the scheduled RPCI Phase 1 meetings and the minutes are forwarded to the IRB for review.

Phase 2 studies: The RPCI Data and Safety Monitoring Board will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMC will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design, (c) suspension of, or (d) or termination of the study.

21.0 Vulnerable Populations

NA

22.0 Community-Based Participatory Research

NA

23.0 Sharing of Results with Subjects

Individual response data is shared with the participant as a part of their clinical care.

24.0 Setting

All treatment will be conducted on an outpatient basis at RPCI's Gastrointestinal Center within Roswell Park Cancer Institute. Roswell. Potential study participants will be identified and recruited from current GI Center patients and from community referral.

25.0 Provisions to Protect the Privacy Interests of Subjects

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26.0 Resources Available

NA

27.0 Prior Approvals

NA

28.0 Compensation for Research-Related Injury

Please refer to the informed consent form (Section 13) related to this study:

29.0 Economic Burden to Subjects

The participant and /or their insurance company will be responsible for charges related to the administration of drugs used in this clinical research study and for charges for medications that may be needed to prevent or control side effects.

30.0 Consent Process

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31.0 Process to Document Consent in Writing

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32.0 Drugs or Devices

32.1 Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

32.1.1 Active Substance and Source:

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Pembrolizumab for injection is a sterile, preservative-free, white-to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide-adjust pH to 5.5.

Pembrolizumab injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

32.1.2 Drug Shipment:

Pembrolizumab will be provided by Merck & Co., Inc. and shipped to the participating site. The investigational drug will be labeled in accordance with regulatory requirements (Drug identity, i.e., name, strength) is included in the label.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.1.3 Preparation:

Refer to Pharmacy Manual.

32.1.4 Storage and Stability:

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, in accordance with the applicable regulatory requirements.

Drug storage temperature will be maintained and recorded, as applicable.

Pembrolizumab for injection (lyophilized powder): Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

Pembrolizumab injection (solution): Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

Refer to Investigator's Brochure for additional details.

32.1.5 Handling and Disposal:

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Merck & Co., Inc., exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate

precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

All unused and/or partially used investigational drug will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

32.1.6 Overdose:

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab.

In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

32.2 Sorafenib

Sorafenib will not be provided for this study and will be paid for by the patient's insurance carrier as part of the standard-of-care treatment for unresectable hepatocellular carcinoma. The starting dose of sorafenib is at the discretion of the physician based on clinical assessment of the patient.

33.0 REFERENCES

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34.0 APPENDICES/SUPPLEMENTS

Appendix A Instructions for Multi-Site Studies

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Quality Assurance (QA) Network Office
CRSNetworkCoordinators@RoswellPark.org

1930 GBSB

Buffalo, New York 14263

Telephone:
Monday - Friday; 8:00 AM to 4:30 PM EST
716-845-8084
After hours, weekends, and holidays request the RPCI Investigator
716-845-2300
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park CRS QA Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CRS QA Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 1 Protocol Registration Instructions

Contact the Roswell Park Network QA Coordinator to verify that a slot is available in the open cohort when a participant has been identified. **Do not have the participant sign consent prior to verifying an open slot.**

- After the participant signs consent, the Subject Screening and Enrollment Log must be faxed or emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park

QA Coordinator Monitor within 1 business day. The Roswell Park QA Coordinator/Monitor will confirm receipt of the Subject Screening and Enrollment Log and email the participant ID number.

- When the participant has met eligibility, a signed eligibility checklist and other requested documentation will be faxed or emailed to the Roswell Park Network QA Coordinator.
- Within 1 business day of receipt of the eligibility check list, the RPCI Network QA Coordinator will fax or email the cohort assignment and dose level.
- An email must be sent by the site to confirm receipt of the cohort assignment and to provide the planned treatment start date.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be faxed or emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park CRS QA Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and fax or email it to the Roswell Park Network QA Coordinator at 716-845-8743.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park Network QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the Roswell Park SAE form:

A complete follow-up report must be sent to the Roswell Park Network QA Coordinator when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.8**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the Roswell Park Network QA Coordinator.

Appendix B ECOG/ Karnofsky Performance Scale

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Descriptions
0	Fully active, able to carry on all pre-disease performance without restriction	100	Normal, no complaints; no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work	80	Normal activity with effort, some signs or symptoms of disease
		70	Cares for self but unable to carry on normal activity or to do active work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours	60	Requires occasional assistance but is able to care for most of personal needs
		50	Requires considerable assistance and frequent medical care
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours	40	Disabled; requires special care and assistance
		30	Severely disabled; hospitalization is indicated although death not imminent
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	20	Very ill; hospitalization and active supportive care necessary
		10	Moribund
5	Dead	0	Dead

Appendix C Child-Pugh Classification

Child-Pugh Classification of Severity of Liver Disease

Modified Child-Pugh classification of severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time and, the degree of encephalopathy.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin, mg/dL	</= 2	2-3	>3
Albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time * Seconds over control * INR	 1-3 <1.8	 4-6 1.8-2.3	 >6 >2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival.

Grade	Points	One-year patient survival (%)	Two-year patient survival (%)
A: well-compensated disease	5-6	100	85
B: significant functional compromise	7-9	80	60
C: decompensated disease	10-15	45	35

Appendix D Medication Dairy

Study No.: _____ **Subject's Name: _____**
Drug Name: _____ **Cycle #: _____**
Medical Record No.: _____

Study Medication Calendar for Sorafenib (Combination Therapy)

You should swallow your medication whole: without cutting, chewing, or crushing. The tablets should be taken in the morning and evening (about 1 hour before or 2 hours after eating.).
Please complete this calendar on a daily basis immediately after you take your tablets. Fill in the date for each day, write the drug dose that you take each day, and write the total number of tablets you take each day. If your dose changes; record the new dose level.
Start Date: _____ Dose: _____

Take _____ tablet(s) each time, about 12 hours apart and at least 1 hour before a meal or, 2 hours after a meal.

Cycle Day	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Cycle Day	Day 8		Day 9		Day 10		Day 11		Day 12		Day 13		Day 14	
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Cycle Day	Day 15		Day 16		Day 17		Day 18		Day 19		Day 20		Day 21	
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Cycle Day	Day 22		Day 23		Day 24		Day 25		Day 26		Day 27		Day 28	
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Cycle Day	Day 29		Day 30		Day 31									
Date														
Time	AM	PM	AM	PM	AM	PM								
Number of tablets taken														

Please remember to bring this calendar with you to your next clinic appointment.

Note: On the day that you start your combination therapy (sorafenib + pembrolizumab) and on Day 1 of every four cycles of the combination after that, your blood will be drawn prior to receiving the intravenous pembrolizumab.

On those days (i.e. Cycle 1-Day 1, Cycle 4-Day 1, etc.), please ***do not*** take your morning dose of sorafenib until after you go to the clinic and have your blood drawn.

Coordinator's Use Only

Subject's Signature: _____ Date: _____

CRC's Signature: _____ Date: _____

Investigator's Signature :_____ Date : _____

Study Medication Calendar for SORAFENIB ONLY (Lead-in Phase)

Study No.: ______________ **Subject's Name: ______________________________**
Drug Name: _____________
Medical Record No.: _________________________

You should swallow your medication whole: without cutting, chewing, or crushing. The tablets should be taken in the morning and evening (about 1 hour before or 2 hours after eating.).

Please complete this calendar on a daily basis immediately after you take your tablets. Fill in the date for each day, write the drug dose that you take each day, and write the total number of tablets you take each day. If your dose changes; record the new dose level.

Start Date: _________________ Dose: ___________________________

Take _____ tablet(s) each time, about 12 hours apart and at least 1 hour before a meal or, 2 hours after a meal.

Day														
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Day														
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Day														
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														
Day														
Date														
Time	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
Number of tablets taken														

* The day that you go into the clinic for your first dose of pembrolizumab is referred to as ***Cycle 1-Day 1***. On the day of Cycle 1-Day, do not take your morning dose of sorafenib until **after** you have had your blood drawn at the Clinic: the blood draw will occur prior to pembrolizumab administration.

Please remember to bring this calendar with you to your next clinic appointment.

Coordinator's Use Only

Subject's Signature: _____ Date: _____

CRC's Signature: _____ Date: _____

Investigator's Signature :_____ Date : _____

Appendix E Schedule of Procedures

Trial Period	Screening	Sorafenib only	Combination (sorafenib + pembrolizumab) Treatment Cycles[3]						End of Study[4]	Post-Treatment		
Phase Ib and Phase II:	**Baseline[1]**	Day -28 to Day -1*	1	2	3	4	5	6 [3a]		**Safety Follow-Up[5]**	**Follow Up [6]**	**Long Term Follow-Up[7]**
Clinical Assessments												
Medical History and Pre-existing Conditions	X									X		
Prior and Concomitant Medication Review	X[8]		X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	X[9]	
Physical Examination[10]; including vital signs, body weight, & height[11]	X	X[2]	X	X	X	X	X	X	X	X		
Child Pugh A	X											
ECOG Performance Status	X		X	X	X				X	X		
Adverse Events		X[2]	X	X	X	X	X	X	X	X	X	
Survival Status			X	X	X	X	X	X		X	X	X
Laboratory Procedures												
Hematology: CBC with Differential[12]	X	X[2]	X	X	X	X	X	X	X	X		
Chemistry: CMP[13]	X	X[2]	X	X	X	X	X	X	X	X		
T3, FT4, and TSH[14]	X						X		X	X		
Viral Titers: Hepatitis B and C[22]: Hepatitis B Surface Antigen (HBsAg) and/or detectable HBV DNA and, Hepatitis C Antibody (anti-HCV	X						X		X			

Trial Period	Screening	Sorafenib only	Combination (sorafenib + pembrolizumab) Treatment Cycles[3]						End of Study[4]	Post-Treatment		
Phase Ib and Phase II:	**Baseline[1]**	Day -28 to Day -1*	1	2	3	4	5	6 [3a]		**Safety Follow-Up[5]**	**Follow Up [6]**	**Long Term Follow-Up[7]**
Ab), and detectable HCV RNA												
Coagulation[15]	X											
Tumor Marker (AFP)[16]	X			X		X			X			
Serum Pregnancy Test	X											
Imaging												
CT of chest, abdomen, and pelvis[17]	X			X		X			X			
Study Drugs												
Sorafenib, po		X	X	X	X	X	X	X				
Pembrolizumab, IV			X	X	X	X	X	X				
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood												
Archival Tissue Collection[18]	X											
Tumor biopsy	X[18]								X[19]			
Correlative Studies Blood Collection[20]	X		X			X			X			
Pharmacokinetic Blood Sampling[21]			X			X			X			

*The sorafenib lead in phase can extend up to Day-42 to Day-1 to allow stabilized dosing.

1 Within 28 days prior to start of sorafenib only study treatment (unless otherwise noted.)

2 Toxicity assessment within 2 weeks of starting sorafenib lead-in to include a directed physical exam and vitals.

3 One cycle = 3 weeks (sorafenib + pembrolizumab). Pembrolizumab to be administered on Day 1 (± 3 days) of each 3-week cycle. Note: After Cycle 1 Day 1, all on-study visit procedures are allowed a window of ± 3 days unless otherwise noted. 3a The number of cycles may vary (with each patient) and additional cycles may occur, as clinically indicated. After a patient has been on pembrolizumab for more than 24 months the PI can decide if the patient can come off pembrolizumab and continue on with sorafenib treatment.

4 End of study or, at time decision is made to discontinue treatment (e.g. toxicity, physician decision, or patient withdraws consent).

5 Safety follow up to be conducted approximately 30 days (± 3 days) after last dose of trial treatment, or until resolution of any drug-related toxicity or before the initiation of a new anti-cancer treatment, whichever comes first.

6 Participants who discontinue treatment for other than disease progression will move into the follow-up phase: assessments every 3 months for 1 year or until death. Telephone contact is acceptable.

7 All patients will be followed by medical review every 6 months for survival.

8 List any medications that are ongoing, or that will be discontinued, within 1 week prior to first dose of study drug (refer to Section 10.3 for Acceptable and Prohibited concomitant medications). All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after that last dose of trial treatment should be recorded.

9 List any ongoing medications with dose changes, as applicable. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 17.0.

10 A physical exam within 1 week of consent is acceptable.

11 Vital signs (temperature, heart rate, respiratory rate, blood pressure), body weight and height. Height collected at baseline only.

12 Hematology (CBC with automated differentials): WBC,RBC, HGB, HCT, platelets, MCV, MCH, MCHC, % neutrophils, absolute neutrophils, % monocytes, absolute monocytes, % eosinophils, absolute eosinophils, % basophils, absolute basophils, % lymphocyte, absolute lymphocyte, platelet confirmation (as clinically indicated), differential confirmation (as clinically indicated). Note: Participants experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the treating physician or Investigator.

13 Chemistry (CMP): chloride, CO2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).

14 Every 12 weeks starting from C1D1.

15 PT/INR and aPTT at screening and as clinically indicated.

16 AFP at screening and at disease assessment: six weeks after C1D1 (end of Cycle two), 12 weeks after C1D1 (end of Cycle four), every nine weeks thereafter, and at disease progression.

17 Imaging at Baseline, at Cycle 2 (± 1 week), at Cycle 4 (± 1 week), and then every 9 weeks (± 1week).

18 Archival tissue collection. If available at baseline. Refer to Section 11.3.1.

19 Tumor biopsy: Optional at end of treatment Refer to Section 11.3.2

20 Prior to the start of sorafenib, at start of Cycle 1, at start of Cycle 4 and Day 1 of every subsequent 4 cycles (Cycle 8, 12, etc.), and end of study treatment. NOTE: At onset of Cycle 1, confirm that patient will actually start pembrolizumab before collecting samples. Refer to Section 11.2 for collection and processing requirements.

21 Pharmacokinetic samples will be collected at the start of combination treatment and processed according to Section 11.1. Patients will be advised to hold morning dose of sorafenib until after PK blood draw but before pembrolizumab.

22 Viral titers will be measured at baseline (and as clinically indicated in patients who have elevated baseline titers) and at every 12 weeks starting from C1D1 to assess possible effects on outcome: Hepatitis B Surface Antigen (HBsAg) and/or detectable HBV DNA and, Hepatitis C Antibody (anti-HCV Ab), and detectable HCV RNA.

Appendix F Table 1

Table 1: Dose Modification Guidelines for Non-Hepatic Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[a]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		Recurrent grade 2	Permanently discontinue
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[b]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Appendix G-Table 2: Infusion Treatment Guidelines, for further management details.

[b] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Appendix G Table 2

Table 2: Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 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	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

Appendix H Immune-Related Response Criteria: irRECIST

Tumor response will be assessed using the Immune-Related response Criteria as described by Nishino et al, (14) and Bohnsack et al, (13).

1 Baseline

1.1 Measurable Lesion Definitions and Target Lesion Selection

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline
- Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
    - 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non- nodal lesions and ≥ 15 mm in short axis for nodal lesions.
    - 10 mm caliber measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
    - 20 mm by chest X-ray
- A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

1.2 Non-measurable Lesion Definitions

- Non-target lesions will include:
    - Measurable lesions not selected as target lesions
    - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), i.e., the longest perpendicular diameter is ≥ 10 and < 15 mm.
    - Other types of lesions that are confidently felt to represent neoplastic tissue but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.
- All lesions or sites of disease not recorded as target lesions (e.g., small lesions and non-measurable lesions) should be identified as non-target lesions and indicated as present in the source documents at baseline. There is no limit to the number of non-target lesions that

can be recorded at baseline. The general location will also be documented on the images, drawing a regularly-shaped Region of Interest.

- Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

1.3 Target and Non-Target Lymph Node Lesion Definitions

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

1.4 Non-Target Lesion Selection

- All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number on non-target lesions that can be recorded at baseline.

1.5 Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.

1.6 Brain Lesions

- Brain Lesions detected on brain scans can be considered as both target or non-target lesions.

1.7 Cystic and Necrotic Lesions as Target Lesions

- 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.
- Lesions that are partially cystic or necrotic can be selected as target lesions.
- The longest diameter of such a lesion will be added to the ***Total Measured Tumor Burden*** (TMTB) of all target lesions at baseline.

If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

1.8 Lesions with Prior Local Treatment

- During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.).

- Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

1.9 No Disease at Baseline

- If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign '***No Disease***' (irND) as the overall tumor assessment for any available follow-up time-points unless new measurable lesions are identified and contribute to the TMTB.

2 Follow-Up

2.1 Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the ***Total Measured Tumor Burden (TMTB)*** at follow-up.

2.2 Definition of New Measurable Lesions

- In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time-point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

2.3 Non-Target Lesion Assessment

- The RECIST 1.1 definitions (15) for the assessment of non-target lesions apply (i.e., measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation).
- The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN).
- Non-target lesions do not affect irPR and irSD assessments.
- Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

2.4 New Non-Measurable Lesions Definition and Assessment

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively.
- Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time-point.
- Persisting new non- measurable lesions prevent irCR.

2.5 irRECIST Overall Tumor Assessments

The irRECIST overall tumor assessment is based on the ***TMTB*** (total measured tumor burden) of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

- **irCR:** Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
- **irPR:** Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
- **irSD:** Failure to meet criteria for irCR or irPR in the absence of irPD.
- **irNN:** No target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
- **irPD:** Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 6 weeks after the first irPD assessment.
- **irNE:** Used in exceptional cases where insufficient data exists.
- **irND:** In adjuvant setting when no disease is detected.

New Lesions: the presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements (the sum of the measurements = the sum of the longest diameters of all target lesions and new lesions, if any).

2.6 Confirmation Measurement

A confirmatory assessment is required no less than 6 weeks after an irPR or irCR is deemed by irRECIST (14)

3 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. The preferred imaging modality for this clinical trial is conventional CT scan using IV contrast.

- **Clinical Lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray:** Chest x-ray is not accurate in assessment of lesion size in the lung and should not be used as a method of measurement. Conventional chest CT is the preferred imaging modality to evaluate response to treatment.

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans) however, conventional CT scan is the preferred modality to determine response to treatment.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the irRECIST or RECIST 1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor Markers:** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.
- **Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Appendix I Suggested Dose Modifications for Dermatologic Toxicities in Patients with Hepatocellular Carcinoma

Dermatologic Toxicity Grade	Occurrence	Suggested Dose Modification
Grade 1: Numbness, dysesthesia, paresthesia, tingling, painless swelling, erythema or discomfort of the hands or feet which does not disrupt the patient's normal activities	Any occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief
Grade 2: Painful erythema and swelling of the hands or feet and/or discomfort affecting the patient's normal activities	1st occurrence	Continue treatment with sorafenib and consider topical therapy for symptomatic relief If no improvement within 7 days, see below
	No improvement within 7 days or 2nd or 3rd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)
	4th occurrence	Discontinue sorafenib treatment
Grade 3: Moist desquamation, ulceration, blistering or severe pain of the hands or feet, or severe discomfort that causes the patient to be unable to work or perform activities of daily living	1st or 2nd occurrence	Interrupt sorafenib treatment until toxicity resolves to Grade 0–1 When resuming treatment, decrease sorafenib dose by one dose level (400 mg daily or 400 mg every other day)
	3rd occurrence	Discontinue sorafenib treatment

Appendix J Guidance for Diagnosis and Management of Hepatic Events of Clinical Interest

In addition to overdose, hepatic events of clinical interest (ECIs) will include any of the following events. All of these events will require holding study treatment until the patient no longer meets the criteria below. Notification of events to Roswell Park within 24 hours is required. Refer to Section 17.4 for reporting guidelines and the definition of hepatic ECIs. Roswell Park will report within 2 working days to Merck Global safety.

All cases of retreatment and permanent discontinuation must be reported to the Sponsor and recorded in the database.

a) ALT:
   i) Among subjects with baseline ALT < 2 x ULN: ALT ≥ 5 x ULN
   ii) Among subjects with baseline ALT ≥ 2 x ULN: ALT > 3 x the baseline level
   iii) ALT >500 U/L regardless of baseline level

b) AST:
   i) Among subjects with baseline AST <2xULN: AST ≥ 5 x ULN
   ii) Among subjects with baseline AST ≥ 2 x ULN: AST > 3 x the baseline level
   iii) AST >500 U/L regardless of baseline level

c) Total Bilirubin:
   i) Among subjects with baseline levels < 1.5 mg/dL: a value of > 2 mg/dL
   ii) Among subjects with baseline levels that are ≥ 1.5mg/dL: a value ≥ 2 x the baseline level
   iii) Total bilirubin > 3.0 mg/dL regardless of baseline level

d) Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
   i) New onset clinically detectable ascites
   ii) Gastrointestinal bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
   iii) Hepatic Encephalopathy

Immediate assessment

All subjects

- All subjects should be evaluated according to directions below within 72 hours of alert for non-overdose ECI
- Procedures:
  - Obtain a work-up for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
  - Assess for ingestion of drugs/supplements with hepatotoxic potential
  - Assess for alcohol ingestion

- Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
- Repeat ALT, AST, total bilirubin (Tbil), direct bilirubin (Dbil), alkaline phosphatase (ALP), y-glutamyl transpeptidase (GGT), INR, and complete blood count (CBC) with differential
- Other laboratories or imaging studies as clinically indicated
- Consider liver biopsy if indicated

Hepatitis C-Infected Subjects (including subjects who previously achieved SVR 12)

- In addition to the above, measure HCV RNA viral load

Hepatitis B-infected Subjects

- HBV DNA, HBsAg, HBeAg, anti-HBc (total and IgM), anti-HBe, and anti-HBs
- Subjects should be questioned about compliance with the use of anti-viral agents

Permanent Discontinuation Criteria for Subjects with Non-overdose Hepatic ECI

Therapy should also be permanently discontinued for any of the following:

- ALT > 20 x ULN
- CP score of ≥ 9 points
- Gastrointestinal bleeding suggestive of portal hype1tension (e.g., esophageal or gastric varices)
- New onset of clinically detectable ascites
- Hepatic Encephalopathy
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related

Diagnosis and Management of Non-Overdose Hepatic ECIs

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in approximately1% of subjects who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects in this study.

a) Hepatitis B Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to > 5 x ULN and/or > 3 x baseline. ALT elevation to ≥ l0 x ULN is common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP). Subjects who are compliant with anti-viral therapy should have continued suppression of HBV DNA at the time of flare; thus, detection of HBV DNA should prompt questioning of subjects for compliance. Laboratory abnormalities secondary to flare are typically observed for 3-5 weeks.

Among subjects with HBV, a flare should be considered if this pattern is observed and there is

no evidence of an alternative etiology. Guidelines for subjects with a diagnosis of HBV flare are no evidence of an alternative etiology; Guidelines for subjects with a diagnosis of HBV flare are as follows:

- Care should be instituted in consultation with a hepatologist if available.
- For subjects who have detectable HBV DNA, re-institute anti-viral therapy.
- If the subject is clinically stable, study treatment dosing may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg and, HBV DNA (if detected at the onset of the flare). Obtain anti-HBe, anti-HBs, and HBV DNA levels (if not detected at the onset of the flare) every 2-3 weeks.
- If ALT returns to normal or Grade **1** (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and subjects are clinically stable, subjects may restart study treatment. If these conditions are not met, then study treatment should be permanently discontinued.

b) Hepatitis C Recurrence or Flare

Subjects who achieved SVR 12 and subjects with ongoing HCV infection are eligible for enrollment. In rare circumstances, HCV subjects who achieve SVR 12 may relapse at later time points. Relapse is characterized by detection of HCV RNA, often accompanied by ALT elevations to > 5 x ULN. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ALP).

Among subjects with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to > 5 x ULN and/or > 3 x baseline along with a rise in HCV RNA. ALT elevation to ≥ 10 x ULN and a 1 log elevation in HCV RNA level are common. In the absence of hepatic decompensation, ALT/AST elevations are typically isolated (i.e., limited/no elevations of bilirubin/ ALP). Laboratory abnormalities secondary to flare or recurrence are typically observed for 3-5 weeks.

Guidelines for subjects with recurrent HCV infection or an HCV flare are described below:

i) Recurrent HCV infection:

If the subject entered the study with an HCV RNA test of "Target not Detected" and has confirmed detectable HCV RNA (2 specimens, 1 week apart), then the subject has experienced a late HCV relapse or a recurrent infection.

- Question the subject about use of injection or inhalation drugs
- At the time of first detection of HCV RNA, send a specimen for HCV genotyping
- Measure AST, ALT, ALP, Tbil, Dbil, and INR weekly
- Measure HCV RNA levels every 2 weeks
- Therapy with HCV anti-viral treatments should be strongly considered.

ii) HCV Flare:

- At the time of first detection of HCV RNA, send a specimen for HCV genotyping

- Measure AST, ALT, ALP, Tbil, Dbil, INR weekly
- Measure HCV RNA levels every 2 weeks
- Therapy with HCV anti-viral treatments should be strongly considered.

iii) For both recurrent infection and HCV flare: if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the subjects are clinically stable, subjects may restart study treatment. If these conditions are not met, then study treatment should be permanently discontinued.

c) Immune-related hepatitis

i) Description: Immune-related hepatitis due to study treatment should be suspected if any of the following is seen:

a. AST or ALT baseline values are less than 2 x ULN, and AST or ALT laboratory values increase to ≥ 5 x ULN

b. Among subjects with baseline ALT or AST ≥ 2 x ULN, levels increase to > 3 x the baseline level

c. AST/ALT >500 U/L regardless of baseline level

d. Among subjects with baseline Tbil levels < 1.5 mg/dL: a value of > 2 mg/dL

e. Among subjects with baseline Tbil levels that are ≥ 1.5 mg/dL: a value of ≥ 2 x the baseline level

f. Total bilirubin > 3.0 mg/dL regardless of baseline level.

Immune-related hepatitis is a diagnosis made after excluding other possible etiologies for the change. Viral flare (if applicable), biliary or vascular obstruction, infection, medications, and alcohol use must be ruled out (see below).

ii) Management

a. Interrupt study treatment and alert the Sponsor as per ECI criteria above for ALT, AST, bilirubin, and hepatic decompensation.

b. Start IV corticosteroid (methylprednisolone: 125 mg or equivalent) followed by oral corticosteroid.

c. Monitor with biweekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR.

d. If symptoms and laboratory tests resolve to Grade ≤ 1 or baseline (if abnormal at baseline), taper steroids over 28 days. Study treatment may be restarted after steroid treatment has been tapered to prednisone ≤ 10 mg/day (or equivalent dose of another agent). Treatment and laboratory results must be reported on a case report form (CRF).

e. If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤ 10 mg/day (or prednisone equivalent) within 12 weeks, or subjects show evidence of decompensation to CP C status or have esophageal or variceal bleeding at any point, treatment must be permanently discontinued.

This must be reported on a CRF.

d) Other Hepatic Events of Clinical Interest

- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest X-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started.
- If Tbil is elevated above baseline, magnetic resonance cholangiopancreatography or ultrasound with Doppler should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression. If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
- A careful review of drugs, including herbal and alternative medications, should be obtained, and alcohol use should be ruled out.
    - Drugs known to be hepatotoxic (i.e., drugs with a warning of hepatotoxicity in the package insert) should be avoided during the dosing period. Investigators are encouraged to review each medication for potential hepatotoxicity by searching the www.livertox.nih.gov website.
- For all of these cases, subjects may resume study treatment if they are clinically stable after appropriate therapy or discontinue the causative agent, as long as laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks.
- Treatment must be permanently discontinued if the subject is off study treatment therapy for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become CP C at any point.