SPONSOR: M.D. Anderson Cancer Center

TITLE: A Phase II Study of Pembrolizumab (MK-3475) in Hepatitis C Virus Positive and Negative Subjects with Advanced Hepatocellular Carcinoma Who Progressed on or Were Intolerant to First-Line Systemic Therapy

IND NUMBER: MDACC to supply if determined

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Table 1 Protocol Change and IRB Approval Tracker

Date	**Protocol Version**	**Change**	**Section**	**Date Approved Merck**	**Date Approved MDACC IRB**
03-30-2017	*1*	*Updated required Pembro language, inserted reviewer comments, edited to align protocol with SOP and procedure manual.*	*All*		
04-05-2017	1.1	Updated trial diagram	All		
04-27-2017	2	Incorporated JT Link's edits	All		
5-24-2017	3	Update Merck standard language	All		
5/27/2017	4	Completed PAT review comments	All		
9/27/2017	4	Final Merck review. Updated Merck standard language, formatting, and consistency. Replaced irRECIST with iRECIST. Updated pembrolizumab dose modification table and survival status langauge.	All		

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1.0 TRIAL SUMMARY

Title	A Phase II Study of Pembrolizumab (MK-3475) in Hepatitis C Virus Positive and Negative Subjects with Advanced Hepatocellular Carcinoma who Progressed on or Were Intolerant to First-Line Systemic Therapy
Trial Phase	Phase II
Clinical Indication	Hepatocellular carcinoma (HCC)
Trial Type	Interventional
Product	Arm A: Pembrolizumab (MK-3475) Arm B: Pembrolizumab (MK-3475) and Zepatier® (grazoprevir [MK-5172] and elbasvir [MK-8742]).
Type of control	No treatment control
Route of administration	Pembrolizumab: Intravenous Zepatier: Oral
Trial Blinding	Unblinded Open-label
Eligibility	Male/female subjects with and without hepatitis C virus (HCV) genotype GT1 or GT4 with advanced HCC with no curative option will be enrolled in this trial.
Treatment Groups	There will be 2 treatment groups within this trial. The first treatment group Arm A will be pembrolizumab monotherapy at 200 mg every 3 weeks (Q3W). The second treatment group Arm B will be pembrolizumab at 200 mg Q3W plus Zepatier (grazoprevir 100 mg and elbasvir 50 mg) administered once daily (qday) for 12 to 16 weeks depending on the HCV GT as per the Zepatier label. Ribavirin (RBV) will be combined as per Zepatier label.
Number of trial subjects	Approximately 15 subjects will be enrolled per arm.
Estimated enrollment period	12-15 months
Estimated duration of trial	It is estimated that the trial will require approximately 18 months from the time the first subject signs the informed consent form (ICF) until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the ICF through the final contact. After a screening phase of up to 28 days, each subject will receive pembrolizumab beginning on Day 1 of each 3-week dosing cycle. Treatment will continue until progressive disease, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the subject, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 35 treatments (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up visits for monitoring disease status until progressive disease, initiating a non-study cancer treatment, withdrawing consent from study participation, or becoming lost to follow-up. All subjects will be followed (by telephone or visit) for overall survival until death, withdrawal of consent from study participation, or the end of the study. After the end of study treatment, each subject will be followed for 30 days for adverse event monitoring. Serious AEs (SAEs) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer

	therapy, whichever is earlier. Virologic response (sustained virologic response [SVR]) will be collected for 12 and 24 weeks after the end of all HCV study therapy.
Estimated average length of treatment per subject	Subjects will be treated for up to 2 years or 35 cycles of pembrolizumab.

2.0 TRIAL DESIGN

2.1 Trial Design

This will be a Phase II study investigating single agent pembrolizumab (Keytruda®) as a second-line therapy for subjects with hepatocellular carcinoma (HCC) who either progressed on or after sorafenib or did not tolerate sorafenib. Subjects who progressed on lenvatinib would also be eligible for enrollment. It will be a multiarm study with Arm 1, pembrolizumab monotherapy and Arm 2, pembrolizumab and Zepatier® (fixed-dose combination [FDC] of grazoprevir [MK-5172] and elbasvir [MK-8742]). Zepatier is not known to be an anti-cancer therapy. In order to be eligible for Arm B, subjects must have chronic hepatitus C virus (HCV) infection with genotype GT1 or GT4 and Child-Pugh class A liver disease.

Arms are designed to test the response rate and biological impact of combinations of the agents. There is no intent to directly compare treatment arms with each other.

This trial aims to test pembrolizumab as monotherapy and in combination with additional agents to assess safety and efficacy in HCC. It will commence as a single-arm, open-label, single-site Phase II trial of pembrolizumab in subjects with previously systemically treated HCC. Three additional arms will be added as an amendment that will test pembrolizumab in combination with other experimental anti-cancer agents. The inclusion and exclusion criteria will be the same for each combination arm unless stipulated by one of the added agents. To be eligible, subjects must have documented objective radiographic progression after stopping treatment with sorafenib monotherapy, progression on sorafenib therapy, or intolerance to sorafenib, and have disease not amenable to a curative treatment approach (e.g., transplant, surgery, or ablation). Intolerance to sorafenib is defined as: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Section 12.4) Grade ≥2 drug-related adverse event(s) (AE[s]) which both a) persisted in spite of comprehensive supportive therapy according to institutional standards and b) persisted or recurred after sorafenib treatment interruption of at least 7 days and a dose reduction and resulted in the subject requesting or the physician recommending discontinuation due to the toxicity. For Arm A, a subject who was treated on sorafenib as their last treatment may start pembrolizumab 14 days after the last dose of sorafenib. In order to be eligible, subjects must have at least 1 measurable lesion that is confirmed by M.D. Anderson radiology per Response Evaluation Criterin in Solid Tumors (RECIST) 1.1, Child Pugh status score of A, an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, and life expectancy of greater than 3 months. For Arm B, a subject with HCV who either progressed or did not tolerate sorafenib may start pembrolizumab and Zepatier as a second-line therapy 14 days after the last dose of sorafenib. In order to eligible for Zepatier treatment, the subjects must have chronic HCV GT1 or GT4 and Child-Pugh class A liver disease. Subjects will be required to provide a tumor tissue sample at enrollment to support the correlative endpoints of the study. Approximately 15 subjects will be allocated to receive pembrolizumab 200 mg IV every 3 weeks (Q3W) and Zepatier orally (PO) once daily (qday) for 12 to 16 weeks depending on the HCV GT and prior HCV therapy as per prescribing information.

The primary objective of this trial is to determine the safety and tolerability of pembrolizumab given as monotherapy. The second arm will have the same primary objectives and will test pembrolizumab in combination with Zepatier. Starting with screening, all imaging assessments will be determined by the investigator's institution using RECIST 1.1. Images may be transferred to Merck for confirmatory RECIST 1.1 reads. On-study imaging assessments will be performed every 9 weeks (Q9W) calculated from the date of allocation and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of progressive disease (PD). Following the first radiologic evidence of PD by RECIST 1.1, treatment decisions may be made by the adaptation of RECIST 1.1 as described in Sections 4.2.3.2 and 7.1.4.1.5 termed modified RECIST 1.1 for immune-based therapeutics (iRECIST) to accommodate the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare). This was first described by Nishino, et al. 2013 (1), but is further modified for the programmed cell death 1 (PD-1) receptor program. For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the site investigator to continue treating the subject with pembrolizumab until PD is confirmed 4 to 8 weeks from the date of the first tumor imaging suggesting PD per the site investigator and subsequently confirmed by the M.D. Anderson Department of Diagnostic Imaging. If radiologic PD is confirmed, the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit; an exception for continued treatment may be considered following consultation with Merck.

Subjects may continue to be treated with Arm A (pembrolizumab) or Arm B (pembrolizumab and Zepatier) until PD is confirmed by RECIST, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator decides to withdraw the subject, subject withdraws consent, pregnancy, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments (approximately 2 years) with pembrolizumab. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed Q9W (63 ± 7 days) by radiologic imaging to monitor disease status for up to 12 months calculated from the date of allocation (independent of treatment delays) and then every 12 weeks (Q12W; 84 ± 7 days) thereafter. Disease status will continue to be monitored until the start of new anti-cancer treatment, disease progression, death, or the end of the study, whichever occurs first. All subjects will be followed Q12W for overall survival (OS) until death, withdrawal of consent from participation in the study, or the end of the study, whichever comes first.

Subjects who attain a complete response (CR) by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months of therapy) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR. Subjects should complete 12 to 16 weeks of dosing of Zepatier before cessation of antivirals. Subjects who do not achieve a complete virologic response 4 weeks after the cessation of 12 weeks of Zepatier may discontinue treatment at the discretion of Merck and the investigator.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the NCI CTCAE version 4.0 (Section 12.4). After the end of treatment,

each subject will be followed for 30 days for AE monitoring. Serious AEs (SAEs) will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Virologic response wil be collected for 12 and 24 weeks after the end of all HCV study therapy.

This study will be conducted in conformance with Good Clinical Practices (GCP).

2.2 Retrospective Risk Stratification by Plasma insulin-like growth factor-1 (IGF-1) score.

We plan on performing retrospective risk-stratification of underlying liver condition using plasma insulin-like growth factor-1 (IGF-1) score (2). The outdated Child-Turcotte-Pugh (CTP) score is the standard hepatic reserve assessment tool in HCC to predict survival and therapy response in systemic therapy trials. Since survival rates are universally low for CTP classes B and C compared with class A, multiple expert panels have reached the consensus that patients with HCC should have a CTP score of A to be considered for aggressive therapies, to facilitate assessment of the effect of treatment without the confounding issues of liver failure and death as a result of underlying poor hepatic reserve (3, 4). However, it is now recognized that clinical outcome can significantly vary among patients within the same CTP class. Furthermore, CTP is partially based on subjective assessment of empiric dynamic clinical parameters (hepatic encephalopathy and ascites) with arbitrary cut-off ranges that are difficult to grade subjectively and may vary in severity according to nutritional status, comorbidities, and in response to medical management (5-7). Therefore, the reliability of the CTP score for survival prediction and clinical decision-making was questioned. Based on our studies and those of others indicating that liver production of plasma IGF-1 is significantly reduced in cirrhotic patients and HCC (8-11), we hypothesized that it could be a valid surrogate for hepatic reserve. We recently reported a new score which substituted IGF-1 for ascites and encephalopathy within CTP to create and prospectively validate (internally and externally) a novel objective score for survival prediction in HCC (2, 12). The IGF-1 score stratified patients more accurately than CTP in both cohorts. Most importantly, patients classified as A by CTP but B by IGF-CTP had significantly worse OS than those who remained under class A by IGF-CTP in both cohorts regardless the type of treatment received ($p=0.034$ and <0.001, respectively). Therefore, we propose to investigate the new score's ability to predict time to progression (TTP), survival, response, and AEs in the current study when measured at baseline (pre-treatment) in a retrospective manner. However, all patients will be CTP class A according to current standard of care (SOC) for HCC patients treated with systemic therapy. Thus, the retrospective IGF-1 score results will help interpret the study outcome results in relation to the status of underlying liver disease independently from the tumor response. This is critical to drug development, given that the degree of the underlying liver dysfunction could affect treatment outcome and survival independently from the systemic therapy effects, especially within the SOC CTP group for active therapy (CTP-A), which was sub-classified by our IGF-1 score into new A, B, C with significantly different survival estimates.

2.3 Independent effect of cirrhosis grade and severity of portal hypertension on HCC survival.

Portal hypertension is a major complication of cirrhosis that accompanies the majority of HCC cases and leads to progression of ascites, and the formation of portosystemic collateral vessels, including gastroesophageal varices that can cause life-threatening bleeding. This process is modulated by angiogenic factors, and reversed by anti-angiogenic agents in animal models (13, 14). Notably, recent studies suggested that a reduction in the portal pressure to less than 12 mm Hg or a reduction of more than 20% from the baseline value resulted in a decreased risk of variceal hemorrhage and improved survival (15, 16).

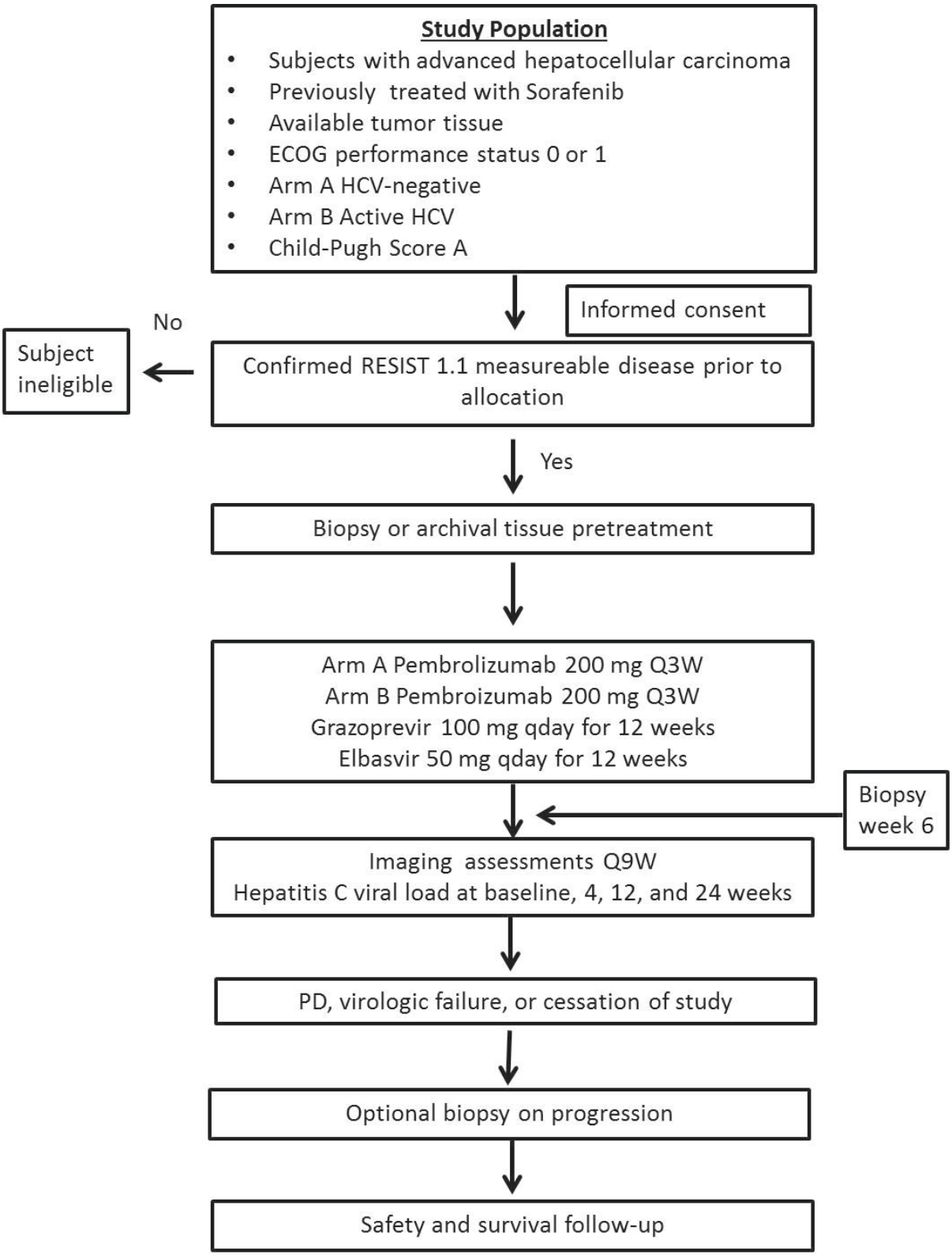
Since cirrhosis and portal hypertension grades affect survival outcomes in patients with HCC, independently of the HCC treatment effect, we propose to initially assess the effect of pembrolizumab on portal pressures and liver fibrosis as assessed by magnetic resonance imaging (MRI) diffusion studies and magnetic resonance elastography (MRE), respectively.

Since the standard tool to assess portal pressures using the standard trans-jugular approach is considered invasive, especially in patients with cirrhosis who often suffer from thrombocytopenia and coagulaopathy, we propose to monitor portal pressures indirectly through MRI assessment: before treatment, and serially at every restaging up to time of progression using the routine MRI performed for tumor assessment. We plan on implementing this alternative technique to allow for direct non-invasive quantification evaluation of flow dynamics, based on recent studies using MRI in HCC patients receiving sorafenib to assess their portal hypertension changes (17, 18). The advantage to using MRI is that it will be used routinely to assess tumor status, as part of routine HCC assessment in therapeutic clinical trials.

Advantages to this technique: Notably, phase-contrast MRI flow has the advantage of avoiding intravenous (IV) injection of the contrast media in this frail population. Phase-contrast flow measurements have been validated in an *in vitro/in vivo* study (19) as well as in other *in vivo* studies, including as an evaluation technique of the portal (20) and azygos venous flows (21). MRI phase-contrast is also a reproducible technique compared to ultrasonographic examination, which is a simpler technique but suffers from a high variability in repeated measurements. Thus, the MRI technique could help improve Doppler flow calculations, thereby allowing standardization of protocols. Therefore, we propose portal pressure assessment before treatment and with each restaging scan until the time of progression, using MRI done routinely for tumor assessment during therapy.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

2.4 Trial Diagram



Abbreviations: ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; Q3W = every 3 weeks; Q9W = every 9 weeks; RECIST = Response Evaluation Criteria In Solid Tumors.

Figure 1 Trial Diagram.

Additional expansion cohorts will be added to study.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Objectives will be different for Arm A and B. Arm A is HCC subjects that are HCV-negative and Arm B is HCC subjects that are HCV-positive.

3.1 Primary Objective(s)

(1) Objective: Arm A and Arm B: To evaluate the tolerability of IV administration of pembrolizumab as second-line therapy in subjects with advanced HCC.

(2) **Objective: Arm B:** To evaluate the efficacy of pembrolizumab in combination with Zepatier as assessed by the proportion of subjects with HCV GT1 or GT4 achieving Sustained Virologic Response 12 weeks after the end of all HCV study therapy (SVR12), defined as HCV RNA below the lower limit of quantitation (LLOQ) (either target detected unquantifiable [TD(u)] or target not detected [TND]) 12 weeks after the end of all study therapy.

3.2 Secondary Objective(s)

(1) **Objective**: To estimate the objective response rate (ORR), per RECIST 1.1 as assessed by M.D. Anderson radiology.

(2) **Objective**: To estimate the duration of response (DOR), disease control rate (DCR), TTP, progression-free survival (PFS), and OS per RECIST 1.1 as assessed by M.D. Anderson Department of Diagnostic Imaging.

(3) **Objective**: To evaluate the safety of pembrolizumab in combination with Zepatier as assessed by the proportion of subjects with HCV GT1 or GT4 achieving SVR12 and SVR24, defined as HCV RNA below the LLOQ (either TD[u] or TND) 12 and 24 weeks after the end of all study therapy.

4.0 BACKGROUND & RATIONALE

4.1 Exploratory Objectives

(1) **Objective:** To estimate ORR, DOR, DCR, TTP, PFS, and OS per iRECIST as assessed by M.D. Anderson radiology.

(2) **Objective:** To explore the relationship between progression on sorafenib versus intolerance of sorafenib and response to pembrolizumab.

(3) **Objective**: To perform exploratory biomarker research to study the correlation between immunological and molecular changes in tumor tissues and peripheral blood with TTP, OS, and the rate of AEs as described in Section 4.2.3.4. Tissue and blood immune monitoring will be conducted through our immune profiling group as detailed in the biomarker section from 3 biopsies done at the following time points: 1) pre-treatment, 2) 6 weeks after pembrolizumab therapy has commenced, and 3) at the time of progression (optional). We will explore the association between PD-1 ligand 1 (PD-L1) expression by immunohistochemistry (IHC), somatic gene expression profiling (GEP) and antitumor efficacy of pembrolizumab based on RECIST 1.1. See section 4.2.3.4.

(4) **Objective:** To explore predictive biomarkers to study the correlation of an independent effect of cirrhosis grade and severity of portal hypertension by MRI classification on OS. See section 2.1.

(5) **Objective:** To explore retrospective risk stratification of the degree of the underlying liver dysfunction by IGF-1 score. See section 2.1.

(6) **Objective:** To assess whether pembrolizumab in combination with Zepatier affects the course of viral infections in subjects with underlying HCV GT1 or GT4. We hypothesize that pembrolizumab in combination with Zepatier will help to reduce viral loads in those with untreated HCV.

(7) **Objective**: To evaluate the response of HCV GT1 and GT4 to treatment as assessed by sustained virologic response at 4 and 12 weeks after the end of 12 to 16 weeks of pembrolizumab in combination with Zepatier dosing. Sustained virologic response is defined as defined as HCV RNA below the LLOQ (either TD[u] or TND).

(8) **Objective:** To evaluate the emergence of viral resistance-associated variants (RAVs) to pembrolizumab in combination with Zepatier in subjects with with HCV GT1 or GT4 without RAVs as baseline .

(9) **Objective:** To evaluate the efficacy of pembrolizumab in combination with Zepatier as assessed by the proportion of subjects with HCV GT1 or GT4 achieving undetectable (TND) HCV RNA and HCV RNA below the LLOQ at Weeks 2, 4, 12 and Follow- Up Week 4 (SVR4), Week 12 (SVR12), and Week 24 (SVR24).

(10) **Objective:** To explore the relationship between genetic variation and subject response to the treatment(s) administered.

4.2 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on pembrolizumab and Zepatier.

4.2.1 Pharmaceutical and Therapeutic Background

4.2.1.1 Background on Hepatocellular carcinoma

Liver cancer is the third leading cause of cancer deaths in the world (22) and has one of the most rapidly rising mortality rates of any cancer in the United States (US) (23). Most HCC arises in the setting of liver cirrhosis from varied causes, including viral hepatitis, excessive alcohol consumption, hemochromatosis, and metabolic syndrome. As a consequence of these different etiologies, HCC is a heterogeneous malignancy. Despite advances in early detection, liver transplantation, and liver-directed therapies, about 70% of HCC patients present with advanced disease with no curative option. HCC is resistant to most traditional chemotherapy agents, and the median survival for patients with advanced disease is typically 6 to 9 months without therapy.

The oral tyrosine kinase inhibitor sorafenib is the current SOC worldwide for first line treatment of patients with advanced HCC (no curative option) and preserved liver function based on a large Phase III trial in a Western population. In this trial, TTP was 5.5 months, and OS was 10.7 months in the treatment arm, compared with 2.8 and 7.9 months in the control arm (24). A similar study conducted in the Asia-Pacific region showed an almost identical hazard ratio for sorafenib of 0.68 [95% CI 0.50-0.93], p=0.014, although OS was shorter in this trial (25). Several recent randomized clinical trials comparing other agents to sorafenib in the first-line setting have been negative, and sorafenib remains the worldwide approved systemic therapy for HCC patients (26). In parts of Asia, the FOLFOX regimen (folinic acid, 5-fluorouracil, and oxaliplatin) has also been approved, based on a randomized trial comparing FOLFOX4 to doxorubicin (27). In this trial, there was a non-significant trend toward improved OS in the FOLFOX arm, with some imbalances in the populations favoring the FOLFOX arm. Lenvatinib has recently shown efficacy in a Phase II study and there are news reports that it has demonstrated noninferiority to sorafenib in a Phase III study (28, 94). The application for lenvatinib was based on findings from the phase III REFLECT trial, in which overall survival (OS) was noninferior for lenvatinib versus sorafenib. Median OS with lenvatinib was 13.6 versus 12.3 months for sorafenib (HR, 0.92; 95% CI, 0.79-1.06). Lenvatinib was also associated with improvements in progression-free survival (PFS), time to progression (TTP) and objective response rate (ORR) compared with sorafenib. In September 2017 the FDA accepted a supplemental new drug application for lenvatinib as a frontline systemic treatment for patients with advanced hepatocellular carcinoma (HCC).

In the second-line setting, there is no clear SOC. Several large randomized trials again failed to show a significant survival advantage against placebo in the second-line setting, including brivanib (29), everolimus (30) and ramucirumab (31). Smaller studies have suggested the possible efficacy for c-MET inhibitors and regorafenib in advanced HCC, and larger randomized trials are underway to investigate these drugs in more detail (32, 33). The results of the Phase III study of regorafenib have recently been published and show a survival advantage (34). Chemotherapy drugs including capecitabine and the gemcitabine/oxaliplatin (GEMOX) combination have also been used in the second-line setting in small studies (35, 36). For second line HCC there was no clear standard of care until the recent approval of Regorafenid. In April 2017 Regorafenib was approved for HCC Bayer HealthCare

Pharmaceuticals Inc.) to include the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Approval was based on an international, multicenter, randomized, double-blind, placebo-controlled trial of 573 patients with Child-Pugh A and Barcelona Clinic Liver Cancer Stage B or C HCC with documented disease progression following sorafenib. Patients were randomly allocated to receive regorafenib160 mg orally once daily plus best supportive care (BSC) or matching placebo plus BSC for the first 21 days of each 28-day cycle (37). Treatment continued until disease progression or unacceptable toxicity. The trial demonstrated a significant improvement in overall survival (HR=0.63, 95% CI: 0.50, 0.79, p<0.0001) with an estimated median overall survival for patients in the regorafenib arm of 10.6 months and 7.8 months for patients in the placebo arm. A statistically significant improvement was also demonstrated for progression-free survival (PFS) based on modified RECIST for HCC (HR=0.46, 95% CI: 0.37, 0.56, p<0.0001), with an estimated median PFS of 3.1 and 1.5 months in the regorafenib and placebo arms, respectively. The overall response rate, based on modified RECIST, was 11% in the regorafenib arm and 4% in the placebo arm. The safety of regorafenib was evaluated in 1142 patients enrolled in randomized, placebo-controlled trials.

In September 2017 the FDA granted accelerated approval to nivolumab the treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib. Approval was based on a 154-patient subgroup of CHECKMATE-040 (95), a multicenter, open-label trial conducted in patients with HCC and Child-Pugh A cirrhosis who progressed on or were intolerant to sorafenib. In addition to including patients without active hepatitis viral infection, the trial enrolled patients with either active HBV (31%) or HCV (21%) but not those with active co-infection with HBV and HCV or with hepatitis D virus infection. Patients received nivolumab 3 mg/kg by intravenous infusion every 2 weeks. The confirmed overall response rate, as assessed by blinded independent central review using RECIST 1.1, was 14.3% (95% CI: 9.2, 20.8), with 3 complete responses and 19 partial responses. Response duration ranged from 3.2 to 38.2+ months; 91% of responders had responses lasting 6 months or longer and 55% had responses lasting 12 months or longer.

Despite these advances, continued investigation of additional agents for advanced HCC patients without a curative option remains crucial.

4.2.1.2 Background Hepatitis C Virus (HCV)

HCV Epidemiology and Natural History

Every year, 3 to 4 million people worldwide are newly infected with HCV, (22) and approximately 80% of these will progress to chronic infection (22). It is estimated that 130 to 170 million people, or 2 to 3% of the world's population, are chronically infected with HCV (39). Long-term complications of chronic HCV infection develop in chronically infected individuals over the course of several years to decades, including cirrhosis, end-stage liver disease and HCC (40). More than 350,000 people die from HCV-related liver diseases every year (22).

HCV has 6 major GTs, which can each be split into multiple subtypes. The global distribution of HCV GTs is diverse, which reflects differences in epidemiology, modes of transmission and ethnic variability. HCV GT1, GT2, and GT3 have a fairly broad geographical distribution, whereas HCV GT4, GT5, and GT6 are generally confined to specific geographical regions (39).

4.2.1.3 Overview of HCV Therapy

Until 2011, the SOC treatment for chronic HCV infection with all GTs was pegylated-interferon (Peg-IFN) plus ribavirin (RBV) administered for either 48 weeks (HCV GT1, GT4, GT5, and GT6) or for 24 weeks (HCV GT2 and GT3). Peg-IFN plus RBV therapy led to SVR rates of 40% to 50% in those with GT1 and of 80% or more in those with GT2 and GT3 infections (41,42).

This combination was replaced from 2011 to 2013 by a combination of Peg-IFN plus RBV and a first-generation NS3/4A protease inhibitor (telaprevir or boceprevir) in patients with HCV GT1, allowing about 70% SVR to be reached and the duration of therapy to be reduced from 48 to 24 weeks in half of the treated patients (43).

These first-generation regimens were quickly replaced by 2014 with the rapid availability of IFN-free regimens combining 2 or 3 second-generation direct-acting antiviral drugs (DAAs) with or without RBV. DAAs target specific nonstructural viral proteins involved in the replication cycle of HCV and include NS3/4A protease inhibitors (simeprevir or paritaprevir boosted by ritonavir), NS5B nucleos(t)idic (sofosbuvir) and non-nucleos(t)idic (dasabuvir) polymerase inhibitors, and NS5A replication complex inhibitors (daclatasvir, ledipasvir,elbasvir, velpatasvir). The combinations are given for 8 to 24 weeks, according to baseline factors such as fibrosis stage, GT and subtype baseline viral load, prior therapeutic history of the patient (naïve or experienced), pre-existing RAVs, and SVR rates greater than 90% with good tolerance. Safety and SVR rates are similar in clinical trials and in the real-life studies, usually higher than 95% in per-protocol analysis (44-47),

One of these combinations is Zepatier which is a combination of elvasvir (NS5A inhibitor) and grazoprevir (NS3 inhibitor) (48-50). The drug combination was assessed in 2 placebo-controlled trials and 4 uncontrolled Phase II and III clinical trials in 1401 subjects with GT1, GT4, or GT6 chronic HCV infection with compensated liver disease (with or without cirrhosis). Zepatier was approved 28 Jan 2016 based upon the C-EDGE DAA treatment-naïve, C-EDGE COINFECTION, C-SCAPE, and C-EDGE treatment-experienced trials. The indication for Zepatier is as follows: the FDC of elbasvir and grazoprevir is indicated with or without RBV for the treatment of chronic HCV GT1 or GT4 infection in adults. Because Zepatier is not indicated for GT6 infection, this GT will not be included in this study.

These DAA agents have distinct mechanisms of action and nonoverlapping resistance profiles to target HCV at multiple steps in the viral lifecycle. Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant HCV GT1a, GT1b, and GT4a NS3/4A protease enzymes with IC_{50} values of 7 pM, 4 pM, and 62 pM, respectively.

Here we propose to use the combination of Zepatier and pembrolizumab in HCV-positive (GT1 and GT4) subjects with with HCC in Arm B of this study.

4.2.1.4 HCV Resistance Mechanisms and Zepatier Treatment Schedule

Cell culture experiements indicated that viral strains with reduced susceptability to Zepatier could be selected. HCV replicons with reduced susceptibility to elbasvir and grazoprevir have been selected in cell culture for GT1a, GT1b, and GT4, which resulted in the emergence of resistance-associated amino acid substitutions in NS5A or NS3, respectively. The majority of amino acid substitutions in NS5A or NS3 selected in cell culture or identified in Phase IIb and 3 clinical trials were phenotypically characterized in GT1a, GT1b, or GT4 replicons.

For elbasvir, in HCV GT1a replicons, single NS5A substitutions M28A/G/T, Q30D/E/H/K/R, L31M/V, H58D, and Y93C/H/N reduced elbasvir antiviral activity by 1.5- to 2,000-fold. In GT1b replicons, single NS5A substitutions L28M, L31F, and Y93H reduced elbasvir antiviral activity by 2- to 17- fold. In GT4 replicons, single NS5A substitutions L30S, M31V, and Y93H reduced elbasvir antiviral activity by 3- to 23-fold (51).

For grazoprevir, in HCV GT1a replicons, single NS3 substitutions Y56H, R155K, A156G/T/V, and D168A/E/G/N/S/V/Y reduced grazoprevir antiviral activity by 2- to 81-fold; V36L/M, Q80K/R, or V107I single substitutions had no impact on grazoprevir antiviral activity in cell culture. In GT1b replicons, single NS3 substitutions F43S, Y56F, V107I, A156S/T/V, and D168A/G/V reduced grazoprevir antiviral activity by 1.5- to 375-fold. In GT4 replicons, single NS3 substitutions D168A/V reduced grazoprevir antiviral activity by 110- to 320-fold (52). In general, in HCV GT1a, GT1b, or GT4 replicons, combinations of grazoprevir RAVs further reduced grazoprevir antiviral activity (53).

A series of Phase II and III studies established the dosing regimens for treatment naïve or experienced patients. In Phase II studies an 8- or 12-week regimen of Zepatier (without RBV) were established that resulted in high SVR rates among treatment-naïve and treatment-experienced patients infected with HCV GT1, including those with compensated cirrhosis (54-57).

The C-WORTHY trial was a randomized, open-label Phase II study (part B) in patients with GT1b (58). Two cohorts of patients received grazoprevir/elbasvir FDC tablet qday with or without RBV for 12 or 18 weeks. Patients were treatment-naïve or null responders with or without cirrhosis. A total of 253 patients were included in the study: 123 patients were treatment-naïve with cirrhosis (Cohort 1) and 130 patients with or without cirrhosis were treated previously with Peg-IFN plus RBV but were null responders (Cohort 2). For Cohort 1, SVR12 rates were achieved in 90% (28/31) and 97% (28/29) in a 12-week course regimen of

grazoprevir/elbasvir with and without RBV, respectively, and 97% (31/32) and 94% (29/31) in an 18-week course, with and without RBV, respectively. Very little difference was seen due to the addition of RBV. In Cohort 2, SVR12 rates were achieved in 94% (30/32) and 91% (30/33) in a 12-week course regimen of grazoprevir/elbasvir with and without RBV, respectively, and in 100% (33/33) and 97% (31/32) in an 18-week course with and without RBV, respectively. Prior treatment falure had minimal effect on outcome.

The C-WORTHY trial (Part C) was a randomized, open-label, Phase II trial. Treatment-naïve, noncirrhotic GT1b-infected patients received grazoprevir/elbasvir FDC tablet qday with (n=30) or without (n=31) RBV for 8 weeks (59). SVR12 was achieved in 93% (27/29) of patients in the RBV arm and in 94% (29/31) of patients in the RBV-free arm, indicating no additive activity from RBV. The C-WORTHY trial established that RBV was not needed for GT1b-infected patients and a 12 week-course of Zepatier without RBV was recommended.

The C-SALVAGE trial was an open-label, Phase II study in HCV patients with GT1b with or without cirrhosis after failing Peg-IFN plus RBV plus a DAA. In this study, patients infected with GT1 with or without cirrhosis who failed to reach SVR after more than 4 weeks of Peg-INF plus RBV plus either boceprevir (35.4%), telaprevir (54.4%) or simeprevir (10.1%) were given grazoprevir/elbasvir FDC tablet qday with RBV (n=79) for 12 weeks. The data demonstrated that a 12-week course of grazoprevir/elbasvir with RBV is recommended in patients infected with GT1, with or without cirrhosis, after failing Peg-INF plus RBV plus a DAA. The follow-on C-SALT trial established that in patients infected with GT1 and with Charles-Pugh-B cirrhosis, a 12-week course of grazoprevir 50 mg and elbasvir 50 mg was highly effective and well tolerated (60).

Several Phase III trials investigated the safety and efficacy of grazoprevir/elbasvir FDC in GT1 and GT4 patient populations. C-EDGE DAA treatment-naïve was a Phase III, randomized, placebo-controlled trial in GT1, GT4, and GT6 patients with or without cirrhosis who previously failed Peg-IFN plus RBV (61). Patients were given grazoprevir/elbasvir without RBV or placebo for 12 or 16 weeks. Ninety-one percent of patients enrolled had GT1 (GT1a 50%, GT1b 41%), 6% had GT4, and 3% had GT6 and only 22% of patients had cirrhosis. SVR12 was achieved in 95% (299/316) of patients overall: 92% (144/157), 99% (129/131), 100% (18/18), and 80% (8/10) of GT1a-, GT1b-, GT4- and GT6-infected patients, respectively. The SVR12 rates were 97.1% (231/246) in cirrhotic patients and 93.9% (68/70) in noncirrhotic patients.

The study provided evidence for the safety and efficacy of the grazoprevir/elbasvir combination, which should be given for 12 weeks without RBV in treatment-naïve patients, irrespective of the fibrosis stage.

The C-EDGE treatment-experienced (C-EDGE TE) study was a Phase III, randomized, open-label trial in HCV GT1 or GT4 patients with or without cirrhosis, who previously failed Peg-IFN plus RBV. Grazoprevir/elbasvir was administered with or without RBV for 12 or 16 weeks. The trial enrolled the following patient types: 43% prior null responders, 21% prior partial responders, and 36% prior relapsers. SVR12 was achieved in 94% (98/104) of patients treated with grazoprevir/elbasvir plus RBV for 12 week, in 92% (97/105) of patients treated

with grazoprevir/elbasvir without RBV for 12 weeks, in 97% (103/106) of patients treated with grazoprevir/elbasvir plus RBV for 16 weeks, and in 92% (97/105) of patients treated with grazoprevir/elbasvir without RBV for 16 weeks. In patients with a history of prior relapse, SVRs were 100% in all arms except in the grazoprevir/elbasvir 16-week arm (92%). In patients with a prior null or partial response, SVRs were 91% in the 12-week grazoprevir/elbasvir regimen with or without RBV, respectively, and 100% and 94% in the 16-week grazoprevir/elbasvir arms with or without RBV, respectively.

In summary, 12 weeks of grazoprevir/elbasvir without RBV achieved SVR12 in 100% of both GT1b-infected patients and patients with history of previous PR relapse whereas 16 weeks of grazoprevir/elbasvir with RBV achieved high SVR rates (94–100%) with no virological failures regardless of the cirrhosis status, prior treatment history, or the presence of NS5A RAVs.

These trials established the doses and schedules used in this study as depicted in Table 4.

4.2.2 Pharmaceutical and Therapeutic Background Pembrolizumab

4.2.2.1 Overview

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (62). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells (Tregs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; HCC; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma (63, 64).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (65,66)

The structure of murine PD-1 has been resolved (67). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (68-71). The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins (72-73). As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in HCC.

4.2.2.2 Preclinical and Clinical Trial Data

Refer to the IB for Preclinical and Clinical pembrolizumab data.

Therapeutic studies in mouse models have shown that the administration of antibodies blocking the PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promotes CD8+ T-cell infiltration into the tumor and the presence of interferon gamma (IFN-γ), granzyme B (GB) and perforin, indicating that the mechanism of action involves local infiltration and activation of effector T cell function in vivo (74-79). Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Clinical trials have demonstrated efficacy using pembrolizumab in subjects with advanced melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma. In addition, recent data demonstrates emerging evidence of single-agent activity in additional tumor types such as mesothelioma, urothelial cancer, ovarian cancer, neuroendocrine carcinoma, and small cell lung cancer.

4.2.2.3 Ongoing Clinical Trials

Ongoing clinical trials of pembrolizumab are being conducted in advanced melanoma, NSCLC, and a number of other advanced solid tumor indications and hematologic malignancies. For study details refer to the IB.

4.2.3 Pharmaceutical and Therapeutic Background for the Combination of Grazoprevir and Elbasvir

4.2.3.1 Overview

Zepatier is a FDC product containing elbasvir, a HCV NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, and is indicated for treatment of chronic HCV GT1 or GT4 infection in adults. Zepatier is indicated for use with RBV in certain patient populations.

Grazoprevir (MK-5172) is a potent inhibitor of the viral protease, NS3/4A, with pangenotypic activity in vitro [49]. Elbasvir (MK-8742) is a potent inhibitor of the HCV NS5A, a pleiotropic protein with important roles in both HCV RNA replication and modulation of host cell physiology, and broad genotypic activity.

Please see US prescribing information for Zepatier dosing and regimens.

4.2.3.2 Summary of Ongoing Clinical Trials

For detailed information on Zepatier, refer to the IB.

4.3 Rationale

4.3.1 Rationale for the Trial and Selected Subject Population

Hepatocellular carcinoma

HCC is often driven by inflammation of various types, including viral infections. In a mouse model of HCC, blockade of PD-1 with immunostimulatory monoclonal antibodies extended survival (80). HCC patients with higher tumor expression of PD-L1 have a significantly poorer prognosis than patients with lower expression, and tumor expression of PD-L1 is also an independent predictor for postoperative recurrence in HCC (81). In addition, high expression levels of PD-1, both in TILs and peripheral blood mononuclear cells (PBMCs) also correlate with increased stage and recurrence in HCC patients after surgical resection (82). The interim analysis of a Phase I/II trial of nivolumab in patients with HCC demonstrated an estimated survival rate in evaluable patients (n=42) of 62% at 12 months with several durable responses. Responses were seen both in viral-mediated cancers and those without an underlying viral etiology. Results also showed the safety profile of nivolumab in HCC to be generally consistent with that previously reported in other tumor types and most recently, Nivolumab has been approved by FDA (83). Similarly, most recently, the FDA granted pembrolizumab (Keytruda) an accelerated approval for the treatment of patients with HCC who have previously received sorafenib based on findings from the phase II KEYNOTE-224 trial, in which single-agent pembrolizumab induced an overall response rate (ORR) of 17% (95% CI, 11-26) among 104 patients with advanced HCC previously treated with sorafenib (Zhu A, et al, Lancet Oncology 2018, PMID: 29875066). Among the 18 patients who responded, there was 1 complete response and 17 partial responses. Forty-six patients had stable disease, 34 patients had progressive disease, and 6 patients were not evaluable.

4.3.2 HCV Disease and Selected Patient Populations

Chronic HCV infection is a major public health problem associated with a substantial medical, social and economic burden. According to the 2006 National Health and Nutrition Examination Survey (NHANES), the prevalence of antibodies to HCV in the US population is approximately 1.6% (84).

Despite the approval of several DAAs by the FDA, the great proportion of HCV infected patients remains undiagnosed as routine screening is not yet common in most countries, and infected patients may not have any symptoms for many years after being infected. It is thus predicted that in the next decade, the treatment naïve population may still be the largest patient population that will require therapy (85). Subjects with HCV GT1 and GT4, will be assessed in this study. Immunotherapy has been studied for the treatment of HCV infection and in chronic HCV patients with HCC. Single dose PD-1 antibody treatment (Nivolumab) was studied in patients with chronic HCV infection demonstrating viral load reduction with tolerable autoimmune side effects that included transaminitis (86). CTLA-4 blockade with tremelimumab showed efficacy against HCC and HCV with transaminitis noted most frequently after the first dose (87). However, treating HCV infection in the setting of active systemic therapy in HCC has not been studied to date. This approach may lead to impoved HCC outcome in patients with concomitant HCV infection. Therefore we aim at combining pembrolizumab (FDA-approved secondline therapy in HCC) wih anti-HCV, oral Zepatier in patients with HCV-related HCC.

4.3.3 Rationale for Dose Selection/Regimen/Modification

4.3.3.1 Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W

(KEYNOTE [KN]001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5 fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols..

4.3.3.2 Zepatier (Grazoprevir and Elbasvir) Dose and Duration

Zepatier is a combination of 2 oral agents. The Zepatier dose regimen is as described in the prescribing information.

A grazoprevir dose of 100 mg qday was selected for Phase 3 trials based on high efficacy and a good safety profile from the Phase 2 dose ranging studies PN003 and PN038, as well as from PN035 and PN039. For detailed information, please refer to the IB.

An elbasvir dose of 50 mg qday was selected for Phase 3 trials based on high efficacy and a good safety profile from a Phase 1b monotherapy study in HCV infected subjects, elbasvir PN002, and a Phase 2a dose ranging study, grazoprevir PN035. For detailed information, please refer to the IB.

Zepatier was approved based upon 2 placebo controlled tirals and 4 uncontrolled trials (49-53). The trials were Phase II or Phase III studies of patients with HCV GT1, GT4, and GT6 with compensated liver disease with and without cirrhosis. The names of the trials include C-EDGE, C-Surfer, C-Scape, and C-Salvage. In these studies Zepatier was given for 12 to 18 weeks with and without RBV. Zepatier was administered qday PO in these trials with the doses of 50 mg elbasvir and 100 mg grazoprevir. For subjects who received RBV, the RBV dosage was weight-

based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered PO in two divided doses with food. Sustained virologic response was the primary endpoint in all trials and was defined as HCV RNA less than the LLOQ at 12 weeks after the cessation of treatment (SVR12).

4.3.3.3 Ribavirin Dose and Duration

The dose and duration of RBV with Zepatier for HCV GT1a: treatment-naïve with baseline NS5A polymorphisms was established in the C-Worthy trial (57,58). See Zepatier prescribing information. For patients with a creatinine clearance (CrCl) greater than 50 mL per minute, the recommended dosage of RBV is weight-based (less than 66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, greater than 105 kg = 1400 mg per day) administered in two divided doses with food. For patients with CrCl less than or equal to 50 mL per minute, including patients receiving hemodialysis, refer to the RBV tablet.

4.3.4 Rationale for Endpoints

4.3.4.1 Primary Endpoints

4.3.4.1.1 Safety

This is a study to estimate the safety and tolerability of the combination of pembrolizumab and Zepatier with or without ribavirin in subjects with advanced HCC treated previously with systemic monotherapy with sorafenib. Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by the NCI CTCAE, Version 4.0.

4.3.4.1.2 Sustained Virologic Response

The goal of therapy for chronic HCV infection is eradication of the virus, which is typically measured as a SVR. Obtaining clinical outcomes from prospective, randomized, controlled clinical trials in drug development programs for chronic HCV infection is a challenge and not feasible for most HCC populations due to the difficulty of maintaining patients on a randomized arm without intervening therapy for a sufficient duration to identify late-occurring clinical events, such as hepatic decompensation or HCC. For many approvals, a virological surrogate (SVR) has been used to measure treatment success in clinical trials supporting approval. SVR is an objective endpoint that signifies long-term clearance of hepatitis C and is generally regarded as a "virological cure." Based on numerous observational cohorts showing strong correlations between SVR and multiple clinically important outcomes, such as development of HCC, end-stage liver complications, and mortality, the FDA considers SVR a "validated" surrogate efficacy endpoint in CHC clinical trials (104-107)

Until recently, SVR at 24 weeks post-treatment (SVR24) has been considered the gold standard for treatment success; this end point is predictive of long-term eradication of the virus and

correlates with a reduction in symptoms and in the rate of negative clinical outcomes (88). All HCV therapies approved by the US FDA to date have been based on the efficacy assessment of the proportion of patients attaining SVR24 in the phase III confirmatory studies.Most patients who achieved SVR24 maintain their serum-negative status for HCV RNA, and <1% of patients would have subsequent detectable HCV RNA after achieving SVR24 (96). SVR24 has been associated with a reduction in liver disease complications and improvement in survival (97-98), and has been accepted as the primary efficacy end point for HCV therapies for regulatory approval (99-101).

However, there is evidence that most patients who have an SVR at earlier time points (such as SVR12) maintain it until week 24 (SVR24) (103). For example from a large metaanalysis the positive predictive value (PPV) of SVR12 was 98% and the negative predictive value (NPV) was 99% for SVR24 among subjects with genotype 1 HCV infection. A similar level of concordance was observed for subjects with HCV genotype 2 or 3 infections, as well as in pediatric studies. About 2% of subjects who achieved an SVR12 subsequently relapsed by week 24 (did not achieve an SVR24). Furthermore, the treatment effect size (difference between treatment and active control arms) was similar for subjects with SVR12 and SVR24. The PPV of SVR4 was 91% and the NPV was 98% for SVR24 in subjects with genotype 1 HCV infection. SVR12 and SVR24 measurements were concordant in a large population of subjects with HCV infection who participated in clinical trials with various treatment regimens and durations (103) . The FDA examined the correlation between SVR12 and SVR24 in over 13,000 subjectspooled from multiple clinical trials of Peg-IFN-basedregimens and found a high rate of concordance between SVR12 and SVR24; sensitivity and specificity forSVR12 were 99% and 98%, respectivelyTherefore, the FDA has concluded that SVR12 is suitable as a primary endpoint for regulatory approval (89).

4.3.4.2 Secondary/Exploratory Endpoints

This study will also utilize standard endpoints used in oncology studies. The secondary objectives of this study are to explore the anti-tumor efficacy or ORR per RECIST 1.1 criteria as assessed by M.D. Anderson radiology. Other secondary/exploratory endpoints will include DOR, DCR, TTP, PFS, and OS as assessed per RECIST 1.1.

1) ORR, defined as the proportion of subjects who have a CR or partial response (PR) using RECIST 1.1 and with confirmatory assessment as required per iRECIST at any time during the trial. Subjects with unknown or missing response information will be treated as non-responders.

2) DOR, defined in the subset of subjects with a CR or PR, based on RECIST 1.1 and with confirmatory assessment as required per iRECIST, as the time from first documented evidence of CR or PR until the first documented sign of PD or death due to any cause, whichever occurs first. Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.

3) PFS, defined as the time from the first dose of study treatment to the first

documented PD according to RECIST 1.1 and with confirmatory assessment as required per iRECIST, or death due to any cause, whichever occurs first. If a subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment.

4) OS, defined as the time from the date of the first dose of study to the date of death due to any cause. Censoring will be performed using the date of last known contact for those who are alive at the time of analysis.

5) Viral resistance measurements will be made on any subject who had detectable virus above 1000 IU/mL after completing Zepatier therapy. Blood samples for viral resistance assays and the determination of the sequence of RAVs will be obtained.

4.3.4.3 Exploratory Endpoints

To estimate ORR, DOR, DCR, TTP, and PFS per iRECIST by M.D. Anderson radiology per iRECIST, instead of per RECIST 1.1.

Tissue and blood immune monitoring will be conducted through our immune platform group as details per the biomarker section based on 3 biopsies done at the following time points: 1) pre-treatment, 2) 6 weeks after therapy, and 3) an optional biopsy upon progression.

4.3.4.4 Modified RECIST 1.1 for Immune-based Therapeutics (iRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen following treatment with pembrolizumab (Section 7.1.4.1.5). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and patients treated with pembrolizumab may manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Thus, standard RECIST 1.1 may, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of subjects with melanoma enrolled in KN001, 7% of evaluable subjects experienced delayed or early tumor pseudo-progression. Of note, subjects who had PD by RECIST 1.1 but not by the immune-related response criteria (90) had longer OS than subjects with PD by both criteria (91). Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of subjects. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical responses in immunotherapy and enables treatment beyond initial radiographic progression, if the subject is clinically stable.

iRECIST assessment has been developed and published by the RECIST Working Group, with input from leading experts from industry and academia, along with participation from the US Food and Drug Administration and the European Medicines Agency (92). The unidimensional measurement of target lesions, qualitative assessment of non-target lesions, and response categories are identical to RECIST 1.1, until progression is seen by RECIST 1.1. However, if

a subject is clinically stable, additional imaging may be performed to confirm radiographic progression. iRECIST will be used by Investigators to assess tumor response and progression and make treatment decisions as well as for exploratory efficacy analyses where specified.

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iRECIST will be used by M.D. Anderson Cancer Center (MDACC) investigators to assess tumor response and progression, and make treatment decisions as well as by M.D. Anderson Department of Diagnostic Imaging in support of all secondary and exploratory response. endpoints. Confirmation of PD for iRECIST endpoints will be taken from central imaging (this will be done by Quantitative Imaging Analysis Core [QIAC] at MDACC) retrospectively, according to iRECIST definition.

4.3.4.5 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of adverse events (AEs)/serious adverse events (SAEs); and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE, Version [4.0].

4.3.4.6 Biomarker Research

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to utilize these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/PD biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Translational studies to be performed on tissue and blood will be detailed in a separate procedure manual.

Sample Collection

1. CNB samples: A new fresh CNB will be obtained in all subjects prior to treatment (15 samples), 6 weeks after treatment has commenced, and an optional CNB biopsy upon progression. At least 5 cores will be obtained from the CNB procedure. The CNB cores (~6-8 mm in length) will be processed as FFPE or fresh frozen specimens. The CNB specimens will be examined for quality control and pathological characterization before being utilized for immune-profiling, as well as for DNA, RNA, protein extractions and flow cytometry. These samples will be stored at -80°C.

2. Blood specimens: Blood collection will be performed at screening, pre-chemo at Week 3 (end of Cycle 1), Week 6 (end of Cycle 2), and at confirmation of progressive disease/end of treatment. Depending on response, 3 to 4 blood samples will be collected per subject. There will be up to a total of 120 blood samples (15 patients × 4 samples × 2 arms = 120 blood samples), which will be collected in 3 CPT- and 2 purple-top tubes.

Three Vacutainer Cell Preparation Tubes (CPT) tubes, 8 ml of blood each with sodium heparin (Becton Dickinson Cat # 362753) will be processed for PBMCs isolation and cryopreserved. PBMCs will be isolated from blood at MDACC Institutional Tissue Bank (ITB). PBMC samples will then be submitted to Biostorage for flow cytometry analyses at Merck. Plasma from these three CPT tubes will be collected and frozen and sent to Biostorage for future use as determined by the Joint Steering Committee.

For TCR analysis, both purple top EDTA tubes of blood (20 ml total) will be processed for PMBCs isolation at MDACC ITB and will be shipped to MDACC TMP for genomic DNA extraction. For liquid biopsy analyses, plasma will be collected from the one EDTA tube being used to make genomic DNA (above) as well as a second EDTA tube (10 ml). These plasma samples will be frozen for future genotyping analysis of circulating free DNA (cfDNA) and/or circulating tumor cells (CTCs) at MDACC MTDL.

Investigations may include but are not limited to:

Blood Analysis

Subjects will have peripheral blood collected at pre-treatment, Week 6, time of response, and time of progression/end of study for both Arm 1 and Arm 2.

Flow cytometry: High order flow cytometry panels will be designed with input from the investigators and Merck at the time of analysis. The panels may include but not be limited to: 1) delineation of major immune cell types (T cells, B cells, NK cells, DCs, MDSCs), 2) determination of T cell differentiation status and limited functionality (IFNg, tumor necrosis factor alpha [TNFα], GB) and 3) defining the expression level of costimulatory and coinhibitory molecules on T cells and myeloid cells. The proposed studies will be conducted on cryopreserved PBMCs.

Liquid Biopsy Analysis (optional): Using plasma specimens, genotyping analysis of circulating free DNA (cfDNA), circulating tumor cells (CTCs), and exosome (exo)-DNA may be performed to monitor tumor response and progression at the Molecular Testing Developmental Laboratory (MTDL; Ignacio Wistuba and Raja Luthra) housed in TMP.

Serum Cytokine Analysis (optional): Serum cytokines to be measured may include IFN-γ, GB, perforin, IL-10, CCL20/MIP3α, and CXCL12/SDF-1. Additional cytokine panels may be selected at the discretion of the investigators or Merck based on emerging literature.

T cell receptor (TCR) Analysis: TCR sequencing analysis will be performed using DNA from PBMC. Total T cell density, TCR diversity and clonality will be evaluated. TCR profile

generated from treatment-refractory tumors at the time of PD will be compared to data from pre-treatment tumor samples to explore the TCR repertoire evolution of these tumors under therapeutic pressure. TCR profile will be correlated to clinical response as well as genomic profile of the tumor.

Blood will also be obtained for HCV viral load using the COBAS assay.

HCV Markers

COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 will be performed according to the manufacturers instructions. The key end point fore the HCV kinetics and response to Zepatier will be the COBAS test.

HCV resistance GTs will be assessed across the entire NS3/4A and NS5A regions for all subjects as per standard clinical testing for resistance .

Tissue Analysis

Tissue immune monitoring will be conducted done at the following time points: 1) pre-treatment, 2) 6 weeks after therapy, and 3) an optional biopsy upon progression.

The analyses will be performed at M.D. Anderson Tissue Molecular Pathology laboratory – in particular, the immunoprofiling lab (TMPIL) directed by Ignacio Wistuba and a Merck research Laboratories. Assays may include but are not be limited to:

Tumor PD-L1 Expression

In the pembrolizumab PN001 and PN012 studies, PD-L1 IHC has successfully been used as a biomarker in the NSCLC to enrich for a subpopulation with high response to pembrolizumab. Therefore, the relationship between PD-L1 expression in tumor tissue and response to treatment with pembrolizumab will be evaluated. PD-L1 expression in tumor cells and inflammatory cells within pre-treatment tumor tissue samples will be characterized by IHC and retrospectively tested for association with response to pembrolizumab. The range of PD-L1 staining in a population of HCC tumors may also be used to identify a cut-off, above which a tissue is scored as biomarker positive.

Multiplex Immunofluorescence Analysis (MIF)

MIF may be performed on tumor core samples utilizing immune marker panels. The panels to be utilized will be developed in collaboration and agreement with Merck Researh Laboratories and MD Andesron. MIF panels will interrogate tumor, immune cell infiltrates, and stromal components of the tumor.

Immune-related Gene Expression Profile

Intratumoral expression levels of select genes may be analyzed using an analytically validated platform, such as the NanoString nCounter Analysis System. Association between the

immune-related GEP and response to pembrolizumab has been established using these genes in melanoma and in cancers from clinical studies KN012 (head and neck, bladder, and gastric cancers) and KN028 (ovarian, esophageal, and other cancers). Data from these cohorts has been used to derive a GEP which combines the expression levels of several key genes into a single scalar score. The pattern of association in the esophageal cohort of KN028 using a prototype GEP suggested the ability to identify patients who may not respond to pembrolizumab by identifying tumors that have low values of the GEP. The GEP includes genes from immune-regulatory pathways and a GEP score will be tested for association with response to pembrolizumab in retrospective fashion. The relationship between GEP and the probability of response will be used to develop cut-offs that may have high clinical utility.

These Nanostring analyses will be performed using FFPE tissue from the core needle biopsy (CNB) specimens at Merck's vendor of choice.

Global Transcriptional Analyses

In addition to examining an immune-related GEP described above, RNA-Seq global messenger RNA profiling will also be pursued. RNAseq wil be performed on fresh core biopsies at a vendor of Merck's choice. Expression of individual genes related to the immune system may also be evaluated such as immune signatures and critical cytokines (e.g., IL-10).

Genetic (DNA) Analyses from Tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a "hyper-mutated" state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer)..

Whole Exome Sequencing

Flash freezing of fresh biopsy cores in liquid nitrogen may allow for RNA-squencing and Whole Exome Sequencing of tumor. This analysis will be performed using fresh frozen tissue specimens from CNB tumor tissues at Merck.

For all biomarker analyses, please refer to laboratory manuals for further details.

Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial

population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might identify optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.3 Benefit/Risk

Subjects in clinical trials may not receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine. However, data using similar drugs in HCC and other cancers suggests that some subjects may benefit from therapy.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and Informed Consent documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

For Arm 1 and 2 male and female subjects with advanced HCC with no curative option of at least 18 years of age will be enrolled in this trial.

For Arm 2 male and female subjects that are HCV-positive with genotype 1 or 4 virus infection will be enrolled.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research (FBR). However, the subject may participate in the main trial without participating in FBR.
2. Be at least 18 years of age on the day of signing informed consent.
3. Have histologically or cytologically confirmed diagnosis of HCC (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible) based on pathology report.
4. For Arm A and B: have Barcelona Clinic Liver Cancer (BCLC) Stage C disease or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach (see Section 12.9).
5. For Arm B have a detectable GT1, GT4, or HCV viral load TD(q) based on the Roche COBAS AmpliPrep/COBAS TaqMan HCV Test, v2.0 from a blood sample. HCV

RNA (≥10,000 IU/mL in peripheral blood) at the time of screening have documented chronic HCV GT1, GT4 (with no evidence of mixed genotype) infection:

a. Positive for anti-HCV antibody, HCV RNA, or any of the above HCV GTs at least 3 months before screening (HCV RNA and HCV GT must be confirmedby screening lab results) OR

b. Positive for anti-HCV antibody or HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before enrollment with evidence of CHC disease, such as the presence of fibrosis) or a Fibroscan performed within 12 months of Day 1 of this study with a result of >12.5 kPa or a FibroSure® (Fibrotest®) performed during Screening with a score of >0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of >2. APRI formula: AST ÷ lab upper limit of normal (ULN) for AST × 100 ÷ {platelet count÷100} (APRI calculation to be provided by the central laboratory.)

6. For Arm B subjects must undergo at screening HCV GT1a testing for resistance polymorphism as per Zepatier label.
7. Have a Child-Pugh A liver score at screening or within 14 days of first dose of study drug.
8. For Arm B have liver disease staging assessment as follows:

Cirrhosis is defined as any one of the following

a. A liver biopsy performed prior to Day 1 of this study showing cirrhosis (F4)

b. Fibroscan performed within 12 calendar months of Day 1 of this study showing cirrhosis with result >12.5 kPa [29]*

c. A FibroSure® (Fibrotest®) performed during Screening with a score of >0.75 and an aspartate aminotransferase (AST): platelet ratio index (APRI) of >2. APRI formula: AST ÷ lab upper limit of normal (ULN) for AST × 100 ÷ {platelet count÷100} (APRI calculation to be provided by the central laboratory.)

Absence of cirrhosis is defined as any one of the following:

a. Liver biopsy performed within 24 months of Day 1 of this study showing absence of cirrhosis

b. Fibroscan performed within 12 months of Day 1 of this study with a result of ≤12.5 kPa [29]*

c. A Fibrosure (Fibrotest) score of ≤0.48 and AST to Platelet Ratio Index (APRI) of ≤1 during Screening

Fibroscan cut-off of 12.5 kPa has a positive predictive value of 90% and a sensitivity of 95% for ≥F3. Based on box and whisker plot of interquartile distribution >12.5 kPa will exclude the majority of subjects with metavir F3 fibrosis. In the absence of a definitive diagnosis of presence or absence of

cirrhosis by the above criteria, a liver biopsy is required. Liver biopsy results supersede the results obtained by Fibroscan or Fibrosure.

9. Have a predicted life expectancy of greater than 3 months.
10. Have measurable disease based on RECIST 1.1 as confirmed by the blinded M.D. Anderson radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

    Note: the same image acquisition and processing parameters should be used throughout the study for a given subject..
11. Have a performance status of 0 or 1 using the ECOG Performance Scale within 7 days of first dose of study drug.
12. Have documented objective radiographic progression after stopping treatment with sorafenib or else intolerance to sorafenib. Intolerance to sorafenib is defined as: NCI CTCAE version 4.0 (Section 12.4) Grade ≥2 drug-related AE(s) which both a) persisted in spite of comprehensive supportive therapy according to institutional standards and b) persisted or recurred after sorafenib treatment interruption of at least 7 days and dose reduction by one dose level. Patients treated on sorafenib as the last treatment may start pembtolizumab at least 14 days after the last dose of sorafenib.
13. For Arm B Subjects with chronic active infection by HCV who are untreated or treated are allowed on study
14. Subjects with a past or resolved hepatitis B virus (HBV) infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test and negative HBV DNA test at screening, are eligible for the study.
15. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of trial medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
16. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.6.3 - Contraception, starting with the first dose of trial therapy through 120 days (Arm A) or 180 days (Arm b) after the last dose of trial therapy.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
17. Be willing to use an adequate method of contraception for the course of the study through 120 days (Arm A) or 180 days (Arm B) after the last dose of study medication (male and female subjects of childbearing potential [Section 5.6.3]). Acceptable methods of contraception are as follows:

    Single method (one of the following is acceptable):

    a. intrauterine device (IUD)

    b. vasectomy of a female subject's male partner

c. contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

d. diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

e. cervical cap with spermicide (nulliparous women only)

f. contraceptive sponge (nulliparous women only)

g. male condom or female condom (cannot be used together)

h. hormonal contraceptive: oral contraceptive pill (estrogen/ progestin pill or progestin- only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

Note: Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Institutional Review Boards (IRBs)/Ethics Review Committees (ERCs). 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 subjects participating at sites in this country/region.

18. Subjecs in Arm B treated with RBV must agree to double barrier birth control from Day 1 to 6 months following last dose of study therapy or they are excluded from this trial.

19. Have adequate organ function as defined in Table 2. Specimens must be collected within 7 days prior to the start of trial treatment.

Table 2 Adequate Organ Function Laboratory Tests

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for subjects with liver metastases)
Coagulation	

System	Laboratory Value
INR or PT aPTT	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; EPO = erythropoietin; GFR = glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal.	

5.1.3 Subject Exclusion Criteria

1. Is currently participating in or has participated in a trial of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of trial treatment.

   Note: Subjects must have recovered from all AEs due to previously therapies to ≤Grade 1 or baseline. Subjects with ≤Grade 2 neuropathy may be eligible Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

   Note: Subjects who have entered the follow-up phase of an investigational trial may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

2. Has had esophageal or gastric variceal bleeding within the last 6 months. All subjects will be screened for esophageal varices, unless such screening has been performed in the past 12 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study treatment.
3. Subjects with alanine aminotransferase (ALT) >5 × ULN at Day 1 are not eligible for enrollment.
4. Subjects with Total Bilirubin (Tbil) >2.0 mg/dL at Day 1 are not eligible for enrollment
5. Subjects with clinically apparent ascites or encephalopathy, or untreated varices are not eligible for enrollment. Subjects with Child-Pugh class B and C liver disease are also ineligible.
6. Portal vein invasion at the main portal branch (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging.
7. Has had encephalopathy in the last 6 months. Subjects on rifaximin or lactulose to control their encephalopathy are not allowed.
8. Had a solid organ or hematologic transplant.
9. Had prior systemic therapy for HCC other than sorafenib and/or regorafenib, or intercurrent local therapy to the liver tumor between sorafenib and/or regorafenib and study drug.

10. For Arm B is taking or plans to take any of the prohibited medications listed in Section 5 of this protocol or taking herbal supplements, including but not limited to St. John's Wort (Hypericum perforatum) within 2 weeks of Day 1.
11. Has evidence of history of chronic active hepatitis not caused by HCV, including but not limited to untreated active HBV (see criteria below under criterion 27), drug-induced hepatitis that is not resolved clinically, and autoimmune hepatitis.
12. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
13. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.
14. Has received locoregional therapy to liver (TACE, TAE, radiation, radioembolization, or ablation) or surgery to liver or other site within 6 weeks prior to the first dose of study drug. Minor surgery must have occurred at least 7 days prior to the first dose of study treatment (Cycle 1, Day 1). Subjects must have recovered adequately (i.e., Grade ≤1 or baseline) from the toxicity and/or complications from any intervention prior to starting therapy.
15. Has a known history of an additional malignancy, except if the participant has undergonepotentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy.

a. Note: *The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer,squamous cell carcinoma of the skin, in situ cervical cancer, in situ breast cancer, or other in situ cancers.*
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16. Has radiographically detectable (even if asymptomatic and/or previously treated) central nervous system (CNS) metastases and/or carcinomatous meningitis as assessed by local site investigator.
17. Has a history of (non-infectious) pneumonitis that required treatment with steroids or has current pneumonitis.
18. Has an active infection requiring systemic therapy.
19. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator, including dialysis.
20. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

21. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
22. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T cell receptor (eg, CTLA-4, OX-40, CD137)..
23. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
24. Has a known history of human immunodeficiency virus (HIV) infection. No HIV testing is required unless mandated by local health authority.
25. Has a known history of active tuberculosis (TB; *Bacillus tuberculosis*).
26. Has received a live vaccine within 30 days prior to the first dose of trial drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
27. Has untreated active HBV.

    Note: Antiviral therapy for HBV must be given for at least 3 months prior to first dose of study drug, and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Those on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment. HBsAg, HBsAb, anti-HBe, anti-HBc and HBV DNA must be measured at baseline and during the study. Those subjects who are anti-HBc (+) and negative for HBsAg and HBV DNA do not require HBV prophylaxis, but need monitoring with HBsAg, HBsAb, anti-HBe, anti-HBc, and HBV DNA

28. HCV-positive subjects received a prior NS5A-containing regimen.
29. Has received a live vaccine within 30 days of planned start of study therapy (Cycle 1, Day 1). Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
30. Subjects with a history of significant or unstable cardiac disease are excluded due to the hemolytic anemia associated with RBV. Subjects with proven coronoary artery disease or angina.
31. For Arm B subjects with HCV GT1a and have reistance polymorphisms are excluded if they have a CrCl of less than 50 mL/min.
32. Has received prior first-line therapy within 14 days of first dose of study medication.
33. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for

the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

34. Has known psychiatric or substance abuse disorders that would interfere with cooperating with the requirements of the trial.

5.2 Trial Treatments

The treatment to be used in this trial are outlined in Table 3, Table 4, and Table 5. Please see prescribing information for Zepatier and RBV.

Table 3 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3-week cycle	Experimental
Zepatier	Tablet: 50 mg elbasvir and 100 mg grazoprevir	qday	PO	Daily See Table 4	Experimental
RBV	Capsule: 200 mg See Table 5	qday	PO	Daily	Experimental
Abbreviations: IV = intravenous; PO = oral; Q3W = every 3 weeks; qday = once daily; RBV = ribavirin.					

The duration of Zepatier is dependent upon HCV GTs and presence or absence of resistance polymorphisms. Please see Table 4.

Table 4 Zepatier Trial Treatment Duration With or Without Cirrhosis

Patient Population	Treatment	Duration
GT1a: treatment-naïve without baseline NS5A polymorphisms[1]	Zepatier	12 weeks
GT1a: Treatment-naïve or PegIFN/RBV-experienced[1] or with baseline NS5A polymorphisms[2]	Zepatier + RBV[3]	16 weeks
GT1b: Treatment-naïve or PegIFN/RBV-experienced[1]	Zepatier	12 weeks
GT1a[4] or GT1b: PegIFN/RBV/PI-experienced[5]	Zepatier + RBV[3]	12 weeks
GT4: Treatment-Naïve	Zepatier	12 weeks
GT4: PegIFN/RBV-experienced[1]	Zepatier + RBV[3]	16 weeks

Abbreviations: GT = genotype; NS5A = non-structural protein 5A; PegIFN = pegylated interferon; RBV = ribavirin.

1. Patients who have failed treatment with PegIFN + RBV.
2. NS5A RAVs at amino acid positions 28, 30, 31, or 93. See Section 2.1 Testing prior to the initiation of therapy, subsection NS5A resistance testing in HCV GT1a-infected patients.
3. For patients with CrCl >50 mL per minute, the recommended dosage of RBV is weight-based (<66 kg = 800 mg per day, 66 to 80 kg = 1000 mg per day, 81 to 105 kg = 1200 mg per day, >105 kg = 1400 mg per day) administered in 2 divided doses with food. For patients with CrCl ≤50 mL per minute, including patients receiving hemodialysis, refer to the RBV tablet prescribing information for the correct RBV dosage.
4. The optimal Zepatier-based treatment regimen and duration of therapy for PegIFN/RBV/PI-experienced GT1a-infected patients with 1 or more baseline NS5A RAVs at positions 28, 30, 31, and 93 has not been established.
5. Patients who have failed treatment with PegIFN + RBV + HCV NS3/4A protease inhibitor (PI): boceprevir, simeprevir, or telaprevir.

Each Zepatier tablet contains 50 mg elbasvir and 100 mg grazoprevir, is beige, oval-shaped, film-coated, debossed with "770" on one side and plain on the other. The tablets are packaged into a carton (NDC 0006-3074-02) containing two (2) 14-count child-resistant dose packs for a total of 28 tablets.

Store Zepatier in the original blister package until use to protect from moisture. Store Zepatier at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (between 59°F to 86°F) [see USP Controlled Room Temperature].

In subjects with CrCl greater than 50 mL per minute, RBV will be administered twice a day (BID) PO (in RBV containing arms) at a total daily dose of 800 mg to 1400 mg based on subject weight on Day 1 (Table 5). RBV will be used for 12 to 16 weeks.

Table 5 Recommended Dosing for RBV in Combination Therapy for Subjects with CrCl Greater Than 50 mL Per Minute.

Body Weight in kg (lbs)	**RBV Dose**	**Ribavrin capsules**
<66 (<144)	800 mg/day	2 × 200 mg capsules A.M. 2 × 200 mg capsules P.M.
66-80 (145-177)	1000 mg/day	2 × 200 mg capsules A.M. 3 × 200 mg capsules P.M.
81-105 (178-231)	1200/mg day	3 × 200 mg capsules A.M. 3 × 200 mg capsules P.M.
>105 (>231)	1400 mg day	3 × 200 mg capsules A.M. 4 × 200 mg capsules P.M.
Abbreviations: A.M. = ante meridian; P.M. = post meridian; RBV = ribavirin.		

Trial Treatment should begin within 3 days of allocation/assignment. However, every effort should be made to begin trial treatment on the day of allocation (ie, Cycle 1 Day 1).

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of trial treatments in accordance with the protocol and any applicable laws and regulations.

All trial treatments will be administered on an out-patient basis.

All products indicated in Table 3 will be provided centrally by Merck or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by Merck.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

Details for Zepatier and RBV dosing will be outlined in the prescribing information.

5.2.1.2 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAEs	**Toxicity grade or conditions (NCI CTCAE v4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with 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.
	Grade 4	Permanently discontinue		

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAEs	**Toxicity grade or conditions (NCI CTCAE v4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue1		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold		• Monitor changes of renal function

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAEs	**Toxicity grade or conditions (NCI CTCAE v4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other irAEs	Intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; irAE = immune-related adverse event; IV = intravenous; NCI = National Cancer Institute; T1DM = type 1 diabetes mellitus.

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:

1. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 7.

Table 7 Pembrolizumab Infusion Reaction Dose Modification and 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 therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** 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 1 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 study drug treatment**	Subject may be premedicated 1.5 h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).
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: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids 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. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov

Other allowed dose interruptions for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with Merck. The reason for interruption should be documented in the subject's study record.

5.2.1.3 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 pembrolizumab treatment, notification of Merck within 24 hours, and a hepatology consultation. Refer to Section 7.2.3.2 for a reporting guidelines and the definition of hepatic ECIs.

All cases of retreatment and permanent discontinuation must be reported to the M.D. Anderson IND office and recorded in the database.

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

b. AST:
   i. Among subjects with baseline AST <2 × ULN: AST ≥5 × ULN
   ii. Among subjects with baseline AST ≥2 × ULN: AST >3 × 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 >2.0 mg/dL
   ii. Among subjects with baseline levels that are ≥1.5 mg/dL: a value ≥2 × the baseline level
   iii. Tbil >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 (GI) bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
   iii. Encephalopathy

(Subjects with clinically apparent ascites or encephalopathy, or untreated varices are not eligible for enrollment)

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 consultation with a hepatologist
  - 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 GI bleeding
  - Repeat ALT, AST, Tbil, direct bilirubin (Dbil), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), International Normalized Ratio (INR), and complete blood count (CBC) with differential
  - Other laboratories or imaging studies as clinically indicated
  - Consider liver biopsy if indicated by hepatologist

HCV-Infected Subjects (including subjects who previously achieved SVR12)

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

Permanent Discontinuation Criteria for Subjects with Non-overdose Hepatic ECI

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

- ALT >20 × ULN
- Child-Pugh score of ≥9 points
- GI bleeding suggestive of portal hypertension (e.g., esophageal or gastric varices)
- New onset of clinically detectable ascites
- 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

Other subjects may be eligible for treatment interruption (and potential restart) of pembrolizumab after discussion with Merck (Section 5.8.1).

Diagnosis and Management of Non-Overdose Hepatic ECIs

HCC subjects 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 ~1% of subjects who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects.

a. HBV Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to >5 × ULN and/or >3 × baseline. ALT elevation to ≥10 × 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 to 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 as follows:

- Care should be instituted in consultation with a hepatologist or infectious diseases.
- For subjects who have detectable HBV DNA, re-institute anti-viral therapy.
- If the subject is clinically stable, pembrolizumab dosing may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg, 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 to 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 pembrolizumab treatment. If these conditions are not met, then pembrolizumab treatment should be permanently discontinued.

b. HCV Recurrence or Flare

Subjects who achieved SVR12 and subjects with ongoing HCV infection are eligible for enrollment. In rare circumstances, HCV subjects who achieve SVR12 may relapse at later time points. Relapse is characterized by detection of HCV RNA, often accompanied by ALT elevations to >5 × 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 HCV, virologic flares are possible. HCV flares are characterized by rapid elevations of ALT and AST to >5 × ULN and/or >3 × baseline along with a rise in HCV RNA. ALT elevation to ≥10 × 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 to 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 "TND" 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 Q2W
- 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 Q2W
- 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 pembrolizumab treatment. If these conditions are not met, then pembrolizumab treatment should be permanently discontinued.

c. Immune-related hepatitis

i. Description: Immune-related hepatitis due to pembrolizumab should be suspected if any of the following is seen:

- AST or ALT baseline values are less than 2 × ULN, and AST or ALT laboratory values increase to ≥5 × ULN
- Among subjects with baseline ALT or AST ≥2 × ULN, levels increase to >3 × the baseline level
- AST/ALT >500 U/L regardless of baseline level

- Among subjects with baseline Tbil levels <1.5 mg/dL: a value of >2.0 mg/dL
- Among subjects with baseline Tbil levels that are ≥1.5 mg/dL: a value of ≥2× the baseline level
- Tbil >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

- Interrupt pembrolizumab treatment and alert Merck as per ECI criteria above for ALT, AST, bilirubin, and hepatic decompensation.
- Start IV corticosteroid (methylprednisolone 125 mg) followed by oral corticosteroid (1-2 mg/kg/day).
- Monitor with biweekly laboratory tests including AST, ALT, Tbil, Dbil, ALP, and INR.
- If symptoms and laboratory tests resolve to ≤Grade 1 or baseline (if abnormal at baseline), taper steroids over 28 days. Pembrolizumab 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).
- 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 CPC 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 should 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. See Section 5.5.2 for drugs which may interfere with hepatic function.

- For all of these cases, subjects may resume pembrolizumab 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 pembrolizumab therapy for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become Child-Pugh C at any point

5.2.1.4 Zepatier Dose Modification (Escalation/Titration/Other)

Dose modification of Zepatier is not permitted with the exception of hepatic events, SAEs, or laboratory abnormalities.

During clinical trials with Zepatier with or without RBV, 1% of subjects experienced elevations of ALT from normal levels to greater than 5 × ULN, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subpopulations: female sex (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2%).For ALT elevations on Zepatier, follow recommendations in full prescribing information.

Hepatic laboratory testing should be performed prior to therapy, at treatment Week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.

- Subjects should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice, or discolored feces.
- Consider discontinuing Zepatier if ALT levels remain persistently greater than 10 × ULN.
- Discontinue Zepatier if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, ALP, or INR.

5.2.1.5 RBV Dose Modification (Escalation/Titration/Other)

If Zepatier is administered with RBV refer to the RBV prescribing information for a description of RBV-associated adverse reactions. Monotherapy RBV for HCV is not permitted in this trial.

The primary toxicity of RBV is hemolytic anemia, which was observed in approximately 10% of RBV/Intron A-treated subjects in clinical trials. While this study does not include Intron A treatment hemolytic anemia surveillance is still warrented. The anemia associated with RBV capsules occurs within 1 to 2 weeks of initiation of therapy. Because the initial drop in

hemoglobin may be significant, it is advised that hemoglobin or hematocrit be obtained before the start of treatment and at Week 2 and Week 4 of therapy, or more frequently if clinically indicated. Subjects should then be followed as clinically appropriate Fatal and nonfatal myocardial infarctions have been reported in patients with anemia caused by RBV. Subjects should be assessed for underlying cardiac disease before initiation of RBV therapy. Subjects with pre-existing cardiac disease should have electrocardiograms (ECGs) administered before treatment, and should be appropriately monitored during therapy. If there is any deterioration of cardiovascular status, therapy should be suspended or discontinued. Because cardiac disease may be worsened by drug-induced anemia, patients with a history of significant or unstable cardiac disease should not use RBV.

RBV should not be used in subjects with CrCl less than 50 mL/min. Subjects with impaired renal function and those over the age of 50 should be carefully monitored with respect to development of anemia.

If severe AEs or laboratory abnormalities develop during the study, RBV can be modified based on the recommended guidelines provided in Table 8.

For subjects with a history of stable cardiovascular disease, a permanent dose reduction is required if the hemoglobin decreases by greater than or equal to 2 g/dL during any 4-week period. In addition, for these cardiac history patients, if the hemoglobin remains less than 12 g/dL after 4 weeks on a reduced dose, the patient should discontinue combination therapy. It is recommended that a patient whose hemoglobin level falls below 10 g/dL have his/her RBV dose modified or discontinued per Table 9.

Subjects exhibiting the following conditions should be closely monitored and may require dose reduction or discontinuation of RBV therapy. Refer to the prescribing information:

- Hemolytic anemia may occur with a significant initial drop inhemoglobin
- Pancreatitis
- Pulmonary infiltrates or pulmonary function impairment
- New or worsening ophthalmologic disorders
- Concomitant administration of azathioprine
- Severe decreases in neutrophil and platelet counts and hematologic, endocrine and hepatic abnormalities
- Dental/periodontal disorders with combination therapy

Table 8 Dose Reduction Rules for RBV

Laboratory Parameters	Reduce RBV if	Discontinue Therapy if
HGB without a history of cardiac disease	8.5 to <10 g/dl	< 8.5 g/dl
HGB with a history of stable cardiac disease	<2 g/dL decrease in hemoglobin during any 4-week period during treatment	<8.5 g/dL or <12 g/dL after 4 weeks of dose reduction

Abbreviations: HGB = hemoglobin; RBV = ribavirin

Table 9 Dose Modifications for RBV

Body Weight on Day 1	FDD (mg/day)	1st RBV Reduction		2nd RBV Reduction		3rd RBV Reduction	
		Dose (mg/day)	Number of 200 mg Capsules	Dose (mg/day)	Number of 200 mg Capsules	Dose (mg/day)	Number of 200 mg Capsules
51-65 kg (112-114 lb)	800	600	1 in AM/ 2 in PM	400	1 in AM/ 2 in PM	200	1 in AM/ 2 in PM
66-80 kg (145-177 lb)	1000	800	2 in AM/ 2 in PM	600	1 in AM/ 2 in PM	400	1 in AM/ 2 in PM
81-105 kg (178-231 lb)	1200	1000	2 in AM/ 3 in PM	800	2 in AM/ 2 in PM	600	1 in AM/ 2 in PM
105-125 kg (232-275 lb)	1400	1000	2 in AM/ 3 in PM	800	2 in AM/ 2 in PM	600	1 in AM/ 2 in PM

Abbreviations: AM = ante meridian; FDD = full daily dose; PM = post meridian; RBV = ribavirin

5.2.1.6 Dose Interruptions

If a subject misses a dose of Zepatier and it is less than 8 hours before the next dose, the missed dose should be skipped and the normal dosing schedule resumed. Subjects should not double the next dose in order to compensate for what has been missed.

If for any reason Zepatier needs to be interrupted it can be interrupted for up to 3 days. If Zepatier is interrupted for more than 3 days, consult Merck for that patient. RBV is not to be taken as monotherapy in the absence of Zepatier.

If pembrolizumab treatment is interrupted then maintain the subject on Zepatier (±RBV) unless due to severe liver toxicity. No dosage adjustment of Zepatier is recommended in patients with mild hepatic impairment (Child-Pugh A). Zepatier is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) or severe hepatic impairment (Child-Pugh C).

If a subject misses a dose of RBV, then they should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then these missed doses should be skipped, and the normal dosing schedule should be resumed. Subjects should not double the next dose in order to "make up" what has been missed.

If for any reason RBV needs to be interrupted (e.g. for safety reasons), if possible, it should be restarted within 3 days.

5.2.2 Timing of Dose Administration

Cycle 1 Day 1 treatment with pembrolizumab should begin on the day of allocation, but no later than 3 days from the date the subject is allocated to study treatment. However, every effort should be made to begin trial treatment on the day of allocation.

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion Q3W. 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 of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

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

Pembrolizumab trial treatment will be administered on an outpatient basis.

Subjects will be instructed to take Zepatier orally without regard to food in regimens not requiring RBV. Subjects will be instructed to take Zepatier and RBV (in RBV containing arms) orally, in the morning. RBV should be taken with food. A second daily dose of RBV should be taken by itself, with food, in the evening.

No more than 12 weeks worth of Zepatier/ treatment are to be given and no more than 16 weeks worth of Zepatier/RBV treatment are to be given.

5.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, Merck, investigators, and subjects will know the treatment administered.

5.3 Randomization or Treatment Allocation

This is a non-randomized trial. Subjects will be allocated per arm based upon inclusion and exclusion criteria. Arms are not compared. All enrolled subjects will be allocated to receive pembrolizumab 200 mg Q3W as monotherapy in an unblinded fashion (Section 2.1).

5.4 Stratification

No stratification based on age, sex or other characteristics will be used in this trial

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

5.5.1 Acceptable Concomitant Medications

All treatments that the Investigator considers necessary for a subject'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 CRF including all prescription, over-the-counter (OTC) products, herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should also be included on the CRF. All concomitant medications received within 28 days prior to the first dose of trial treatment and up to 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

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

- 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. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an ECI that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with Merck.
- Chronic use of NSAIDs with a high risk of bleeding, for example, indomethacin, ibuprofen, naproxen, or similar agents. Chronic use of aspirin up to 325 mg/day is permitted.

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

It is important for investigators to review each medication (prescription and non-prescription) the subject is taking before starting the study and at each study visit.

- At each visit, subjects should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- 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.

Listed below are specific restrictions for concomitant therapy during the course of the trial.

The following medications/therapies are discouraged during the dosing period and for 14 days thereafter:

Known hepatotoxic drugs, including but not limited to:

- Etifoxine
- Isoniazid
- Nitrofurantoin
- Ketoconazole
- Amiodarone
- Phenytoin
- Herbal supplements

The Exclusion Criteria describes other medications which are prohibited in this trial. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.3 Zepatier Concomitant Medications/Vaccinations (Allowed & Prohibited)

Zepatier is contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of cytochrome P450 3A (CYP3A), and efavirenz.

If Zepatier is administered with RBV, the contraindications to RBV also apply to this combination regimen. Refer to the RBV prescribing information for a list of contraindications for RBV.

- Co-administration of Zepatier with moderate CYP3A inducers is not recommended as they may decrease the plasma concentration of Zepatier.
- Co-administration of Zepatier with certain strong CYP3A inhibitors is not recommended as they may increase the plasma concentration of Zepatier.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the dosing period. If there is a clinical indication for any medication or vaccination specifically prohibited during the dosing period, discontinuation from trial therapy or

vaccination may be required. The investigator should discuss any questions regarding this with Merck's Clinical Director. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, Merck and the subject.

It is important for investigators to review each medication (prescription and non-prescription) the subject is taking before starting the study and at each study visit.

- At each visit, subjects should be questioned about any new drug they are taking.
- To minimize the risk of adverse drug interactions, every effort should be made to limit the number of concomitant drugs to those that are truly essential.
- 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.

The following medications/therapies are contraindicated during the dosing period:

Known hepatotoxic drugs, including but not limited to:

- Etofoxine
- Isoniazid
- Nitrofurantoin
- Phenytoin

Herbal supplements

- Strong and moderate CYP3A/P-gp inducers, including but not limited to:
- Anti-infectives: nafcillin, rifampin
- Anticonvulsants: carbamazepine, phenytoin, phenobarbital
- bosentan
- modafinil
- St. John's Wort

OATP inhibitors, including but not limited to:

- Immunosuppressants: cyclosporine
- Anti-infectives: rifampin
- gemfibrozil
- eltrombopag
- lapatinib

HMG-CoA reductase inhibitors (statins):

- simvastatin
- fluvastatin
- rosuvastatin greater than 10 mg (see Allowed Medications, below)

- atorvastatin greater than 10 mg (see Allowed Medications, below)

In general, CYP3A4 substrates with narrow therapeutic ranges (e.g. alfentanil, astemizole, cisapride, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, terfenadine) are not prohibited, but their levels have the potential to be increased by approximately 30%. Therefore, subjects taking these medications should be monitored closely or dose adjusted appropriately.

In general, P-glycoprotein (P-gp) substrates with narrow therapeutic ranges (e.g., digoxin and colchicine) are not prohibited, but their levels have the potential to be increased. Therefore, subjects taking these medications should be monitored closely.

Investigational agents are not permitted.

Systemic corticosteroids (dose equivalent to ≥ 10 mg prednisone per day, except in the case of rapid steroid tapers <1 week in duration) are not permitted.

Refer to the Zepatier prescribing information for additional details on the drugs contraindicated with Zepatier.

Allowed Medications:

The following concomitant medications are allowed in this study:

Anti-coagulants: warfarin, heparin, low molecular weight heparin, aspirin, fondaparinux, desirudin, acenocoumarol

Antihypertensives:

- ACE inhibitors/ARB: enalapril, captopril, lisinopril, ramipril, valsartan, losartan, telmisartan
- Beta blockers: atenolol, metoprolol, propranolol. Note: for other beta blockers, please consult with Merck
- Calcium-channel blockers: verapamil, diltiazem, amlodipine. Note: for other calcium-channel blockers, please consult with Merck
- hydralazine, clonidine, minoxidil, isosorbide nitrates

Anemia: erythropoietin

Diuretics: HCTZ, furosemide, spironolactone, triamterene

Hypoglycemic agents: insulin, metformin, sitagliptin, glipizide

Contraceptives: oral contraceptive pills, progesterone injects, intrauterine devices

Antidepressants/anxiolytics: citalopram, paroxetine, duloxetine, escitalopram, fluoxetine, bupropion, trazodone, diazepam, clonazepam, temazepam, lorazepam

Acid reflux: H2 blockers, proton pump inhibitors

HMG-CoA reductase inhibitors (statins):

- Pravastatin and pitavastatin: may be coadministered without dose adjustment
- Rosuvastatin: use the lowest possible effective dose of rosuvastatin, but do not exceed a daily dose of 10 mg
- Atorvastatin: use the lowest possible effective dose of atorvastatin, but do not exceed a daily dose of 10 mg

Concomitant medications and therapies discontinued during the dosing period may be restarted 2 weeks after the last dose of study drug is administered and may continue during the follow-up period.

Note: For other medications not listed here, please consult with Merck.

5.5.4 RBV Concomitant Medications/Vaccinations (Allowed & Prohibited)

Concomitant Administration of Azathioprine

Pancytopenia (marked decreases in red blood cells, neutrophils, and platelets) and bone marrow suppression have been reported in the literature to occur within 3 to 7 weeks after the concomitant administration of Peg-IFN/RBV and azathioprine. In this limited number of patients (n=8), myelotoxicity was reversible within 4 to 6 weeks upon withdrawal of both HCV antiviral therapy and concomitant azathioprine and did not recur upon reintroduction of either treatment alone. PegIntron, RBV, and azathioprine should be discontinued for pancytopenia, and Peg-IFN/RBV should not be reintroduced with concomitant azathioprine.

Concomitant Administration of Didanosine

Exposure to didanosine or its active metabolite (dideoxyadenosine 5'-triphosphate) is increased when didanosine is coadministered with RBV, which could cause or worsen clinical toxicities; therefore, coadministration of RBV capsules or oral solution and didanosine is contraindicated. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported in clinical trials.

5.6 Rescue Medications & Supportive Care

5.6.1 Rescue Medications

No rescue medications are specified to be used in this trial.

5.6.2 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, (Table 6). Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 6 in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.6.3 Contraception

Pembrolizumab may have adverse effects on a fetus in utero.

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 meet 1 of the following criteria:

- She is postmenopausal, defined as at least 12 months with no menses without an alternative medical cause. In women <45 years of age who are not using hormonal contraception or hormonal replacement therapy, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- She had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening.
- She has a congenital or an 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 trial drug and for 120 days after the last dose of trial drug by complying with 1 of the following:

- Practice abstinence from heterosexual activity.

  Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IRBs/ERCs. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

Acceptable methods of contraception are‡:

- Single method (1 of the following is acceptable):
  - IUD
  - Vasectomy of a female subject's male partner
  - Contraceptive rod implanted into the skin
- Combination method (requires use of 2 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

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

Subjects should be informed that taking the trial medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the trial. In order to participate in the trial, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of trial medication initiation (or 14 days prior to the initiation of trial medication for oral contraception) throughout the trial period up to 120 days (Arm A) or 180 days (Arm B) after the last dose of trial medication. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

5.6.4 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will be immediately discontinued from trial treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Merck without delay and within 24 hours if the outcome is a SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The trial 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 Merck. If a male subject impregnates his female partner,

the trial personnel at the site must be informed immediately and the pregnancy must be reported to Merck and followed as described in Section 7.2.

5.6.1 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

5.6.2 Discontinuation of Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

As certain data on clinical events beyond study treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued study treatment. Therefore, all subjects who discontinue study treatment prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 6 and Section 7.1.6.4.

Subjects may discontinue study treatment at any time for any reason or be dropped from the study treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from study treatment by the investigator or Merck if study treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study treatment discontinuation are provided in Section 7.1.5.1.

A subject must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) requests to discontinue treatment.
- Confirmed radiographic disease progression outlined in Section 7.1.4 (exception if Merck approves treatment continuation).
- Unacceptable AEs as described in Section 7.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- A confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Completed 35 treatments with pembrolizumab

Note: 35 treatments (approx. 2 years) are calculated from the first dose.

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.6 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for AE monitoring (SAEs will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented PD each subject will be followed by telephone for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.6.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a centrally confirmed CR that have received at least 8 cycles (approximately 6 months) of pembrolizumab and had at least 2 cycles of pembrolizumab beyond the date when the initial CR was declared.

5.6.2 Treatment after Initial Radiologic Progression (iRECIST-based Management)

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial apparent increase in tumor burden (i.e., pseudoprogression) or even the appearance of new lesions. Standard RECIST-based assessment of disease progression may, thus, not provide an accurate assessment of response to immunotherapeutic agents such as pembrolizumab. For this reason, iRECIST has been developed to help guide treatment decisions during tumor immunotherapy.

For subjects who have initial radiological evidence of radiological PD by RECIST 1.1, the investigator may elect to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the investigator should only be made if the subject is clinically stable, based on clinical factors including performance status, clinical symptoms, and laboratory data. Such subjects may continue to receive study treatment and an imaging-based tumor assessment should be repeated ≥4 weeks later in order to reassess PD per investigator assessment (Section 7.1.4.2.4).

5.7 Subject Replacement Strategy

Subjects will not be replaced on trial.

5.8 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form (ICF). The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

5.9 Clinical Criteria for Early Trial Termination

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems, or the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart Initial Treatment with Pembrolizumab

Trial Period:	**Screening Phase**	**Treatment Cycles (3-Week Cycles). 1 year or treatment or 17 cycles in total.**								**End of Treatment**	**Virologic Failure – Arm B[s]**	**Post-treatment**		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**DC**		**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Week (approximate)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	At DC		30 days post last dose	Q9W post-DC	Q12W
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Administrative Procedures														
ICF	X													
Inclusion/exclusion criteria	X													
Demographics and medical history	X													
Prior and concomitant medication review	X	X	X	X	X	X	X	X	X	X		X		
Post-study anticancer therapy status												X	X	X
Zepatier and Ribavirin Medication adherence		X	X	X	X	X	X	X	X					
Survival status[u]		X	X	X	X	X	X	X	X	X		X	X	X
Clinical Procedures/Assessments														
Review AEs	X	X	X	X	X	X	X	X	X	X		X	X[l]	
Full physical examination	X									X		X		
Directed physical examination		X	X	X	X	X	X	X	X					
Child-Pugh score	X													

Trial Period:	**Screening Phase**	**Treatment Cycles (3-Week Cycles). 1 year or treatment or 17 cycles in total.**								**End of Treatment**	**Virologic Failure – Arm B[s]**	**Post-treatment**		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**DC**		**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Week (approximate)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	At DC		30 days post last dose	Q9W post-DC	Q12W
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Height, weight, and vital signs (T, P, RR, BP)[c]	X	X	X	X	X	X	X	X	X	X				
12-Lead ECG	X													
Upper endoscopy	X													
ECOG performance status	X[e]	X	X	X	X	X	X	X	X	X				
Pembrolizumab administration		X[b]	X	X	X	X	X	X	X					
LOCAL Laboratory Assessments														
Pregnancy test[d]	X	X	X	X	X	X	X	X	X	X		X		
PT/INR and aPTT	X[e]		X	X	X	X	X	X	X	X		X		
CBC with differential[f]	X[e]		X	X	X	X	X	X	X	X		X		
Chemistry panel[f]	X[e]		X	X	X	X	X	X	X	X		X		
Liver panel[g,t]	X[e]		X	X	X	X	X	X	X	X		X		
Urinalysis[h]	X[e]		X		X		X		X	X				
T3, FT4, and TSH[h,]	X[e]		X	X	X		X		X	X		X		
AFP[m]	X[e]	X		X			X			X		X		
C-Reactive protein		X	X			X				X				
Fibrotest	X													
APRI	X													
Coagulation														
Serum IGF-1	X[p]			X			X			X				

Trial Period:	**Screening Phase**	**Treatment Cycles (3-Week Cycles). 1 year or treatment or 17 cycles in total.**								**End of Treatment**	**Virologic Failure – Arm B[s]**	**Post-treatment**		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**DC**		**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Week (approximate)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	At DC		30 days post last dose	Q9W post-DC	Q12W
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Child-Turcotte-Pugh (CTP) Calculation	X													
Viral testing														
HCV Ab	X													
HCV genotype Arm B	X													
HCV viral load[q, r] Arm B	X	X	X	X	X	X	X	X	X	X	X	X		
If (1) HBV+ or (2) anti-HBc+ and HBsAg- and viral load-negative:														
Anti-HBc (total and IgM), anti-HBs,	X													
HBsAg and HBV viral load[m]	X	X	X	X	X	X	X	X	X			X		
Anti-HBc (total), anti-HBe, anti-HBs, and HBeAg[m]	X				X				X			X		
Plasma for HCV viral resistance testing Arm B[r]	X	X[r]									X[s]			
CENTRAL Laboratory Assessments														
Blood for genetic analysis[k]		X												
Whole blood for biomarker studies (serum and plasma)[k]	X	X	X							X				
Whole blood for correlative studies (RNA and DNA)[k]	X	X	X							X				

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles). 1 year or treatment or 17 cycles in total.								End of Treatment	Virologic Failure – Arm B[s]	Post-treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**DC**		**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Week (approximate)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	At DC		30 days post last dose	Q9W post-DC	Q12W
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7
Newly Obtained Tissue Collection [k]	X		X							X				
Efficacy Measurements														
Tumor imaging[i]	X[j,n]	X[o]		X			X			X		X	X	

Abbreviations: AEs = adverse events; AFP = alpha fetoprotein; APRI = aspartate aminotransferase:platelet ratio index; aPTT = activated partial thromboplastin time; BP = blood pressure; CBC = complete blood count; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FT4 = free thyroxine; HBV = hepatitis B virus; HBcAg = hepatitis B core antigen; HBsAb = anti-HBsAg antibody; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = informed consent form; IGF-1 = insulin-like growth factor-1; INR = international normalized ratio; P = pulse; Q3W = every 3 weeks; Q9W = every 9 weeks; Q12W = every 12 weeks; RR = respiratory rate; T = temperature; PT = prothrombin time; T3 = triiodothyronine; TSH = thyroid-stimulating hormone.

a. In subjects that experience site-assessed PD or start a new anti-cancer therapy, contact should be made (eg; by telephone) Q12W to assess for survival status.

b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ±3 days until the end of treatment and ±7 days during follow-up.

c. Height will be measured at screening only. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to Day 1 of each treatment cycle and 30 days post treatment.

d. A serum test can be done if urine is not appropriate. Additionally, if urine test is positive or is not evaluable, a serum test is required. Subjects must be excluded/discontinued in the event of a positive test results Monthly pregnancy testing should be conducted as per local regulations where applicable.

e. ECOG Performance Status and laboratory tests for screening and determining eligibility are to be performed within 7 days and 10 days, respectively, prior to the first dose of trial treatment.

f. CBC with differential and chemistry to be performed every cycle

g. Liver panel (albumin, ALT, AST, total and direct bilirubin, and alkaline phosphatase) to be performed at screening and then every week for the first 2 cycles followed by every cycle starting at cycle 3. Liver panel will also be done at discontinuation and safety follow-up.

h. Urinalysis will be performed at screening and then every other cycle. Thyroid function will be at screening, every second cycle starting at cycle 2, discontinuation, and safety follow-up. Blood will be collected at baseline pre-dose at day 1 Cycle 1 of Pembrolizumab (week 3), Cycle 2 (week 6 before the 2nd dose of Pembrolizumab), confirmed response, and again at treatment discontinuation (confirmed progression or end of therapy) (collections, 60 samples per study Arm). . This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/ERC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles). 1 year or treatment or 17 cycles in total.								End of Treatment	Virologic Failure – Arm B[s]	Post-treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**DC**		**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Week (approximate)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	At DC		30 days post last dose	Q9W post-DC	Q12W
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7

will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR

i. Screening tumor imaging will be performed within 28 days prior to allocation. Confirmation of baseline measurable disease per RECIST 1.1 by M.D. Anderson radiology is required prior to subject allocation. Tumors will be imaged Q9W (63±7 days) calculated from the date of allocation and will continue to be performed Q9W (63±7 days).

j. The first on-study imaging time point will be performed at 9 weeks (63±7 days) calculated from the date of allocation and will continue to be performed Q9W (63±7 days

k. **Blood samples** Blood collection will be performed at screening, pre-chemo at Week 3 (end of Cycle 1), Week 6 (end of Cycle 2), and at confirmation of progressive disease/end of treatment. Depending on response, 3 to 4 blood samples will be collected per subject. There will be up to a total of 120 blood samples (15 patients × 4 samples × 2 arms = 120 blood samples), which will be collected in 3 CPT- and 2 purple-top tubes. **Biopsies** will be required pre-treatment, after 6 weeks of Pembrolizumab therapy, and voluntarily upon progression. Biopsies will be taken 6 weeks after treatment has commenced with an optional biopsy upon progression. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/ERC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

l. SAEs will be followed through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier.

m. AFP and HBV viral loads (for subjects who were positive) will be measured. Anti-HBc antibody, HBV e antigen and Ab, and anti-HBs will be measured every 12 weeks (84±7 days) calculated from the date of allocation , or earlier if clinically indicated. HBV viral load and HbsAg are measured every 3 weeks.

n. The following imaging studies are required at baseline: CT chest with or without contrast; MRI of abdomen and pelvis with or without contrast unless patient has contraindication for MRI or severly claustrophobic. After screening, triple-phase abdominal imaging and CT chest will be performed every 9 weeks until 1progression. .

o. Every time imaging is done for re-staging

p. If not previously determined. If previously determined a copy of the pathology report must be made available to MD Anderson

q. HCV Serum RNA test at screening, every cycle for the first 8 cycles. This will give SVR4, SVR12 and SVR24 data and allow determination of kinetics of HCV serum RNA with pembrolizumab

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles). 1 year or treatment or 17 cycles in total.								End of Treatment	Virologic Failure – Arm B[s]	Post-treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**DC**		**Safety Follow-up[l]**	**Follow-Up Visits**	**Survival Follow-Up[a]**
Week (approximate)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	At DC		30 days post last dose	Q9W post-DC	Q12W
Scheduling Window (Days)[b]	-28 to -1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7	±7

r. Blood samples will be collected for HCV genotype and viral resistance mutation testing at baseline on day 1 prior to first dose. Blood might be collected if an increase in HCV viral load is detected for resistance genotype identification. This is stored in case of virologic failures and to characterize the resistance patterns of the subjects enrolled.

s. Arm B. In subjects who achieve HCV RNA <LLOQ on therapy, who subsequently develop HCV RNA >LLOQ, the subject needs to return for viral assessment and determination of need to discontinue Zepatier.

t. Arm B. Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.

u. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by Merck and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or FBR. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Merck requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the FBR consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the FBR sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Subject Identification Card

There will be no subject identification card for this trial.

7.1.1.4 Medical History

7.1.1.5 Medical History

A medical history will be obtained by the Investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the Investigator considers to be clinically significant. Details regarding the disease for which the subject has enrolled in this trial will be recorded separately and not listed as medical history.

If the subject has lost at least 15 lbs. (6.8 kg) over the 3 months prior to screening, “weight loss” should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

7.1.1.6 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject’s HCC.

7.1.1.7 Prior and Concomitant Medications Review

7.1.1.7.1 Prior Medications

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

7.1.1.7.2 Concomitant Medications

The Investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Safety Follow-up visit. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.8 Disease Treatments

7.1.1.8.1 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.8.2 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.9 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.6.1.1.

7.1.1.10 Assignment of Allocation Number

All eligible subjects will be allocated by non-random assignment, and will receive a treatment number referred to as an allocation number. The allocation number identifies the subject for all procedures occurring after treatment allocation to pembrolizumab. Once an allocation number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 allocation number.

7.1.1.11 Study Medication Administration

All subjects will be administered pembrolizumab 200 mg Q3W. The window for each visit is

± 3 days unless otherwise noted. The first dose of the treatment is counted as Cycle 1 Day 1.

7.1.1.12 Survival Status

After the start of new anti-cancer treatment or documented disease progression, the subject should be contacted Q12W to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.1.13 Trial Compliance (Medication/Diet/Activity/Other)

7.1.1.14 Trial Compliance (Medication/Diet/Activity/Other)

Dosing interruptions are permitted as outlined in Section 5.2.1. Administration of trial medication(s) will be witnessed by the Investigator and/or trial staff. The total volume of trial medication infused will be compared with the total volume prepared to determine compliance with each dose administered.

For those medications taken at home, subjects will be provided a medication diary in which they will record trial medication doses and will be instructed to bring this diary and trial medication containers with them when they at the time of clinic visits.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart (Section 6) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 (see [Section 12.4]). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 12-Lead Electrocardiogram

As specified in the Study Flow Chart (Section 6.0), a standard 12-lead ECG will be performed using local standard procedures once during the screening phase and then as clinically indicated. Clinically significant abnormal findings at screening phase should be recorded in the medical history. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Full Physical Exam

The Investigator or qualified designee will perform a complete physical exam during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for complete physical exams are described in Section 6. After the first dose of trial treatment, new clinically significant abnormal findings should be recorded as AEs.

An upper endoscopy is required for all subjects within 12 months of first dose. Any varices must be treated according to institutional standards at that time.

7.1.2.4 Directed Physical Exam

For cycles that do not required a full physical exam as defined in Section 6.0, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to the administration of the trial treatment. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.5 Vital Signs

Vital signs include temperature, pulse, respiratory rate, weight and blood pressure. The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and during the follow-up period as specified in the Trial Flow Chart (Section 6.0). Height will be measured at screening only.

7.1.2.6 Eastern Cooperative Oncology Group Performance Scale

The Investigator or qualified designee will assess ECOG status (see [Section 12.7]) at screening, prior to the administration of each dose of trial treatment and during the follow-up period as specified in the Trial Flow Chart (Section 6.0).

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

See Section 4.2.3.4

Sample collection and processing. Both diagnostic and research tissue collection activities will be performed by members of the MDACC ITB supervised by specialized pathologists. Tissue, cell and blood specimens will be processed immediately after procurement in order to preserve the quality of tissue, cells and analytes. All biospecimens will be collected using the *Biorepository NCI Best Practices*, and standard operating procedures (SOPs). All specimens and derivatives are given de-identified numbers.

A tumor tissue sample from a newly obtained core biopsy must be submitted for characterization of PD-L1 expression, GEP, and microsatellite instability (MSI). The submitted tumor tissue specimen must be of sufficient quality and quantity for assessment of all three of these primary biomarkers.

Submission of an FFPE tumor tissue block is preferred, but tumor tissue from a new biopsy in formalin is also acceptable. If unstained slides are submitted, the slides must be freshly cut and submitted to the testing laboratory within 14 days from the slide sectioning date. All submitted slides must be cut from a single tumor tissue sample specimen. Tissue sample collection date and slide cut date will be are documented. Slides submitted more than 14 days after cutting or cut from more than one tissue specimen is not acceptable and a new specimen will be required.

In cases in which an adequate amount of tumor tissue has not been provided to allow for evaluation of all 3 primary biomarkers, additional tumor tissue must be provided. If additional tumor tissue from the same specimen is available, tumor tissue from that specimen of sufficient quantity and quality for assessment of the remaining required biomarkers must be submitted. If a sufficient amount of additional tumor tissue from the same specimen is NOT available, a different newly obtained tumor tissue specimen of sufficient quantity and quality for assessment of all three primary biomarkers must be submitted.

7.1.2.8 Child-Pugh score

Originally developed in 1973, the Child-Pugh score was used to estimate the risk of operative mortality in patients with bleeding esophageal varices. It has since been modified, refined, and become a widely used tool to assess prognosis in patients with chronic liver disease and cirrhosis (Section 12.5). The score considers 5 factors, 3 of which assess the synthetic function of the liver (i.e., Tbil level, serum albumin, and INR) and 2 of which are based on clinical assessment (i.e., degree of ascites and degree of hepatic encephalopathy). Additionally, we plan on performing risk-stratification of underlying liver condition using plasma IGF-1 score (2): The outdated CTP score is the standard hepatic reserve assessment tool in HCC to predict survival and therapy response in systemic therapy trials. Since survival rates are universally low for CTP classes B and C compared with class A, multiple expert panels have reached the consensus that patients with HCC should have a CTP score of A to be considered for aggressive therapies, to facilitate assessment of the effect of treatment without the confounding issues of liver failure and death as a result of underlying poor hepatic reserve (3, 4).

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Trial Procedures Manual. Refer to the Trial Flow Chart (Section 6.0) for the timing of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count WBC (total and differential)[d] RBC Absolute lymphocyte count[e] Absolute neutrophil count[e]	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate[c] Calcium Chloride Creatinine Glucose Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein Blood urea nitrogen	Blood Glucose Protein Specific gravity Microscopic exam, if abnormal results are noted	Pregnancy test (serum or urine)[a] PT/INR aPTT Total T3 or free T3, FT4, and TSH[b,] Anti-HCV HCV viral load HCV genotype anti-HBs HBsAg Anti-HBc (total and IgM) HBeAg anti-HBe HBV viral load Anti-HDV AFP CRP GGT

[a] Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.

[b] T3 is preferred; if not available free T3 may be tested.

[c] If this test is not done as part of local standard of care, this test does not need to be performed.

[d] Report % or absolute results per standard of practice. Report the results in the same manner throughout the trial.

Abbreviations: AFP=alpha-fetoprotein; aPTT=activated partial thrombin time; CRP=C-reactive protein; FT4=free thyroxine; GGT=gamma-glutamyl transferace; HBc=Hepatitis B core; HBeAg=Heptatitis B e antigen; HBe=hemoglobin E; HBs=hepatitis B surface; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDV=hepatitis D virus; IgM=gamma M immunoglobulin; INR=insulin receptor; PT=prothrombin time; RBC=red blood cells; T3=triothyronine; TSH=thyroid stimulating hormone (thyrotropin); WBC=white blood cells.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1 pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the trial flow chart. Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within normal range.

The following laboratory tests are recommended for all subjects treated with RBV, prior to beginning treatment and then periodically thereafter.

- Standard hematologic tests - including hemoglobin (pretreatment, Week 2 and Week 4 of therapy, and as clinically appropriate).
- Complete and differential white blood cell counts, and platelet count.

- Blood chemistries - liver function tests and TSH.
- Pregnancy - including monthly monitoring for women of childbearing potential.
- ECG

7.1.3.1.1 Pregnancy Tests

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post treatment. If a urine test is positive or not evaluable a serum test will be required. Subjects must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

7.1.3.2 Central Laboratory Assessments

Sample collection timing, storage and shipment instructions for the Central Laboratory assessments will be provided in the laboratory manual.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

There will be no PK/pharmacodynamic evaluations in this study

7.1.3.3.1 Blood Collection for Serum Pembrolizumab

There will be no blood collection for serum pembrolizumab in this study.

7.1.3.3.2 Blood Collection for Anti-Pembrolizumab Antibodies

There will be no blood collection for anti-pembrolizumab antibody detection.

7.1.3.3.3 Blood Collection for RNA Analysis and Plasma and Serum Biomarker Analyses

Blood should be collected pre-dose for Cycles 1 and 2, at time of response and at the time of discontinuation. Leftover RNA, plasma, and serum will be stored at the end of the trial for FBR if the subject has consented (see Section 4.2.3.5).

Further details are provided in the Procedures Manual.

7.1.3.4 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/ERC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

Leftover DNA extracted from planned genetic analysis samples will be stored for FBR only if subject signs the FBR consent.

Tissue and blood immune monitoring will be conducted through our immune platform group as details per the biomarker section based on 3 biopsies done at the following time points: 1) pre-treatment, 2) 6 weeks after therapy, and 3) optional biopsy at time of progression.

7.1.3.5 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of FBR:

- DNA for future research
- Leftover plasma and serum from biomarker analyses
- Leftover RNA
- Leftover main trial tumor tissue

7.1.3.6 HCV Evaluation and HCV Resistance Testing

The following specimens are to be obtained as part of Efficacy/Pharmacogenetic Measurements:

- Samples for HCV GT evaluation must be obtained for inclusion in the study.
- NS5A Resistance Testing in HCV GT1a-Infected Patients Testing patients with HCV GT1a infection for the presence of virus with NS5A RAVs is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. In subjects receiving Zepatier for 12 weeks, SVR12 rates were lower in GT1a-infected patients with 1 or more baseline NS5A RAVs at amino acid positions 28, 30, 31, or 93.
- Blood must be drawn from each subject to assess HCV RNA plasma levels at various time points as shown in the trial flow chart (Section 6.0). HCV-RNA in plasma will be measured using the Roche COBAS AmpliPrep/COBAS Taqman HCV Test, v2.0 assay. Leftover plasma may be used for FBR only if the subject signed for FBR consent.
- Blood must be drawn from each subject to assess viral resistance mutation and processed as instructed by the central laboratory manual. GT1a: Testing for the presence of virus with NS5A RAVs is recommended. Testing patients with HCV GT1a infection for the presence of virus with NS5A RAVs is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. In subjects receiving Zepatier for 12 weeks, SVR12 rates were lower in genotype 1a-infected patients with one or more baseline NS5A RAVs at amino acid positions 28, 30, 31, or 93. Refer to the Zepatier prescribing information for more details.
- Protein and metabolites may be measured from blood samples to compare biomarkers measured prior to treatment, to biomarkers measured at several time points during treatment that correlate with subject response to treatment (sustained viral response).

- Samples collected for genetic analysis are obtained at Day 1.

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to M.D. Anderson radiology can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging should be used only when CT is contraindicated or for imaging in the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden.

Expedited confirmation of measurable disease based on RECIST 1.1 by M.D. Anderson radiology at screening will be used to determine subject eligibility. Confirmation of measurable disease by M.D. Anderson radiology per RECIST 1.1 is required prior to subject allocation. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ.

All scheduled images will be assessed by M.D. Anderson radiology for all studies. In addition, images (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be assessed by M.D. Anderson radiology.

We intend to look at portal pressure as an exploratory imaging methodology to assess response. We propose to monitor portal pressures indirectly through MRI assessment: before treatment, and serially at every restaging up to time of progression using the routine MRI performed for tumor assessment. We plan on implementing this alternative technique to allow for direct non-invasive quantification evaluation of flow dynamics, based on recent studies using MRI in HCC patients receiving sorafenib to assess their portal hypertension changes (17, 18). The advantage to using MRI is that it will be used routinely to assess tumor status, as part of routine HCC assessment in therapeutic clinical trials.

7.1.4.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. Prior to allocation, the screening images must be submitted to M.D. Anderson radiology for confirmation of measurable disease per RECIST 1.1.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging if they are of diagnostic quality, were performed within 28 days prior to the date of allocation, and can be assessed by M.D. Anderson radiology .

7.1.4.1.2 Tumor Imaging During the Trial

The first on-trial imaging assessment should be performed at 9 weeks (63 days ±7 days) from the date of allocation. Subsequent tumor imaging should be performed Q9W (63 days ±7 days) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression or notification by Merck, whichever occurs first. All supplemental imaging, done outside from M.D. Anderson, must be submitted to M.D. Anderson radiology for retrospective review.

Per RECIST 1.1, PR and CR should be confirmed by a repeat tumor imaging assessment obtained 4 weeks or longer from the date the response was first documented. The tumor imaging performed to confirm a response may be performed, at the earliest, 4 weeks after the first indication of a response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging Q9W (63 days ±7 days), starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 7.1.4.1.5), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.4.1.5. Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression bu iRECIST, as assessed by the site, will discontinue trial treatment. Exceptions are detailed in Section 7.1.4.1.5.

7.1.4.1.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 63 days ±7 days) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, or the end of the trial, whichever occurs first.

7.1.4.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by M.D. Anderson investigators as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of trial therapy). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, Merck allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

7.1.4.1.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, subjects should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Section 12.2. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the subjects may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

If a subject has confirmed radiographic progression (iCPD) as defined in Section 12.2, study treatment should be discontinued; however, if the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with Merck. In this case, if study treatment is continued, tumor imaging should continue to be

performed following the intervals as outlined in Section 6 and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Section 12.2, with additional details in the iRECIST publication [Seymour et al, 2017]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 11 and illustrated as a flowchart in Figure 2.

Table 11 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Merck).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

Abbreviations: iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; PD=progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1.

Note: If progression has been verified, further management is by the site, based on iRECIST. Any further imaging should still be reviewed. If RECIST 1.1 disease progression has not been verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and reviewed.

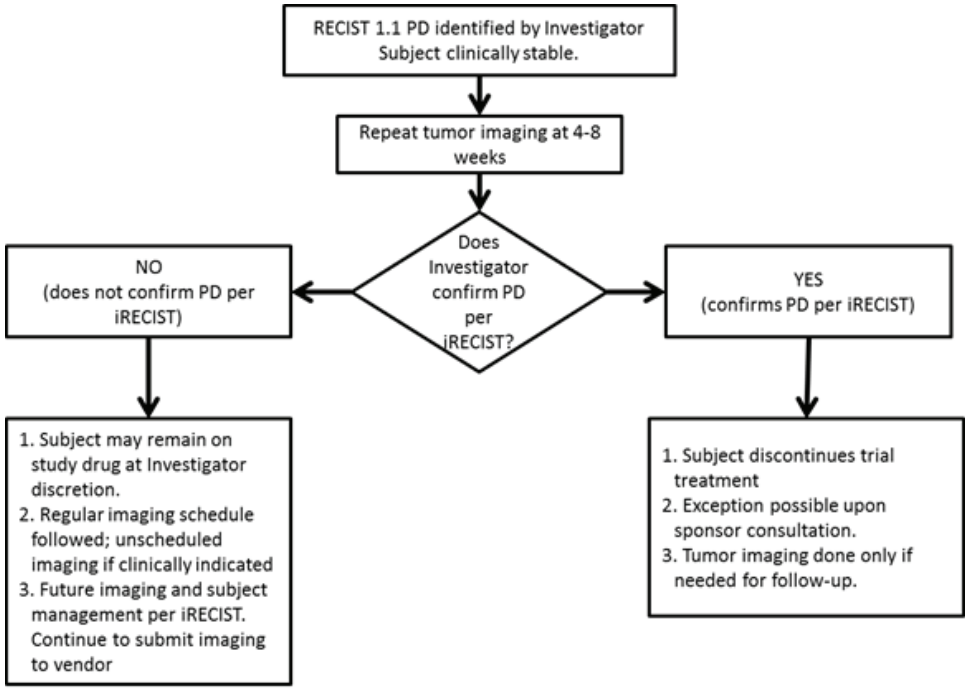


Figure 2 Imaging and Treatment for Clinically Stable Subjects Treated with Pembrolizumab after First Radiologic Evidence of PD Assessed by the Site

Abbreviations: iRECIST = modified Response Evaluation Criteria In Solid Tumors 1.1 for immune-based therapeutics; PD = progressive disease; RECIST = Response Evaluation Criteria In Solid Tumors.

7.1.4.2 Assessment of Viral Load

7.1.4.2.1 Measurement of HCV RNA

HCV-RNA levels in plasma will be measured using the Roche COBAS® AmpliPrep/COBAS TaqMan HCV Test, v2.0 on blood samples drawn from each subject at various time points prior to, during, and after dosing, as indicated in the Study Flow Chart (Section 6.0). Samples are collected and processed as per instructions provided.

Results from the sample collected at the screening visit are used to determine eligibility. Samples collected at other time points are used for efficacy analyses. They are also used to identify subjects who meet HCV virologic failure criteria. The nomenclature detailed in Table 12 will be used when describing HCV RNA levels.

Table 12 Nomenclature for Describing HCV RNA Levels

Abbreviation	Defintiion	HCV RNA level
TND	Target not detected	HCV RNA not detected
TD(u)	Target detected but unquantifiable	HCV RNA <LLOQ
TD(q)	Target detected, quantifiable	HCV RNA ≥LLOQ
Abbreviations: HCV = hepatitis C virus; LLOQ = lower limit of quantification.		

The LLOQ of the COBAS test is 25 IU/mL and its limit of detection is 15·IU/mL. We define virological breakthrough to be confirmed HCV RNA concentration of at least 25 IU/mL after a previous value of less than 25 IU/mL. We define relapse as a confirmed HCV RNA concentration of at least 25 IU/mL following an undetectable (HCV RNA <15·IU/mL) the at end of treatment. For both virological breakthroughs and relapses, we defined confirmation as an HCV RNA concentration of at least 25 IU/mL from a separate blood draw repeated within 2 weeks.

7.1.4.2.1.1 Definition of Efficacy Endpoints

Efficacy will be defined at different timepoints during the trial. Specific endpoints are:

- SVR4: The subject has HCV RNA <LLOQ [either TD(u) or TND] 4 weeks after the end of all study therapy.
- SVR12: The subject has HCV RNA <LLOQ [either TD(u) or TND] 12 weeks after the end of all study therapy.
- SVR24: The subject has HCV RNA < LLOQ [either TD (u) or TND] 24 weeks after the end of all study therapy.

7.1.4.2.1.2 Definition of HCV Virologic Failure: Non-response, Rebound, Virologic Breakthrough, and Relapse

Lack of efficacy at different timepoints in the trial will be categorized as:

- Non-response: Subject has HCV RNA detected at end of treatment without HCV RNA <LLOQ on treatment (note that breakthrough is captured elsewhere).
- Rebound: Subject has a rebound defined as >1 log10 IU/mL increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks.
- Virologic breakthrough: Subject has a confirmed HCV RNA ≥LLOQ [TD quantifiable (TD[q]) after being <LLOQ previously while on treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks.
- Relapse: Subject has a confirmed HCV RNA ≥LLOQ [TD(q)] following end of all study therapy, after becoming undetectable (TND) at end of treatment. Confirmation is defined as an HCV RNA ≥LLOQ from a separate blood draw repeated within 2 weeks.

7.1.4.2.2 Viral Resistance Measurements and Mechanisms

<u>HCV resistance measurements</u>

Resistance-associated variants of the HCV can lead to failure of therapy. This is one of the most important considerations when treating with some DAAs. To better understand the potential for RAVs with either grazoprevir and/or elbasvir, samples will be retained at virologic failure confirmation visits, and RAVs will be assessed for any subject who has detectable virus above 1000 IU/mL and has met an HCV virologic failure criteria. To limit the risk of RAVs, subjects are not allowed to have monotherapy with grazoprevir or elbasvir in this protocol.

Blood samples for viral resistance assays are collected at screening and Day 1 Cycle 1 to determine resistance to grazoprevir and/or elbasvir. Additional resistance testing on these samples may be performed. Blood samples for resistance testing are also collected during the follow-up period, as well as at the virologic failure confirmation visit for genotypic and investigational assays to assess resistance to grazoprevir and elbasvir.

In a pooled analysis of subjects treated with regimens containing Zepatier with or without RBV in Phase 2 and 3 clinical trials, resistance analyses of both drug targets were conducted for 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44 with post-treatment relapse). Treatment-emergent substitutions observed in the viral populations of these subjects based on HCV GTs and subtypes are shown in Table 13. Treatment-emergent NS5A substitutions were detected in 30/37 (81%) GT1a-, 7/8 (88%) GT1b-, and 5/5 (100%) GT4-infected subjects. The most common treatment-emergent NS5A substitutions in GT1a were at position Q30 (n=22). Treatment-emergent NS3 substitutions were detected in 29/37 (78%) GT1a-, 2/8 (25%) GT1b-, and 2/5 (40%) GT4-infected subjects. The most common treatment-emergent NS3 substitutions in GT1a were at position D168 (n=18). Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) GT 1a-, 1/8 (13%) GT1b-, and 2/5 (40%) GT4-infected subjects.

Table 13. Treatment-Emergent Amino Acid Substitutions Among Virologic Failures in the Pooled Analysis of ZEPATIER with and without Ribavirin Regimens in Phase 2 and Phase 3 Clinical Trials

Target	Genotype 1a N = 37	Genotype 1b N = 8	Genotype 4 N = 5
NS5A	M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D, Y93H/N/S	L28M, L31F/V, Y93H	L28S/T, M31I/V, P58D, Y93H
NS3	V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A, D168A/G/N/V/Y	Y56F, V107I, A156T	A156M/T/V, D168A/G, V170I

Persistence of Resistance-Associated Variations

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A and NS3, respectively, was assessed in HCV GT1-infected subjects in Phase 2 and 3

trials whose virus had treatment-emergent RAVs in the drug target, and with available data through at least 24 weeks post-treatment using population nucleotide sequence analysis.

Viral populations with treatment-emergent NS5A RAVs were generally more persistent than those with NS3 RAVs. Among GT1a-infected subjects, NS5A RAVs persisted at detectable levels at follow-up week 12 in 95% (35/37) of subjects and in 100% (9/9) of subjects with follow-up week 24 data. Among GT1b-infected subjects, NS5A RAVs persisted at detectable levels in 100% (7/7) of subjects at follow-up week 12 and in 100% (3/3) of subjects with follow-up week 24 data.

Among GT1a-infected subjects, NS3 RAVs persisted at detectable levels at follow-up week 24 in 31% (4/13) of subjects. Among GT1b-infected subjects, NS3 RAVs persisted at detectable levels at follow-up week 24 in 50% (1/2) of subjects.

Due to the limited number of GT4-infected subjects with treatment-emergent NS5A and NS3 RAVs, trends in persistence of treatment-emergent substitutions in this GT could not be established.

The lack of detection of a virus containing a RAV does not necessarily indicate that viral populations carrying that substitution have declined to a background level that may have existed prior to treatment. The long-term clinical impact of the emergence or persistence of virus containing Zepatier-RAVs is unknown.

Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response in Genotype 1-Infected Subjects

Analyses using population nucleotide sequencing were conducted to explore the association between NS5A or NS3 amino acid polymorphisms and treatment response among treatment-naïve and treatment-experienced GT1-infected subjects. Baseline NS5A polymorphisms at resistance-associated positions (focusing on any change from subtype reference at NS5A amino acid positions 28, 30, 31, or 93) were evaluated. Baseline NS3 polymorphisms at positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175 were evaluated. Analyses of SVR12 rates pooled data from subjects naïve to DAAs and who received Zepatier with or without RBV in Phase 3 clinical trials, and censored subjects who did not achieve SVR12 for reasons unrelated to virologic failure.

Genotype 1a

In GT1a-infected subjects, the presence of 1 or more HCV NS5A amino acid polymorphisms at position M28, Q30, L31, or Y93 was associated with reduced efficacy of Zepatier for 12 weeks (Table 14), regardless of prior treatment history or cirrhosis status. The prevalence of polymorphisms at any of these positions in GT1a-infected subjects was 11% (62/561) overall, and 12% (37/309) specifically for subjects in the US. across Phase 2 and Phase 3 clinical trials evaluating Zepatier for 12 weeks or Zepatier plus RBV for 16 weeks. The prevalence of polymorphisms at these positions in GT1a-infected subjects was

6% (35/561) at position M28, 2% (11/561) at position Q30, 3% (15/561) at position L31, and 2% (10/561) at position Y93. Polymorphisms at NS5A position H58 were common (10%) and were not associated with reduced Zepatier efficacy, except for a single virologic failure subject whose virus had baseline M28V and H58D polymorphisms.

The SVR12 rates for subjects treated with Zepatier for 12 weeks were 88% (29/33) for subjects with M28V/T/L polymorphisms (n=29, 3, and 1, respectively), 40% (4/10) for subjects with Q30H/R/L polymorphisms (n=5, 3, and 2, respectively), 38% (5/13) for subjects with an L31M polymorphism, and 63% (5/8) for subjects with Y93C/H/N/S polymorphisms (n=3, 3, 1, and 1, respectively). Although data are limited, among GT1a-infected subjects with these NS5A polymorphisms who received Zepatier plus RBV for 16 weeks, 6 out of 6 subjects achieved SVR12. The specific NS5A polymorphisms observed in subjects treated with Zepatier plus RBV for 16 weeks included M28V (n=2), Q30H (n=1), L31M (n=2), or Y93C/H (n=1 each).

Table 14 SVR12 in HCV Genotype 1a-Infected Subjects without or with Baseline NS5A Polymorphisms

NS5A Polymorphism Status	**Zepatier 12 Weeks SVR12 % (n/N)**	**Zepatier + RBV 16 Weeks SVR12 % (n/N)**
Without baseline NS5A polymorphism (M28, Q30, L31, or Y93)	98% (441/450)	100% (49/49)
With baseline NS5A polymorphism (M28*, Q30*, L31*, or Y93*)	70% (39/56)	100% (6/6)
*Any change from GT1a reference.		

There are insufficient data to determine the impact of HCV NS5A amino acid polymorphisms in treatment-experienced subjects who failed prior Peg-IFN + RBV + HCV protease inhibitor therapy and received Zepatier with RBV.

In GT1a-infected subjects, the NS3 Q80K polymorphism did not impact treatment response. Polymorphisms at other NS3 RAVs were uncommon and were not associated with reduced treatment efficacy.

Genotype 1b

In GT1b-infected subjects treated with Zepatier for 12 weeks, SVR12 rates (non-virologic failure-censored) were 94% (48/51) and 99% (247/248) for those with and without one or more NS5A polymorphisms at position 28, 30, 31, or 93. In GT1b-infected subjects, baseline NS3 polymorphisms did not impact treatment response.

Effect of Baseline HCV Polymorphisms on Treatment Response in Genotype 4-Infected Subjects

Phylogenetic analysis of HCV sequences from GT4-infected subjects (n=71) in the pooled analyses of subjects (non-virologic failure-censored) treated with regimens containing Zepatier with or without RBV in Phase 2 and 3 clinical trials identified 4 HCV GT4 subtypes (4a, 4d, 4k, 4o). Most subjects were infected with either subtype 4a (42%) or 4d (51%); 1 to 2 subjects were infected with each of the other GT4 subtypes. Among subjects enrolled at US study sites, 11/13 (85%) were infected with HCV subtype 4a. There were 2 subjects infected with HCV subtype 4d who experienced virologic failure with the regimen containing grazoprevir and elbasvir.

In GT4-infected subjects, SVR12 rates for subjects with baseline NS5A polymorphisms (any change from reference at NS5A amino acid positions 28, 30, 31, 58, and 93 by population nucleotide sequencing) were 100% (28/28) and for subjects without baseline NS5A polymorphisms were 95% (41/43).

In GT4-infected subjects, SVR12 rates for subjects with baseline NS3 polymorphisms (any change from reference at NS3 amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 by population nucleotide sequencing) were 100% (18/18) and for subjects without baseline NS3 polymorphisms were 96% (51/53).

Cross Resistance

Cross resistance is possible among NS5A inhibitors and NS3/4A protease inhibitors by class. Elbasvir and grazoprevir are fully active against viral populations with substitutions conferring resistance to NS5B inhibitors.

In the C-SALVAGE trial, subjects with GT1 infection who had failed prior treatment with boceprevir (n=28), simeprevir (n=8), or telaprevir (n=43) in combination with PegIFN plus RBV received elbasvir 50 mg qday + grazoprevir 100 mg qday + RBV for 12 weeks. There are limited data to determine the impact of HCV NS3 RAVs detected at baseline in treatment-experienced subjects who failed prior Peg-IFN + RBV + HCV protease inhibitor therapy and received Zepatier with RBV. SVR was achieved in 88% (21/24) of GT1a and GT1b infected subjects with NS3 RAVs detected at baseline. Specific NS3 substitutions observed at baseline included one or more of the following: V36L/M (n=8), T54S (n=4), S122G/T (n=9), R155K/T (n=9), A156S/T (n=1), and D168E/N (n=3). SVR was 100% (55/55) in subjects without baseline NS3 resistancesubstitutions. The 3 virologic failure subjects had the following NS3 or NS5A substitutions/polymorphisms at baseline: NS3 R155T/D168N, NS3 R155K plus NS5A H58D, and NS3 T54S plus NS5A L31M.

The efficacy of Zepatier has not been established in patients who have previously failed treatment with other regimens that included an NS5A inhibitor.

7.1.4.2.3 HCV Genomic Exploratory Measurements

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. A biosample will be collected and may be used for exploring the relationship between genetic variation and subject response to the treatment(s) administered. Variation across the human genome may be analyzed for association with clinical data collected in this study (For example: to assess the genetic variation in the humanrs12979860 genotype (previously known as Interleukin 28B genotype) as a predictor of virologic response in each treatment arm, for ADME and HLA genes associated with liver injury). This research contributes to understanding genetic determinants of efficacy and toxicity associated with the treatments in this study. Pharmacogenomic data from this study may be combined with data from other studies using these treatments.

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the end of study visit should be performed at the time of discontinuation. Any AEs which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.5.2 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

7.1.5.3 Calibration of Critical Equipment

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion laboratory tests and trial assessments

- Imaging equipment – as required for trial objectives

See protocol-specified guidance in the Administrative Binder, Procedures Manual, Pharmacy Manual and SIM.

7.1.6 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.1 Screening

7.1.6.1.1 Screening Period

7.1.6.2 Screening Visit

Within 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Screening procedures may be repeated.

Written consent must be obtained prior to performing any protocol-specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of trial treatment. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of trial treatment.
- Evaluation of ECOG is to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).
- To meet the requirement for the submission of tumor tissue from a newly obtained core needle biopsy specimen, the tissue sample must have been collected since the completion of the most recent cancer therapy.
- HCV GT determination and resistance GT detection must be performed prior to the first dose of treatment on Day 1.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of repeat screening test if performed within the specified time frame and the

inclusion/exclusion criteria is met. Subjects who are rescreened will retain their original screening number. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

7.1.6.3 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided above in the Trial Procedures (Section 7.1 - Trial Procedures).

Subjects are eligible for up to 35 cycles (approximately 2 years) of treatment on pembrolizumab.

7.1.6.4 Post-Treatment Visits

7.1.6.4.1 Safety Follow-up Visits

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first.

All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anticancer therapy, whichever occurs first. Serious AEs that occur within 90 days of the end of treatment or before initiation of a new anticancer treatment should also be followed and recorded.

7.1.6.4.2 Follow-up visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately Q9W by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or the end of trial, whichever occurs first. Information regarding post-trial anticancer treatment will be collected if new treatment is initiated.

7.1.6.4.3 Survival Follow-up

Subjects who experience confirmed disease progression or start a new anticancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone approximately Q12W to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.6.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by Merck. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Merck notification, all subjects who do not/will not have a scheduled study visit or study contact during the Merck-defined time period will be contacted for their survival status (excluding subjects that have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

7.2.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (ie, any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of Merck's product, is also an AE.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered AEs. Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

Merck's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an AE.

All AEs that occur after the ICF is signed but before treatment allocation 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.

From the start of treatment through 30 days following cessation of treatment, all AEs must be reported by the investigator. Such events will be recorded at each examination on the AE CRF.

The reporting timeframe for AEs meeting any serious criteria is described in Section 7.2.4.1. The investigator will make every attempt to follow all subjects with non-serious AEs for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.2.2 Definition of an Overdose

For this trial, an overdose of pembrolizumab will be defined as any dose of 1000 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 subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

In this trial, an overdose of other aents is any dose higher than intake in excess of the prescribed dose of Zepatier or RBV per calendar day.

7.2.3 Reporting of Pregnancy and Lactation to Merck

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a subject (spontaneously reported to the investigator or their designee) that occurs during the trial, through 120 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, are reportable to Merck.

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.

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 Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Merck and followed as described above.

7.2.4 Serious Adverse Events and Events of Clinical Interest

7.2.4.1 Serious Adverse Event

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

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

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

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

- Serious AEs will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the subject withdraws consent or starts a new anti-cancer medication. Serious AEs must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any SAEs that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

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

It is the responsibility of the Investigator and the research team to ensure SAEs are reported according to the Code of Federal Regulations, GCPs, the protocol guidelines, Merck's guidelines, and IRB policy.

7.2.4.2 Events of Clinical Interest

Selected non-serious and SAEs are also known as ECIs and must be reported to Merck Global Safety and the M.D. Anderson IND office.

For the time period beginning when the ICF is signed until treatment allocation, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 2 working days to Merck 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.

For the time period beginning at treatment allocation through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to Merck's product, must be reported within 2 working days to Merck, either by electronic media or paper.

Events of clinical interest for this trial include:

1. an overdose of Merck's product, as defined in Section 7.2.2 - Definition of an Overdose, that is not associated with clinical symptoms or abnormal laboratory results.
3. 2. In addition to overdose, Hepatic ECIs will include any of the following events. All of these events will require holding pembrolizumab, notification of Merck within 24 hours (as an AE), and, if appropriate, hepatology consultation. All cases of permanent discontinuation must also be reported within 7 days. For dose interval modification and treatment guidelines for these events, refer to Section 5.2.1.

   a. ALT:

i. Among subjects with Day 1 ALT <2 × ULN, ALT ≥5 × ULN

ii. Among subjects with Day 1 ALT ≥2 × ULN, ALT >3 × the Day 1 level

iii. ALT >500 U/mL regardless of baseline level

(Subjects with ALT >5 × ULN at Day 1 are not eligible for enrollment)

b. AST:

i. Among subjects with Day 1 AST <2 × ULN, AST ≥5 × ULN

ii. Among subjects with Day 1 AST ≥2 × ULN, AST >3 × the Day 1 level

iii. AST >500 U/mL regardless of baseline level

(Subjects with ALT >5 × ULN at Day 1 are not eligible for enrollment)

c. Total Bilirubin:

i. Among subjects with Day 1 levels <1.5 mg/dL, a value of >2.0 mg/dL

ii. Among subjects with Day 1 levels that are ≥1.5 mg/dL, a value ≥2 × the D1 level

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

(Subjects with Total Bilirubin >2.0 mg/dL at Day 1 are not eligible for enrollment)

d. Regardless of laboratory values, hepatic decompensation diagnosed <u>clinically</u>, including:

i. New onset ascites

ii. GI bleeding suggestive of portal hypertension (eg esophageal or gastric varices)

iii. Encephalopathy

(Subjects with clinically apparent ascites or encephalopathy, or untreated varices are not eligible for enrollment)

4. Reactivation of HBV and HCV for those with underlying infection.

7.2.4.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.1. Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The investigator will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to the IND office and Merck Global Safety as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.5 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all AEs according to the NCI CTCAE, version 4.0. Any AE which changes NCI CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRF.

All AEs regardless of NCI CTCAE grade must also be evaluated for seriousness.

7.2.6 Responsibility for Reporting Adverse Events

All AEs will be reported to regulatory authorities, IRB/ERCs and investigators in accordance with all applicable global laws and regulations. regulations, i.e., per International Council for Harmonisation (ICH) Topic E6 (R1) Guidelines for GCP.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to final database lock, will be documented as a procotol amendment. There will be a separate biomarker plan. HCV end points will be combined and described in Section 8.13.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in Table 15. The comprehensive plan is provided in Sections 8.2 to 8.13.

Table 15 Key Elements of the Statistical Analysis Plan

Study Design Overview	A Phase II Study of Pembrolizumab (MK-3475) in Hepatitis C Virus Positive and Negative Subjects with Advanced Hepatocellular Carcinoma Who Progressed on or Were Intolerant to First-Line Systemic Therapy
Treatment Assignment	This is a single arm open-label study.
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: ASaT
Primary Endpoints	Correlative Biomarkers, Safety and Tolerability.
Statistical Methods for Key Efficacy Analyses	Objective Response Rate (ORR) based on RECIST 1.1 assessed by the MDACC imaging staff. The estimate of the ORR, along with its 90% confidence interval (CI) based on the Clopper-Pearson method (48), will be provided.
Statistical Methods for Key Safety Analyses	Counts and percentages of subjects with AEs will be provided.

Interim Analysis	No planned interim analysis for this Phase II study.
Multiplicity	No multiplicity adjustment is planned in this Phase II study.
Sample Size and Power	The planned sample size is 15 subjects per Arm

8.2 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of Merck.

This trial is being conducted as a non-randomized, open-label study, i.e., subjects, investigators, and Merck personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule(s).

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Exploratory Efficacy Endpoints

8.4.1.1 Primary Endpoints

The primary endpoints are safety and tolerability of pembrolizumab (Section 4.2.4.1) and SVR12 (Section 4.2.4.1).

8.4.1.2 Secondary Exploratory/Efficacy Endpoints

- ORR is defined as the proportion of the subjects in the analysis population who have a CR or PR. Responses are based on assessments by the blinded M.D. Anderson radiology per RECIST 1.1
- DOR is defined as the time from first response to disease progression in subjects who achieve a PR or better, based on assessments by the blinded M.D. Anderson radiology per RECIST 1.1.
- DCR is defined as the percentage of subjects who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression, based on assessments by the blinded M.D. Anderson radiology per RECIST 1.1
- TTP is defined as the time from randomization to the first documented disease progression. If there is no documented disease progression, TTP is censored at last

tumor assessment date. It will be assessed by the blinded M.D. Anderson radiology per RECIST 1.1.

- PFS is defined as the time from allocation to the first documented disease progression per RECIST 1.1 based on assessments by the blinded M.D. Anderson radiology or death due to any cause, whichever occurs first.
- OS is defined as the time from first dose of study medication to death due to any cause.

8.4.1.3 Exploratory Efficacy Endpoints

The exploratory endpoints listed in Section 3.0 (i.e., ORR, DOR, DCR, TTP, PFS, and OS per iRECIST), are defined in the same way as their counterpart in Section 8.4.1.2, except that their disease progression will be assessed, and then confirmed (4 weeks later), by M.D. Anderson radiology per iRECIST, instead of per RECIST 1.1.

8.4.1.4 Biomarker Endpoints

Biomarker endpoints are described in Section 4.2.4.5.

8.4.2 Safety Endpoints

Safety endpoints are described in Section 4.2.4.1.

8.5 Analysis Populations

Eligible subjects enter the study when the treatment allocation number is assigned by M.D. Anderson.

8.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, TTP, PFS, and OS. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders (PR and CR).

Details on the approach to handling missing data are provided in Table 17.

8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.6 Statistical Methods

8.6.1 Statistical Methods and Data Analysis

This section describes the statistical methods that address the primary and secondary objectives.

This is a single arm, open-label exploratory Phase II study. Since no effective treatments are available in this setting, a response rate of 15% (within 95% CI) is considered acceptable (i.e., the signal for launching further, larger studies with pembrolizumab in this patient population is ≥ 1 response in the current study). If no response is observed, the treatment with pembrolizumab will be considered ineffective. A total of 15 patients will be enrolled and treated to rule out a response rate of 15% or less with 90% power when at least one response is observed. In other words, with 15 patients treated, the probability of observing at least one response is more than 90% if the response rate is at least 15% (Table 16). Descriptive statistics including with 90% confidence interval will be computed. Observed response profile, clinical benefit rate at 6 months and PFS along with relevant confidence intervals will be used to guide future development decisions.

Table 16 Analysis Strategy for Efficacy Variables

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

* Exact confidence interval computed by the method of Clopper and Pearson (Biometrika 26:404-413, 1934)
**Actual response rate with corresponding CI will be calculated. Exact confidence interval was calculated for all responses.

Kaplan-Meier method will be used to compute the survival rate for the time-to-event endpoints such as PFS. The efficacy in biomarker subgroups will be summarized by descriptive statistics.

Table 17 Statistical Methods Per Endpoint Anaylsis

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint			

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Biomarkers and Safety/tolerability	exact method based on binomial distribution (Clopper-Pearson method)	ASaT	Subjects with missing data are considered non-responders
Key Secondary/Exploratory Endpoints			
DOR – RECIST 1.1 by M.D. Anderson radiology	Summary statistics using Kaplan-Meier method, if sample size permits	All responders	Non-responders are excluded from analysis. Responders are censored according to the censoring rules listed in Table 18.
DCR – RECIST 1.1 by M.D. Anderson radiology	Exact method based on binomial distribution (Clopper-Pearson method)	ASaT	Subjects with missing data are considered as subjects with disease not under control
TTP – RECIST 1.1 by M.D. Anderson radiology	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
PFS – RECIST 1.1 by M.D. Anderson radiology	Summary statistics using Kaplan-Meier method	ASaT	Censored at last assessment
OS	Summary statistics using Kaplan-Meier method	ASaT	Censored at last known alive date

Table 18 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥2 consecutive missed adequate disease assessments	Last adequate disease assessment prior to the after ≥2 consecutive missed adequate disease assessments	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments	PD or death	End of response (Event)

Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

Counts and percentages of subjects with AEs will be provided. Analysis of AEs will be descriptive.

Bayesian toxicity monitoring will be performed to ensure that treatment is safe. Dose-limiting toxicity (DLT) is defined as Grade 3 or higher non-hematologic toxicity or Grade 4 or higher hematologic toxicity as per below. DLTs will be assessed during the first cycle of combination therapy. A DLT rate of 30% or higher is consider excessive. We will hold the patient enrollment if the probability of excessive toxicity is high (i.e., Prob(DLT > 0.3) > 0.8). This corresponds to withhold new patient entry when 3 DLTs are observed in 5 to 6 patients, 4 DLTs in 7 to 9 patients, 5 DLTs in 10 to 12 patients, or 6 DLTs in 13 to14 patients, respectively. The probability of withholding new patients upon entry (early stopping) is 0.02, 0.15, 0.41, 0.68, and 0.88) if the true DLT rates are 0.1, 0.2, 0.3, 0.4, and 0.5, respectively. The calculation assumes that the prior distribution of the probability of DLT is beta(0.5, 0.5).

8.6.2.1 Definition of Dose-Limiting Toxicities

All toxicities will be graded using National Cancer Institute (NCI) CTCAE Version 4.0 (Appendix 12.7).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be possibly, probably or definitely related to study treatments.

1. Grade 4 hematologic toxicity lasting ≥14 days.
2. Grade 4 non-hematologic toxicity (not laboratory).
3. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care except inadequately treated hypersensitivity reactions
4. Any Grade 3 or higher non-hematologic laboratory value if:
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week.
5. Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour.
    - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4

degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

6. Thrombocytopenia <25,000/mm3 if associated with:
    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit.
7. Grade 5 toxicity (i.e., death).
8. Delay in the scheduled administration of any component of therapy (IPI, PEG-INF, MK-3475) of >14 days
9. A delay of > 1 week due to drug-related toxicity in initiating Cycle 2.
10. Unable to complete at least 80% of any of the three treatments during the first course of therapy due treatment-related toxicity (even if not meeting above DLT criteria).

8.6.3 Demographic and Baseline Characteristics

The number and percentage of subjects screened, allocated, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for all enrolled subjects.

8.7 Interim Analyses

No Interim analysis planned. Analysis of DLTS will be performed continuously as subjects are enrolled.

8.8 Multiplicity

No multiplicity adjustment is planned in this study.

8.9 Sample Size

In this study, approximately 15 subjects will be enrolled per Arm.

8.10 Subgroup Analyses and Effect of Baseline Factors

No subgroup analysis planned.

8.11 Compliance (Medication Adherence)

Drug accountability data for pembrolizumab will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for the ASaT population.

8.13 Statictical Analysis of HCV Endpoints

8.13.1 HCV endpoints

1. Primary endpoint

Objective: To evaluate the efficacy of pembrolizumab in combination with Zepatier as assessed by the proportion of subjects with HCV GT1 or GT4 achieving Sustained Virologic Response 12 weeks after the end of all HCV study therapy (SVR12), defined as HCV RNA below the lower limit of quantitation (LLOQ) (either target detected unquantifiable [TD(u)] or target not detected [TND]) 12 weeks after the end of all study therapy.

2. Seconday endpoint

(4) **Objective:** To evaluate the safety of pembrolizumab in combination with Zepatier as assessed by the proportion of subjects with HCV GT1 or GT4 achieving SVR12 and SVR24, defined as HCV RNA below the LLOQ (either TD[u] or TND) 12 and 24 weeks after the end of all study therapy.

3. Exploratory endpoints

The proportion of subjects achieving undetectable HCV RNA (TND) and HCV RNA <LLOQ (TD[u]) at Week 2, Week 4, and Week 12 or Week 16 (for those treated for 16 weeks), and the proportion of subjects achieving SVR4 in the immediate treatment arm.

(1) **Objective:** To assess whether pembrolizumab in combination with Zepatier affects the course of viral infections in subjects with underlying HCV GT1 or GT4. We hypothesize that pembrolizumab in combination with Zepatier will help to reduce viral loads in those with untreated HCV..

(2) **Objective**: To evaluate the response of HCV GT1 and GT4 to treatment as assessed by sustained virologic response at 4 and 12 weeks after the end of 12 to 16 weeks of pembrolizumab in combination with Zepatier dosing. Sustained virologic response is defined as defined as HCV RNA below the LLOQ (either TD[u] or TND).

(3) **Objective:** To evaluate the emergence of viral resistance-associated variants (RAVs) to pembrolizumab in combination with Zepatier in subjects with with HCV GT1 or GT4 without RAVs as baseline ..

(4) **Objective:** To evaluate the efficacy of pembrolizumab in combination with Zepatier as assessed by the proportion of subjects in the immediate treatment arm achieving

undetectable (TND) HCV RNA and HCV RNA <LLOQ at Weeks 2, 4, 12 and Follow-Up Week 4 (SVR 4), Week 12 (SVR 12), and week 24 (SVR 24)..

8.13.2 Efficacy Analysis Populations

The ASaT population will serve as the primary population for the analysis of HCV efficacy data in this study. A supportive analysis using the Per- protocol (PP) population will be performed for the primary (SVR12) and key secondary efficacy endpoints. The PP population is a subset of the ASaT population. The PP population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary and key secondary efficacy endpoints. Potential violations that may result in the exclusion of a subject from the PP population include:

- Violations of specific inclusion/exclusion criteria:
    - The subject is infected with HCV of genotype other than GT1 or GT4, at entry or during the course of the study, including a mixed GT infection (with a non-GT1 or GT4) or non-typeable genotype.
    - The subject received concomitant medications that are prohibited due to their potential to result in a clinically significant lowering of Zepatier concentration (see Section 5.5.2 for specific details of prohibited medications). Further, any co-administered medication, currently unidentified, but for which subsequent clinical drug-drug interaction data indicate that co-administration with Zepatier leads to a clinically significant lowering of Zepatier concentrations.

Other violations may be identified during the course of data collection and they will be listed specifically in the clinical study report (CSR).

A subject with important deviations from the protocol as described above at randomization will be excluded from the PP population. For subjects with important deviations from the protocol as described above during course of the treatment, data obtained subsequent to the violation will be excluded from analysis.

Subjects will be included in the treatment group to which they are randomized for the analysis of efficacy data using both the ASaT and PP populations. Details on the approach to handling missing data are provided in Section 8.13.3.

8.13.3 Statistical Methods for Efficacy Analyses

Missing values

A missing data point for a given study visit may be due to any one of the following reasons: a visit occurred but data were not collected or were unusable; a visit did not occur; or a subject discontinued from the study before reaching the visit. Subjects who prematurely discontinued the assigned treatment are encouraged to remain in the study for the follow-up, if possible.

The HCV RNA outcome is categorized as TND, TD(u), and TD(q). There are 3 types of missing data handled by different approaches.

1. Intermittent missing: If a missing data point is immediately preceded and followed by non-missing HCV RNA outcomes, the missing value would be imputed to the worse outcome of the two. For example, if a missing data point is preceded by TD(q) and followed by TD(u) or TND, then the missing value would be imputed as TD(q); if a missing data point is preceded by TD(u) and followed by TND, then the missing value would be imputed as TD(u); when a missing value is flanked by two TND, then the missing value would be imputed as TND.
2. Non-intermittent missing related to the study drug: For missing values due to premature study discontinuations due to treatment related reasons either for safety or efficacy, the missing values will be considered as treatment failures.
3. Non-intermittent missing unrelated to the study drug: For missing data due to premature study discontinuations with reasons unrelated to treatment such as loss to follow-up, protocol violation, withdrawal of consent, administrative reasons, etc., the missingness mechanism is unlikely to be related to subjects' response to the HCV treatment, and therefore the missing at random (MAR) assumption is reasonable. The approaches to address this type of missing data depend on the analytical strategy, and they are described in the following sections.

In addition, a missing baseline/Day1 HCV RNA result will be replaced with a screening result, if available.

Approaches to handle non-intermittent missing values due to prematurely discontinuing from the study:

- Treatment-Related Discontinuation = Failure (TRD=F) approach: The treatment related type 2 missing will be considered as failure; whereas the subjects who have the type 3 missing value and do not have virologic failure during the observed study period will be excluded from the analysis for the time points following their study withdrawal. Note that subjects with documented virologic failure during the treatment or follow-up period, even if they withdrew prematurely due to reasons not related to study drug, are classified as failures.
- Missing = Failure (M=F) approach: Any non-intermittent missing (i.e., the type 2 and 3 missing) will be imputed as failure, regardless of the reason for study discontinuation.

8.13.4 Subgroup Analyses and Effects of Baseline Factors

To assess the consistency of the response across various subgroups, the SVR12 rate with 95% CIs will be estimated within each category of the following classification variables:

- Sex (female, male)

- GT (1a, 1 non-a, 4)
- Stage of fibrosis (Non-cirrhotic vs. Cirrhotic)
- *IL28B* CC genotype vs. non-CC genotype
- HCV RNA at baseline, low (≤ 800,000 IU/mL) versus high (> 800,000 IU/mL)
- IFN treatment eligibility status (eligible or ineligible)

8.13.5 Subject Virologic Failure: Non-response, Rebound, Breakthrough, and Relapse

Summary statistics will be provided to describe the rates of occurrence of subject virologic non-response, rebound, breakthrough, and relapse. Definitions for subject virologic onresponse, rebound, breakthrough, and relapse are in Section 4.2.4.3.1.2. Viral resistance testing will focus on the entire NS3/4A and NS5A regions for all subjects and for those who meet the subject virologic failure criteria.

8.13.6 Compliance (Medical Adherence)

In this study, as part of the routine recording of the amount of study treatment taken by each subject, the number of tablets remaining in study packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate subject compliance. A day within the study will be considered an "On-Therapy" day if the subject takes the Zepatier. The "Number of Days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study medication for that subject. Note, the date of the last dose of study medication would be the last scheduled day for treatment administration for subject who completed the assigned treatment.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical supplies of pembrolizumab and Zepatier will be provided by Merck as summarized in Table 19. Refer to the prescribing information for drug handling requirements.

Table 19 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 100 mg/4 mL. Commercial supply.	Solution for Injection
Zepatier. Clinical supply.	Each oral tablet contains 50 mg elbasvir and 100 mg grazoprevir, The tablets are packaged

Product Name & Potency	Dosage Form
	into a carton (NDC 0006-3074-02) containing two (2) 4-count child-resistant dose packs for a total of 28 tablets.
RBV	200 mg Capsules are white, opaque capsules, 200 mg, and the Schering Corporation logo imprinted on the capsule shell; the capsules are packaged in a bottle containing 56 capsules (NDC 0085-1351-05), 70 capsules (NDC 0085-1385-07), and 84 capsules (NDC 0085-1194-03).

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

All supplies will be provided open label. Pembrolizumab will be provided as non-kitted single vials.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, Merck and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol

9.5 Returns and Reconciliations

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for

proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

Financial Disclosure requirements are outlined in the FDA Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is Merck's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by Merck in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with Merck to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by Merck or through a secure password-protected electronic portal provided by Merck. The investigator/subinvestigator(s) also consent to the transmission of this information to Merck in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.2 Confidentiality of Subject Records

Merck (or Merck representative), IRB/ERC, or regulatory authority representatives may consult and/ or copy trial documents in order to verify source documents/CRF data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying source documents/CRF information, the subject will be identified by unique code only; protected health information, such as full names and medical records number, will be masked prior to transmission to Merck.

All subject data used and disclosed in connection with this trial must be treated in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

Certain personal identifying information with respect to the investigator, and all sub-investigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to Merck, and subsidiaries, affiliates and agents of Merck, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, Merck may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/ERC Information

Merck is required to record the name and address of each IRB/ERC member that reviews and approves this trial. Merck is also required to document that each IRB/ERC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/ERC members and to make these records available for regulatory agency review upon request by those agencies.

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the FDA Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is Merck's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by Merck in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with Merck to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by Merck or through a secure password-protected electronic portal provided by Merck. The investigator/subinvestigator(s) also consent to the transmission of this information to Merck in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good

Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by Merck.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to Merck as required by this protocol or as otherwise required pursuant to any agreement with Merck.

Trial documentation will be promptly and fully disclosed to Merck by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of Merck or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by Merck as a result of an audit to cure deficiencies in the trial documentation and worksheets/CRFs.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/CRFs, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. Merck will determine the minimum retention period and notify the investigator when documents may be destroyed.

Merck will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. Merck also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by Merck prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform Merck of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Merck's trials. The investigator will immediately disclose in writing to Merck if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event Merck prematurely terminates a particular trial site, Merck will promptly notify that trial site's IRB/ERC.

According to European legislation, Merck must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, Merck must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial (CSR CI). Merck may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the FDA Modernization Act (FDAMA) and the FDA Amendments Act (FDAAA), Merck of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central

contact number for further information on appropriate trial locations and trial site contact information.

10.5 Quality Management System

By signing this protocol, Merck agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

All participating patients should be registered with the Data Management Office PDMS/CORE system. The Data Management Infrastructure (DMI) will also be used. An efficacy and toxicity summary will be submitted to the Medical Monitor at the IND office after 15 subjects have been completed treatment.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

11.0 LIST OF REFERENCES

1. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res 2013;19(14):3936-43.

2. Kaseb AO, Xiao L, Hassan MM, et al. Development and validation of insulin-like growth factor-1 score to assess hepatic reserve in hepatocellular carcinoma. Journal of the National Cancer Institute 2014;106(5).

3. Llovet JM, Di Bisceglie AM, Bruix J, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. Journal of the National Cancer Institute 2008;100(10):698-711.

4. Wilson SR, Greig P, Kaseb AO. Pretreatment assessment of hepatocellular cancer: expert consensus conference. HPB (Oxford) 2010;12(5):300-1.

5. Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. Journal of hepatology 2005;42 Suppl(1):S100-7.

6. Oellerich M, Burdelski M, Lautz HU, et al. Assessment of pretransplant prognosis in patients with cirrhosis. Transplantation 1991;51(4):801-6.

7. Testa R, al. e. Can the MEGX test and serum bile acids improve the prognostic ability of Child-Pugh's score in liver cirrhosis. Eur J Gastroenterol Hepatol 1999;11(5):559-63.

8. Kaseb AO, Morris JS, Hassan MM, et al. Clinical and prognostic implications of plasma insulin-like growth factor-1 and vascular endothelial growth factor in patients with hepatocellular carcinoma. J Clin Oncol 2011;29(29):3892-9.

9. Kaseb AO, Abbruzzese JL, Vauthey JN, et al. I-CLIP: improved stratification of advanced hepatocellular carcinoma patients by integrating plasma IGF-1 into CLIP score. Oncology 2011;80(5-6):373-81.

10. Bonefeld K, Moller S. Insulin-like growth factor-I and the liver. Liver Int 2011;31(7):911-9.

11. Rehem RN, El-Shikh WM. Serum IGF-1, IGF-2 and IGFBP-3 as parameters in the assessment of liver dysfunction in patients with hepatic cirrhosis and in the diagnosis of hepatocellular carcinoma. Hepato-gastroenterology 2011;58(107-108):949-54.

12. Abdel-Wahab R, Shehata S, Hassan MM, et al. Validation of an IGF-CTP scoring system for assessing hepatic reserve in Egyptian patients with hepatocellular carcinoma. Oncotarget 2015;6(25):21193-207.

13. Fernandez M, Mejias M, Garcia-Pras E, Mendez R, Garcia-Pagan JC, Bosch J. Reversal of portal hypertension and hyperdynamic splanchnic circulation by combined vascular endothelial growth factor and platelet-derived growth factor blockade in rats. Hepatology (Baltimore, Md 2007;46(4):1208-17.

14. Mejias M, Garcia-Pras E, Tiani C, Miquel R, Bosch J, Fernandez M. Beneficial effects of sorafenib on splanchnic, intrahepatic, and portocollateral circulations in portal hypertensive and cirrhotic rats. Hepatology (Baltimore, Md 2009;49(4):1245-56.

15. D'Amico G, Pietrosi G, Tarantino I, Pagliaro L. Emergency sclerotherapy versus vasoactive drugs for variceal bleeding in cirrhosis: a Cochrane meta-analysis. Gastroenterology 2003;124(5):1277-91.

16. Abraldes JG, Tarantino I, Turnes J, Garcia-Pagan JC, Rodes J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. Hepatology (Baltimore, Md 2003;37(4):902-8.

17. Coriat R, Gouya H, Mir O, et al. Reversible decrease of portal venous flow in cirrhotic patients: a positive side effect of sorafenib. PloS one 2011;6(2):e16978.

18. Hidaka H, Nakazawa T, Kaneko T, et al. Portal hemodynamic effects of sorafenib in patients with advanced hepatocellular carcinoma: a prospective cohort study. Journal of gastroenterology 2012;47(9):1030-5.

19. Evans AJ, Iwai F, Grist TA, et al. Magnetic resonance imaging of blood flow with a phase subtraction technique. In vitro and in vivo validation. Investigative radiology 1993;28(2):109-15.

20. Burkart DJ, Johnson CD, Ehman RL, Weaver AL, Ilstrup DM. Evaluation of portal venous hypertension with cine phase-contrast MR flow measurements: high association of hyperdynamic portal flow with variceal hemorrhage. Radiology 1993;188(3):643-8.

21. Debatin JF, Zahner B, Meyenberger C, et al. Azygos blood flow: phase contrast quantitation in volunteers and patients with portal hypertension pre- and postintrahepatic shunt placement. Hepatology (Baltimore, Md 1996;24(5):1109-15.

22. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet (London, England) 2012;379(9822):1245-55.

23. Llovet JM, Villanueva A, Lachenmayer A, Finn RS. Advances in targeted therapies for hepatocellular carcinoma in the genomic era. Nature reviews 2015;12(7):408-24.

24. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. The New England journal of medicine 2008;359(4):378-90.
25. Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. The Lancet 2009;10(1):25-34.

26. Cheng AL, Kang YK, Lin DY, et al. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. J Clin Oncol 2013;31(32):4067-75.

27. *Randomized, multicenter, open-label study of oxaliplatin plus fluorouracil/leucovorin versus doxorubicin as palliative chemotherapy in patients with advanced hepatocellular carcinoma from Asia. Qin S1, Bai Y, Lim HY, Thongprasert S, Chao Y, Fan J, Yang TS, Bhudhisawasdi V, Kang WK, Zhou Y, Lee JH, Sun Y. J Clin Oncol. 2013 Oct 1;31(28):3501–8.*

28. Ikeda K, Kudo M, Kawazoe S, Osaki Y, Ikeda M, Okusaka T, Tamai T, Suzuki T, Hisai T, Hayato S, Okita K, Kumada H. Phase 2 study of lenvatinib in patients with advanced hepatocellular carcinoma. J Gastroenterol. 2017 Apr;52(4):512-519.

29. Llovet JM, Decaens T, Raoul JL, et al. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. J Clin Oncol 2013 ;31(28):3509-16.

30. Zhu AX, Kudo M, Assenat E, et al. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. Jama 2014 312(1):57-67.

31. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. The Lancet; 2015 16(7):859-70.

32. Bruix J, Tak WY, Gasbarrini A, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. Eur J Cancer 2013;49(16):3412-9.

33. Santoro A, Rimassa L, Borbath I, et al. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. The Lancet 2013;14(1):55-63.

34. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt

G, Han G; RESORCE Investigators.. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66.

35. Granito A, Marinelli S, Terzi E, et al. Metronomic capecitabine as second-line treatment in hepatocellular carcinoma after sorafenib failure. Dig Liver Dis 2015;47(6):518-22.

36. Patrikidou A, Sinapi I, Regnault H, et al. Gemcitabine and oxaliplatin chemotherapy for advanced hepatocellular carcinoma after failure of anti-angiogenic therapies. Investigational new drugs 2014;32(5):1028-35.

37. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators.. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Jan 7;389(10064):56-66.

38. Global Hepatitis Report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0IGO. ISBN 978-92-4-156545-5.

39. Arnolfo Petruzziello, Samantha Marigliano, Giovanna Loquercio, Anna Cozzolino, and Carmela Cacciapuoti. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016 Sep 14; 22(34): 7824–7840.

40. Blach et al. The Polaris Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The Lancet. Gastroenterology and Hepatology. Volume 2, No. 3, p161–176, March 2017

41. He T, Lopez-Olivo MA, Hur C, Chhatwal J. Systematic review: cost-effectiveness of direct-acting antivirals for treatment of hepatitis C genotypes 2-6. Aliment Pharmacol Ther. 2017 Oct;46(8):711-721. doi: 10.1111/apt.14271. Epub 2017 Aug 24.

42. Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, Poropat G, Djurisic S, Weiss KH, Bjelakovic M, Bjelakovic G, Klingenberg SL, Liu JP, Nikolova D, Koretz RL, Gluud C. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev. 2017 Jun 6;6:CD012143. doi: 10.1002/14651858.CD012143.pub2

43. Hezode, C., Serfaty, L., Vierling, J., Iugelmasa, M., Pearlmans, B. and Sieverf, W. Safety and efficacy of the all-oral regimen of MK-5I72/ MK-8742± ribavirin in treatment-naïve, noncirrhotic patients with hepatitis C virus genotype 1 infection: the C-WORTHY study. J Hepatol 2014 60: S5

44. European Association for the Study of the Liver (EASL). (2011) EASL clinical practice guidelines:management of hepatitis C infection. J Hepatol 55:245–264. Mini Rev Med Chem. 2017 Sep 12. doi:

45. Das D, Pandya M. J. Recent advancement of Direct-acting antiviral agents (DAAs) in Hepatitis C therapy. Transl Int Med. 2017 Mar 31;5(1):8-17.

46. Geddawy A, Ibrahim YF, Elbahie NM, Ibrahim MA. Direct acting anti-hepatitis C virus drugs: Clinical pharmacology and future direction. Expert Opin Pharmacother. 2017 Aug;18(12):1235-1242.

47. Soriano V, Fernandez-Montero JV, de Mendoza C, Benitez-Gutierrez L, Peña JM, Arias A, Barreiro P. Treatment of hepatitis C with new fixed dose combinations. Therap Adv Gastroenterol. 2017 Jan;10(1):155-167..

48. Vallet-Pichard A, Pol S. Grazoprevir/elbasvir combination therapy for HCV infection 2. Elbasvir and grazoprevir for chronic hepatitis C genotypes 1 and 4. Therap Adv Gastroenterol. 2017 Jan;10(1):155-167.

49. El Kassas M, Elbaz T, Abd El Latif Y, Esmat G. Elbasvir and grazoprevir for chronic hepatitis C genotypes 1 and 4. Expert Rev Clin Pharmacol. 2016 Nov;9(11):1413-1421.

50. Landaverde C, Wells J, Hamner R, Goldstein JL. Dual therapy of grazoprevir and elbasvir for the treatment of hepatitis C infection. Expert Rev Gastroenterol Hepatol. 2016;10(4):419-29.

51. Merck & Co., Inc. ZepatierTM (elbasvir and grazoprevir) tablets, for oral use: US prescribing information 2016. http://www.merck.com/. Accessed 4 Apr 2017.

52. Merck & Co., Inc. ZepatierTM (elbasvir and grazoprevir) tablets, for oral use: US prescribing information 2016. http://www.merck.com/. Accessed 4 Apr 2017.

53. Zaina T. Al-Salama1• Emma D. Deeks1 Elbasvir/Grazoprevir: A Review in Chronic HCV Genotypes 1and 4 Drugs (2017) 77:911–921

54. Buti, M., Gordon, S., Zuckerman, E., Lawitz, E., Calleja, J., Hofer, H. et al. Grazoprevir, elbasvir, and ribavirin for chronic hepatitis C virus genotype 1 infection after failure of pegylated interferon and ribavirin with an earlier-generation protease inhibitor: final 24-week results from C-SALVAGE. Clin Infect Dis 2016 62: 32–36.

55. Forns, X., Gordon, S., Zuckerman, E., Lawitz, E., Calleja, J., Hofer, H. et al. Grazoprevir and elbasvir plus ribavirin for chronic HCV genotype-1 infection after failure of combination therapy containing a direct-acting antiviral agent. J Hepatol 2015 63: 564–572.

56. Hezode, C., Serfaty, L., Vierling, J., Iugelmasa, M., Pearlmans, B. and Sieverf, W. Safety and efficacy of the all-oral regimen of MK-5I72/MK-8742± ribavirin in treatment-

naïve, noncirrhotic patients with hepatitis C virus genotype 1 infection: the C-WORTHY study. J Hepatol 2014 60: S5.

57. Lawitz, E., Gane, E., Pearlman, B., Tam, E., Ghesquiere, W., Guyader, D. et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK- 8742) with or without ribavirin for hepatitis C virus GT 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase II trial. Lancet 2015 385: 1075–1086.

58. Lawitz, E., Gane, E., Pearlman, B., Tam, E., Ghesquiere, W., Guyader, D. et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. Lancet. 2015 Mar 21;385(9973):1074.

59. Hezode, C., Fontaine, H., Dorival, C., Zoulim, F., Larrey, D., Canva, V. et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology 12014 47: 132–142

60. Jacobson, I., Poordad, F., Firpi-Morell, R., Everson, G., Verna, E., Bhanja, S. et al. Efficacy and safety of grazoprevir and elbasvir in hepatitis C genotype 1-infected patients with Child–Pugh class B cirrhosis (C-SALT part A). J Hepatol 2015 62(Suppl. 2): S193–S194

61. Kwo, P., Gane, E., Peng, C., Pearlman, B., Vireling, J., Serfaty, L. et al. P0886 : Efficacy and safety of grazoprevir/elbasvir +/- RBV for 12 weeks in patients with HCV G1 or G4 infection who previously failed peginterferon/RBV: C-edge treatment-experienced trial. Journal of Hepatology. 2015Volume 62, Supplement 2, Pages S674–S675.

62. Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

63. Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following nonmyeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

64. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703

65. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

66. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domaincontaining tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

67. Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

68. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domaincontaining tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

69. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

70. Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

71. Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits Tcell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.

72. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit Tcell activation by distinct mechanisms. Mol Cell Biol 2005;25(21):9543-53.

73. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev 2010;236:219-42.

74. Dudley ME, Wunderlich JR, Yang JC, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

75. Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annual review of immunology 2005;23:515-48.

76. Hunder NN, Wallen H, Cao J, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. The New England journal of medicine 2008;358(25):2698-703.77. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proceedings of the National Academy of Sciences of the United States of America 2001;98(24):13866-71.

78. Polcher M, Braun M, Friedrichs N, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.

79. Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma VM. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. The Journal of pathology 1997;182(3):318-24.

80. Morales-Kastresana A, Sanmamed MF, Rodriguez I, et al. Combined immunostimulatory monoclonal antibodies extend survival in an aggressive transgenic hepatocellular carcinoma mouse model. Clin Cancer Res; 2013 19(22):6151-62.

81. Gao Q, Wang XY, Qiu SJ, et al. Overexpression of PD-L1 significantly associates with tumor aggressiveness and postoperative recurrence in human hepatocellular carcinoma. Clin Cancer Res 2009;15(3):971-9.

82. Shi F, Shi M, Zeng Z, et al. PD-1 and PD-L1 upregulation promotes CD8(+) T-cell apoptosis and postoperative recurrence in hepatocellular carcinoma patients. International journal of cancer;2011 128(4):887-96.

83. El-Khoueiry AB, Melero I, Crocenzi TS, et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellularcarcinoma (HCC): CA209-040. J Clin Oncol 2015;33:suppl; abstr LBA101.

84. Maxine M. Denniston, Ruth B. Jiles, Jan Drobeniuc,R. Monina Klevens, John W. Ward, Geraldine M. McQuillan, and Scott D. Holmberg. Chronic Hepatitis C Virus Infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. Ann Intern Med. 2014 March 4; 160(5): 293–300.

85. Rocío González-Grande, Miguel Jiménez-Pérez, Carolina González Arjona, José Mostazo Torres. New approaches in the treatment of hepatitis C. World J Gastroenterol 2016 January 28; 22(4): 1421-1432

86. Gardiner D[1], Lalezari J, Lawitz E, DiMicco M, Ghalib R, Reddy KR, Chang KM, Sulkowski M, Marro SO, Anderson J, He B, Kansra V, McPhee F, Wind-Rotolo M, Grasela D, Selby M, Korman AJ, Lowy I. A randomized, double-blind, placebo-controlled assessment of BMS-936558, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with chronic hepatitis C virus infection. PLoS One. 2013 May 22;8(5):e63818.

87. Sangro B[1], Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, Riezu-Boj JI, Larrea E, Alfaro C, Sarobe P, Lasarte JJ, Pérez-Gracia JL, Melero I, Prieto J. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. J Hepatol. 2013 Jul;59(1):81-8.

88. Chen J, Florian J, Carter W, Fleischer RD, Hammerstrom TS, Jadhav PR, Zeng W, Murray J, Birnkrant D. .Earlier Sustained Virologic Response End Points for Regulatory Approval and Dose Selection of Hepatitis C Therapies. Gastroenterology 2013;144:1450–1455

89. Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment Guidance for Industry U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) November 2017 Clinical/Microbial. Office of Communications, Division of Drug Information Center for Drug Evaluation and Research Food and Drug Administration 10001 New Hampshire Ave., Hillandale Bldg., 4th Floor Silver Spring, MD 20993-0002.

90. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, LebbéC, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009;15(23):7412-20.

91. Hodi FS, Ribas A, Daud A, Hamid O, Robert C, Kefford R, et al. Patterns of response in patients with advanced melanoma treated with Pembrolizumab (MK-3475) and evaluation of immune-related response criteria (irRC). J Immunother Cancer. 2014;2(Suppl 3):P103.

92. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152

93. Toshiyuki Tamai, Seiichi Hayato, Seiichiro Hojo, Takuya Suzuki, Takuji Okusaka, Kenji Ikeda, and Hiromitsu Kumada. Dose Finding of Lenvatinib in Subjects With Advanced Hepatocellular Carcinoma Based on Population Pharmacokinetic and Exposure–Response Analyses. J Clin Pharmacol. 2017 Sep; 57(9): 1138–1147.

94. Cheng et al. Phase III trial of lenvatinib (LEN) vs sorafenib (SOR) in first-line treatment of patients (pts) with unresectable hepatocellular carcinoma (uHCC). Journal of Clinical Oncology 35, no. 15_suppl (May 2017) 4001-4001.

95. Anthony B El-Khoueiry, Bruno Sangro, Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan,Theodore H Welling 3rd, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely,Hao Tang, Homa B Dastani, Ignacio Melero.Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative,phase 1/2 dose escalation and expansion trial. Lancet 2017; 389: 2492–502

96. M.G. Swain, M.Y. Lai, M.L. Shiffman, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology, 139 (2010), pp. 1593-1601

97. Pearlman BL, Traub N. Sustained virologic response to antiviral therapy for chronic hepatitis C virus infection: a cure and so much more. Clin Infect Dis 2011;52:889–900.

98. Tsuda N, Yuki N, Mochizuki K, et al. Long-term clinical and virological outcomes of chronic hepatitis C after successful interferon therapy. J Med Virol 2004;74:406–413.

99. Ghany MG, Strader DB, Thomas DL, et al. Diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49:1335–1374.

100. Lindsay KL. Introduction to therapy of hepatitis C. Hepatology 2002;36:S114–S120.

101. US Food and Drug Administration. Chronic hepatitis C virus infection: developing direct-acting antiviral agents for treatment. 10
AD.

102. Poonam Mishra, Jeffrey Murray, and Debra Birnkrant Direct-Acting Antiviral Drug Approvals for Treatment of Chronic Hepatitis C Virus Infection: Scientific and Regulatory Approaches to Clinical Trial Designs HEPATOLOGY, Vol. 62, No. 4, 2015

103. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011;9:509-516.

104. Singal AG, Volk ML, Jensen D, Di Bisceglie AM, Schoenfeld PS. A sustained viral response is associated with reduced liver related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-288.

105. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012;308:2584-2593.

106. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP,Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann InternMed 2007;147:677-684.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

B. Publication and Authorship

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.

III. Subject Protection

A. IRB/ERC review

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

D. Genomic Research

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the

wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

V. Investigator Commitment

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

12.2 Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For subjects who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a subject on study treatment until repeat imaging is obtained (using iRECIST for subject management (see Table 11 and Figure 2). This decision by the Investigator should be based on the subject's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any subject deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
  - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, subjects will be discontinued from study treatment.

NOTE: If a subject has confirmed radiographic progression (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with Merck. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions

- If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
- If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour et al, 2017].

12.3 HBV Definitions and Treatment Considerations

Table 20 describes the various definitions of hepatitis B as well as the treatment considerations for subjects with HBV:

Protocol will exclude history of HBV infection with viral load detectable by qPCR testing (with sensitivity to detect at least a minimum of 20 IU/mL); unless initiation of treatment with nucleotide analogs such as those used in the treatment of HBV (eg, lamivudine, adefovir, tenofovir, telbivudine, entecavir), is entertained and hepatitis B vius becomes undetected.

Table 20 Hepatitis B Definitions and Treatment Considerations

Test	Patient Status	Any HBV Treatment Needed?
HBsAg (–) Total anti-HBc (+) HBsAb (+)	Immune after natural infection	No
HBsAg (–) Total anti-HBc (–) HBsAb (+)	Immune after vaccination	No
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (+) HBsAb (–)	Acute infection	—
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–)	Chronic infection	Yes, need to be on a HBV treatment for at least 12 weeks prior to start of pembrolizumab without evidence of a flare during that period Exclude if: (a) <12 weeks of therapy; (b) HBV DNA not under control during this time frame; (c) Documented HBV flare in the past 12 weeks
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV DNA (negative)	Unclear. Could be: (1) Resolved infection (2) False positive anti-HBc ((3) Low level infection (4) Resolving Acute infection	No
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV DNA (+)	(5) Low level infection (6) Resolving acute infection	Yes (as above)

12.4 Common Terminology Criteria for Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html).

12.5 Child-Pugh Score

The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation.

Scoring

The score employs five clinical measures of liver disease. Each measure is scored from 1 to 3, with 3 indicating most severe derangement (Table 21).

Table 21 Child-Pugh Scoring

Measure	1 point	2 points	3 points
Total bilirubin (µmol/L or mg/dL)	<34 or <2	34–51 or 2–3	>51 or >3
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time, prolongation (sec)	<4.0	4.0–6.0	>6.0
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3–4 (or refractory)

In primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/L (4 mg/dL) and the upper limit for 2 points is 170 µmol/L (10 mg/dL).

Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Table 22 One and two year survival based on Child-Pugh score

Points	Class	One-year survival	Two-year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

Table 23 Original Child-Turcotte-Pugh Score and new IGF-1-modified Score

Parameter	Original Child-Turcotte-Pugh Score* (points)			Modified CTP Score** (points)		
	1	2	3	1	2	3
Encephalopathy	The same as in CTP	The same as in CTP	The same as in CTP			
Ascites	The same as in CTP	The same as in CTP	The same as in CTP			
Albumin (g/dL)	The same as in CTP	The same as in CTP	The same as in CTP	The same as in CTP		
PT (seconds)	The same as in CTP	The same as in CTP	The same as in CTP	The same as in CTP		
Bilirubin (mg/dL)¶	The same as in CTP	The same as in CTP	The same as in CTP	The same as in CTP		
IGF-1 (ng/mL)				≥50	26-50	≤26

Abbreviations: IGF-1, insulin-like growth factor-1; PT, prothrombin time; CTP, Child-Turcotte-Pugh.
***CTP classes:** A (5-6), B (7-9), C (>9)
****Modified CTP classes:** A (4-5), B (6-7), C (>7)

¶ In primary biliary cirrhosis and primary sclerosing cholangitis, the upper limit of bilirubin for 1 point is 4 mg/dL and the upp er limit for 2 points is 10 mg/dL.

12.6 List of Abbreviations

Table 24 List of Abreviations

Abbreviation/Term	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APRI	Aspartate Aminotransferase:Platelet Ratio Index
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
CI	Confidence Interval
CNB	Core Needle Biopsy
CNS	Central Nervous System
CPT	Cell Preparation Tubes
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated Protein 4
CTP	Child-Turcotte-Pugh
CYP	Cytochrome P450
DAA	Direct Acting Antiviral
Dbil	Direct Bilirubin
DCR	Disease Control Rate
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERC	Ethics Review Committee
FBR	Future Biomedical Research
FDA	US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDC	Fixed Dose Combination
FFPE	Formalin-fixed Paraffin-embedded
FSH	Follicle Stimulating Hormone
GB	Granzyme B
GCP	Good Clinical Practice

Abbreviation/Term	Definition
GEP	Gene Expression Profile
GI	Gastrointestinal
GGT	γ-glutamyl transpeptidase
GT	Genotype
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCC	Hepatcellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGF	Insulin Growth Factor-1
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
iRECIST	Modified RECIST 1.1 for Immune-based Therapeutics
ITB	Institutional Tissue Bank
IUD	Intrauterine Device
IV	Intravenous(ly)
KN	KEYNOTE
LLOQ	lower Limit of Quantification
mAb	Monoclonal Antibody
MDACC	M.D. Anderson Cancer Center
MRI	Magnetic Resonance Imaging
NA or N/A	Not Applicable
NCI	National Cancer Institute
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PBMCs	Peripheral Blood Mononuclear Cells
PBPK	Physiologically-based PK
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death 1 Ligand 1
PD-L2	Programmed Cell Death 1 Ligand 2
Peg-IFN	Pegylated-interferon
PFS	Progression-free Survival

Abbreviation/Term	Definition
PK	Pharmacokinetic
PO	Oral Administration
PP	Per Protocol
PR	Partial Response
qday	Once Daily
RAV	Resistance-Associated Variants
RBV	Ribavirin
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
Q12W	Every 12 Weeks
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
Q9W	Every 9 Weeks
SAE	Serious Adverse Events
SD	Stable Disease
SIM	Site Imaging Manual
SOP	Standard Operating Procedures
SVR	Sustained Virologic Response
SVR4	Sustained Virologic Response 4 weeks after the end of all study therapy: The subject has HCV RNA <25 IU/mL (either TD(u) or TND) 4 weeks after the end of all study therapy
SVR12	(Sustained Virologic Response 12 weeks after the end of all study therapy): The subject has HCV RNA <25 IU/mL (either TD(u) or TND) 12 weeks after the end of all study therapy
SVR24	(Sustained Virologic Response 24 weeks after the end of all study therapy): The subject has HCV RNA <25 IU/mL (either TD(u) or TND) 24 weeks after the end of all study therapy
Tbil	Total Bilirubin
TCR	T Cell Receptor
TD(u)	Target Detected but Unquantifiable
TD(q)	Target Detected, Quantifiable
TIL	Tumor-Infiltrating Lymphocytes
TND	Target NOT detected (HCV RNA not detected)
Treg	Regulatory T Cells
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
US	United States

12.7 ECOG Performance Status

Table 25 ECOG Performance

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

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

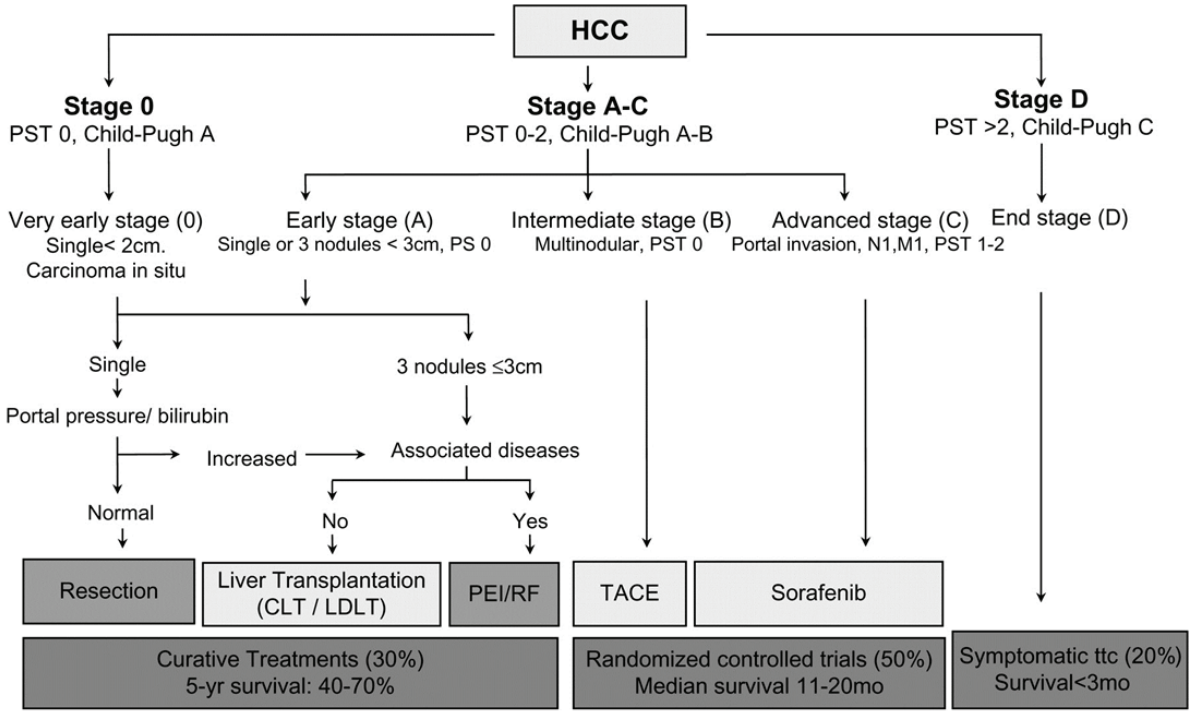
RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

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

In addition, volumetric analysis will be explored by central review for response assessment.

12.9 Barcelona Clinic Liver Cancer Staging System



CLT = cadaveric liver transplantation; LDLT = living donor liver transplantation; PEI = percutaneous ethanol injection; RF = radio frequency (ablation); TACE = transarterial chemoembolization.