Official Protocol Title:	A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care as Second-Line Therapy in Subjects with Previously Systemically Treated Advanced Hepatocellular Carcinoma (KEYNOTE-240)
NCT number:	NCT02702401
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TITLE:

A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care as Second-Line Therapy in Subjects with Previously Systemically Treated Advanced Hepatocellular Carcinoma (KEYNOTE-240)

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
3475-240-04	03-FEB-2021	Language was added to include the requirement of roll over of trial participants into an extension trial (if available) when this trial is completed
3475-240-03	21-DEC-2017	A second interim analysis was added
3475-240-02	20-JUL-2016	Subject eligibility by radiographic diagnosis for HCC was added to address investigator feedback; caps on Asian and HBV population was widened following consultation with Regulatory and SAC members to help facilitate accrual rate.
3475-240-01	23-FEB-2016	Program wide decision for pembrolizumab to remove health economic assessment from patient reported outcomes
Original Protocol	15-JAN-2016	Not applicable

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0; 2.1;	Trial Summary	Sentence added: Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available	Language was added to include the requirement of roll over of trial participants into an extension trial (if available) when this trial is completed
2.1; 6.1 and 6.2; 7.1.4.1.3; 7.1.4.1.4;	Trial Design; Trail Flow Chart; End of Treatment and Follow-up Tumor Imaging; Second Course (Retreatment) Tumor Imaging;	The frequency of follow up visits and imaging were changed from every 6 weeks (42±7 days) to 12 weeks (84±7 days)	To align with current follow-up schedule for pembrolizumab studies
7.1.6.3.2	Follow-Up Visits	Sentence 'Follow-up Phase and should be assessed Q6W by radiologic imaging' changed to 'Follow-up Phase and should be assessed Q12W by radiologic imaging'	The duration of follow up phase was revised.
12.9	List of Abbreviations;	Q12W was added	Additional abbreviation for 12 weeks duration was added.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care as Second-Line Therapy in Subjects with Previously Systemically Treated Advanced Hepatocellular Carcinoma
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	Phase III
Clinical Indication	Hepatocellular carcinoma
Trial Type	Interventional
Type of control	Placebo plus best supportive care (BSC)
Route of administration	Intravenous (IV)
Trial Blinding	Double-blind
Treatment Groups	Pembrolizumab plus BSC or placebo plus BSC
Number of trial subjects	Approximately 408 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 44 months from the time the first subject signs the informed consent 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 informed consent form through the final contact. After a screening phase of up to 28 days, each subject will receive pembrolizumab or placebo beginning on Day 1 of each 3-week dosing cycle. Treatment will continue until progressive disease, unacceptable adverse events, 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 (approx. 2 years) of study drug, or administrative reasons requiring cessation of treatment. Subjects who stop study drug as a result of obtaining a centrally confirmed complete response or those subjects who stop after receiving 35 trial treatments may be eligible, at the discretion of the investigator, for an additional 17 trial treatments (approx. 1 year) after progressive disease if they meet the criteria for re-treatment (Second Course Phase) and the study is ongoing. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up visits for monitoring disease status as if they were still on treatment 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 (e.g., by telephone or visit) for overall survival until death, withdrawal of consent from study participation, or the end of the study, whichever comes first. After the end of study treatment, each subject will be followed for 30 days for adverse event monitoring. Serious adverse events 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. Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

Randomization Ratio	Pembrolizumab plus BSC or placebo plus BSC at a 2:1 ratio

A list of abbreviations used in this document can be found in Section 12.9.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a double-blind randomized Phase III trial of pembrolizumab (MK-3475) plus best supportive care (BSC) versus placebo plus BSC in previously systemically treated subjects with a hepatocellular carcinoma (HCC) diagnosis confirmed by radiology, histology, or cytology (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible). To be eligible, subjects must have documented objective radiographic progression of disease (PD) during or after treatment with sorafenib, or else be intolerant of sorafenib as defined in Section 5.1.2. They also must have disease not amenable to a curative treatment approach (e.g., transplant, surgery, or ablation). Subjects must have at least one measurable lesion that is confirmed by the blinded central imaging vendor per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, Child-Pugh liver class A, an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, and predicted life expectancy of > 3 months. Subjects will be enrolled regardless of tissue programmed death ligand 1 (PD-L1) biomarker status. Subjects will not be required to provide a tumor tissue sample for biomarker analysis, but are strongly urged to do so if tissue is available. Approximately 408 subjects will be randomized at a 2:1 ratio to receive pembrolizumab 200 mg IV plus BSC every 3 weeks (Q3W) or placebo IV plus BSC (Q3W).

Enrollment of subjects in the Asian population will be capped to approximately 30% of the study population (approximately 122 subjects total); hepatitis B subjects will be capped also to approximately 30% of the study population (approximately: 122 subjects total; 61 from Asia without Japan population [i.e., 15% of 408]; and 61 subjects from non-Asian with Japan population [i.e., 15% of 408]). Additionally, the sorafenib-intolerant population will be capped at approximately 20% within each region (approximately: 82 subjects total; 25 from Asia without Japan population [i.e., 20% of 122]; and 57 from non-Asia with Japan population [i.e., 20% of 286]), to ensure that the study population is representative of the U.S. population.

The primary objectives of this trial are to determine progression-free survival (PFS) and overall survival (OS) of pembrolizumab plus BSC compared with placebo plus BSC. On-study imaging assessments will be performed every 6 weeks (Q6W) calculated from the date of randomization 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). PD will also be confirmed by the blinded central imaging vendor.

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 Section 4.2.4.2 termed immune-related RECIST (irRECIST) 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 pembrolizumab 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 study drug until PD is confirmed at least 4 weeks after the date of the first tumor imaging suggesting PD per the site investigator and subsequently confirmed by the central imaging vendor. 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 the Sponsor.

Subjects may continue on study treatment until PD is confirmed by RECIST 1.1, unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator decides to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments (approx. 2 years). Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 12 weeks (84±7 days) by radiologic imaging to monitor disease status. 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 approximately every 12 weeks for OS until death, withdrawal of consent from participation in the study, or the end of the study, whichever occurs first. In addition to that, survival status will be monitored as needed for analysis during the course of the trial.

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), may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR. Subjects who stop study drug after receiving 35 trial treatments (approximately 2 years) for reasons other than PD or intolerability or who stop after attaining a CR may be eligible for retreatment with up to an additional 17 treatments (second course of treatment, approximately 1 year) after they have experienced radiographic PD (see Section 5.8.1). The decision to retreat will be at the discretion of the investigator only if no other cancer treatment was administered since the last dose of study drug, the subject still meets the parameters listed in the inclusion and exclusion criteria, and the trial remains open.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Section 12.6). After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (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. Treatment switching between the two arms is not allowed.

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

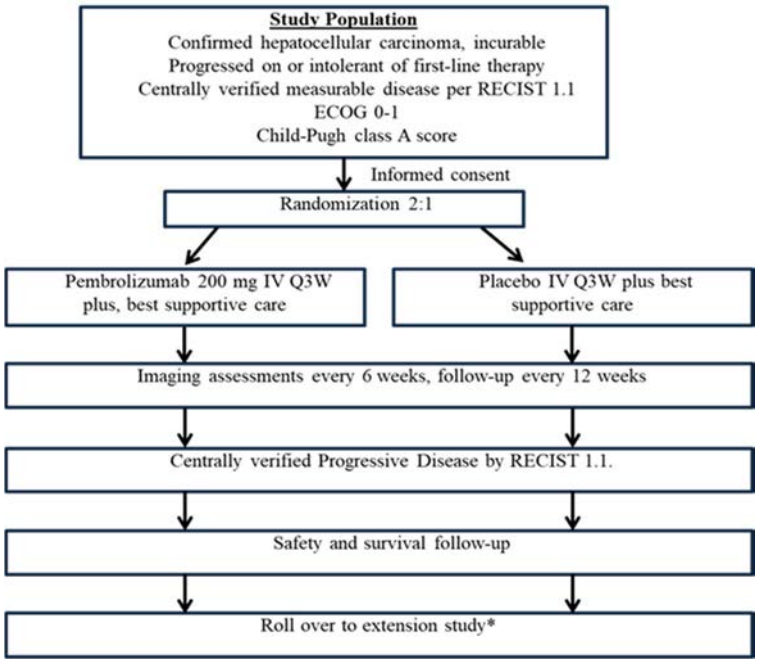
This study will be conducted in conformance with Good Clinical Practices (GCP).

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.

This trial will use a group sequential design, using an independent, external Data Monitoring Committee (eDMC). Details regarding the role of the eDMC are provided in the eDMC Charter. There will be 2 planned efficacy interim analyses (see Section 8.7). The results of the interim analyses will be reviewed by the eDMC, which will make recommendations to

the Sponsor to continue, modify, or end the trial according to the plan described in detail in Section 8.0 - Statistical Analysis Plan (SAP).

2.2 Trial Diagram



*Participants may roll over if extension study is available

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IV = intravenous; Q3W = every 3 weeks
RECIST = Response Evaluation Criteria in Solid Tumors;

Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

Intravenous administration of pembrolizumab or placebo as second-line treatment after sorafenib systemic monotherapy in subjects with advanced HCC:

3.1 Primary Objective(s) & Hypothesis(es)

In subjects with HCC receiving pembrolizumab plus BSC vs. placebo plus BSC:

1) Objective: To compare PFS per RECIST 1.1 assessed by a blinded central imaging vendor.

   Hypothesis: Pembrolizumab prolongs PFS per RECIST 1.1, assessed by a blinded central imaging vendor.

2) Objective: To compare OS between pembrolizumab plus BSC versus placebo plus BSC.

   Hypothesis: Pembrolizumab improves OS compared with placebo.

The trial will be deemed positive if either OS or PFS null hypotheses are rejected.

3.2 Secondary Objective(s) & Hypothesis(es)

In subjects with HCC receiving pembrolizumab plus BSC vs. placebo plus BSC:

1) Objective: To compare objective response rate (ORR) per RECIST 1.1 assessed by a blinded central imaging vendor.

   Hypothesis: Pembrolizumab increases ORR per RECIST 1.1, assessed by a blinded central imaging vendor.

2) Objective: To evaluate the duration of response (DOR), disease control rate (DCR) and time to progression (TTP), per RECIST 1.1 assessed by a blinded central imaging vendor.

3) Objective: Evaluate the safety and tolerability profile of pembrolizumab.

3.3 Exploratory Objectives

In subjects with HCC receiving pembrolizumab plus BSC vs. placebo plus BSC:

1) Objective: To evaluate PFS, ORR, DOR, DCR, and TTP, assessed by the investigator using RECIST 1.1.

2) Objective: To evaluate PFS, ORR, DOR, DCR, and TTP per modified RECIST for HCC (mRECIST) assessed by blinded central imaging vendor review.

3) Objective: To evaluate PFS, ORR, DOR, DCR, and TTP per irRECIST assessed by blinded central imaging vendor review.

4) Objective: To identify molecular (genomic, metabolic and/or proteomic) determinants of response or resistance (e.g., PD-L1 IHC, gene expression profiling, and/or genomic variation) to pembrolizumab and other treatments in this study, using blood and/or tumor tissue to define novel predictive and pharmacodynamic biomarkers, to better understand the mechanism of action of pembrolizumab.

5) Objective: To evaluate score change from baseline of health related quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire—Core 30 (QLQ-C30) and the EORTC Quality of Life Questionnaire—HCC 18 (QLQ-HCC18).

6) Objective: To characterize health utilities using EuroQol-5 Dimension (EuroQol EQ-5D™).

7) Objective: To explore the relationship between cause of sorafenib discontinuation (intolerant vs. radiographic progression of disease) and response to pembrolizumab.

8) Objective: To explore the response of underlying hepatitis B virus (HBV) or hepatitis C virus (HCV) (if present) to pembrolizumab as assessed by viral loads and viral serologies.

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

Liver cancer is the second leading cause of cancer deaths worldwide and has one of the most rapidly rising mortality rates of any cancer in the United States. Most HCC arises in the setting of liver cirrhosis from varied causes, including viral hepatitis, excessive alcohol consumption, hemochromatosis, and metabolic syndrome [2]. 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. As HCC is resistant to most traditional chemotherapy agents, the median survival for patients with advanced disease is typically 6–9 months without therapy.

The multi-targeted tyrosine kinase inhibitor sorafenib is the current standard of care worldwide for the treatment of patients with advanced HCC 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, respectively. The hazard ratio for OS was 0.69, [95% CI 0.55-0.87], $p<0.001$ [3]. 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 [4]. In parts of Asia, the FOLFOX regimen (folinic acid, 5-fluorouracil, and oxaliplatin) has also been approved, based on a randomized trial comparing FOLFOX with doxorubicin [5]. In this trial, there was a nonsignificant trend toward improved OS in the FOLFOX arm, with some imbalances in the populations favoring the FOLFOX arm. Despite these advances, continued investigation of additional agents for advanced HCC patients remains crucial.

In the second-line setting, there is no clear worldwide standard of care for treatment of advanced HCC. Several large randomized trials had failed to show a significant survival advantage of various agents against placebo in the second line, including brivanib [6], everolimus [7] and ramucirumab [8]. Smaller studies suggested the possible efficacy for MET inhibitors and regorafenib in advanced HCC, and larger randomized trials were underway to investigate these drugs in more detail [9], [10]. Chemotherapy drugs including capecitabine and the gemcitabine/oxaliplatin (GEMOX) combination also used in the second line in small trials [11], [12].

4.1.1 Pharmaceutical and Therapeutic Background

Pembrolizumab (MK-3475) is a potent and highly-selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between programmed cell death 1 (PD-1) and its ligands, PD-L1 and programmed death ligand 2 (PD-L2). KEYTRUDA (pembrolizumab) has been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab or a BRAF inhibitor, if BRAF V600 mutation-positive. Pembrolizumab was also approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by a Food and Drug

Administration (FDA)-approved test, with disease progression on or after platinum-containing chemotherapy.

The importance of intact immune surveillance in controlling neoplastic growth has been known for decades [13]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and a favorable prognosis in various malignancies [14], [15], [16], [17], [18]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells to FoxP3+ regulatory T-cells seem to correlate with improved prognosis and long-term survival in many solid tumors.

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 CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [19], [20].

The structure of murine PD-1 has been identified [21]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig variable-type (V-type) domain responsible for ligand binding, and a cytoplasmic tail which is 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 (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70 which are involved in the CD3 T-cell signaling cascade [19], [22], [23], [24]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [25], [26]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T-regulatory cells, and natural killer cells [27], [28]. Expression has also been shown during thymic development on CD4–/CD8– (double negative) T-cells as well as subsets of macrophages and dendritic cells [29].

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [30], [31], [32], [25]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand (PD-L1 or PD-L2) to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [25]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma [33].

4.1.2 Pre-clinical and Clinical Trials

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 and anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as 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-γ, granzyme B and perforin, indicating that the mechanism of action involves local infiltration and activation of effector T-cell function in vivo [34], [35], [36], [37], [38], [39]. 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 demonstrate emerging evidence of single-agent activity in additional tumor types such as mesothelioma, urothelial cancer, ovarian cancer, neuroendocrine carcinoma, and small cell lung cancer.

In a mouse model of HCC, blockade of PD-1 with immunostimulatory monoclonal antibodies extended survival [40]. HCC patients with higher expression of tumoral PD-L1 had a significantly poorer prognosis than patients with lower expression, and tumor expression of PD-L1 has also been shown to be an independent predictor for postoperative recurrence in HCC patients [41]. High expression levels of PD-1 on tumor-infiltrating lymphocytes [TILs] and peripheral blood mononuclear cells [PBMCs] have also been correlated with a poor prognosis in HCC patients after surgical resection [42]. An interim analysis of a Phase I/II trial of nivolumab in previously treated patients with HCC demonstrated that the estimated survival rate in evaluable patients (n=42) was 62% at 12 months. Results also show the safety profile of nivolumab to be generally consistent with that previously reported in other tumor types [43].

4.1.3 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.

4.1.4 Information on Other Trial-related Therapy

There is no standard second-line therapy for advanced HCC. Best supportive care will include pain management and management of other potential complications, including ascites, per local standards of care.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

HCC often develops in the setting of inflammation of various types, including viral infections. In a gene-expression profiling study, non-tumoral tissue from patients with HCC with an inflammatory signature predicted worsened OS [44]. As discussed above, HCC patients with higher tumor expression of PD-L1 have a significantly poorer prognosis than patients with lower expression [41]. In addition, high expression levels of PD-1 on T-cells (both tumor infiltrating lymphocytes and peripheral blood mononuclear cells) also correlate with higher recurrence rates in HCC patients after surgical resection [42].

Recently, immunotherapy has been shown to produce antitumor effects in HCC, a tumor which has shown resistance to traditional forms of chemotherapy. Cytotoxic T-lymphocyte-associated protein (CTLA)-4 inhibition with tremelimumab was evaluated in a small study of HCV-associated HCC patients [45]. Seventeen patients were evaluable for response, and 3 partial responses (PRs) were seen lasting for 3.6, 9.2 and 15.8 months. Stable disease was the best response seen in 59%, and of these, 45% were stable for over 6 months. Toxicity was manageable, despite early elevations in transaminases.

As discussed above, an interim analysis of a Phase I/II trial of the anti–PD-1 antibody, nivolumab, in subjects with advanced HCC demonstrated an estimated survival rate in evaluable patients 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 no maximum tolerated dose (MTD) has been identified [43].

4.2.2 Rationale for Dose Selection/Regimen

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma and NSCLC subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001 is an open-label Phase I study conducted to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and anti-tumor activity of single-agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified. In addition, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and one randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide a similar response to that seen with 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety was seen in subjects with melanoma at doses ranging from 2 mg/kg to 10 mg/kg. Exposures for 200 mg Q3W are expected to lie within this range and will be close to those obtained with the 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized mAb, which typically have low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma and NSCLC associated with maximal clinical response. The PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with the absence of a meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

4.2.3 Rationale for the Use of Comparator/Placebo

Subjects will be randomized to receive IV pembrolizumab or placebo. Both treatment arms are eligible to receive BSC based on the discretion of the investigator.

In the second-line setting, there is no clear worldwide standard of care for advanced HCC therapy. Several large randomized trials failed to show a significant survival advantage against placebo in the second line setting, including brivanib [6], everolimus [7], and ramucirumab [8]. Smaller studies have suggested the possible efficacy for MET inhibitors and regorafenib in advanced HCC, and larger randomized trials are underway to investigate these drugs [9], [10]. However, at the time of the study start, there were no agents or combinations yet approved for second-line HCC, underscoring the high unmet need for treatment of this disease, and the rationale for a placebo arm. Subjects randomized to pembrolizumab and to the placebo arm will be treated with BSC at the investigator's discretion.

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

4.2.4.1.1 Primary Efficacy Endpoint

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in subjects with HCC who were previously treated with sorafenib. The primary endpoints will be PFS per RECIST 1.1 criteria as assessed by the blinded central imaging vendor and OS. The endpoint of OS is the standard for demonstrating superiority of antineoplastic therapy in clinical studies in the area of oncology. PFS is being included as a second primary endpoint in case of unplanned treatment switching.

4.2.4.1.2 Secondary Efficacy Endpoint

The secondary efficacy objectives of this study are to:

(1) Compare ORR per RECIST 1.1 assessed by a blinded central imaging vendor.

(2) Evaluate DOR, DCR and TTP per RECIST 1.1 assessed by a blinded central imaging vendor.

Measurable disease will be confirmed centrally at enrollment, prior to subject randomization, to ensure that the assessment of measurable disease is accurate. These endpoints have been chosen as ancillary markers of efficacy in a population with few treatment options.

4.2.4.1.3 Exploratory Efficacy Endpoint

Exploratory efficacy objectives of this study are to explore ORR, DOR, DCR, TTP and PFS per 1) irRECIST assessed by the central imaging vendor, 2) investigator assessment using RECIST 1.1, 3) measurements based on RECIST 1.1 assessed by the central imaging vendor, and 4) measurements based on mRECIST assessed by the blinded central imaging vendor, to assess these different evaluations in the HCC population. Additional objectives of this study are to explore the association between genomic, metabolic and/or proteomic biomarkers and antitumor efficacy of pembrolizumab based on RECIST 1.1 as assessed by the central imaging vendor. The relationship of biomarkers in tumor compared with blood samples will be explored. Quality of life and health utilities will be examined, along with an assessment between groups with respect to hepatitis serologies and viral loads. The relationship between cause of sorafenib discontinuation (intolerance vs. radiographic progression to disease) and response to pembrolizumab in terms of overall survival will also be explored.

4.2.4.2 Immune-Related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. 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 a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may,

thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab.

Based on an analysis of patients with melanoma enrolled in KEYNOTE-001, 7% of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by immune-related response criteria had longer OS than patients with progressive disease by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in Nishino et al. 2013 [1]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. Therefore, irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions as well as by the central imaging vendor in support of all secondary and exploratory response endpoints. Confirmation of PD for irRECIST endpoints will be taken from central imaging retrospectively, according to irRECIST definition.

For further information on irRECIST, see Section 7.1.4.1.7. In addition, Modified RECIST (mRECIST) for HCC allows evaluation of treatment effects that are not reflected in simple total size changes of lesions. Details are fully described in [46], and key differences from RECIST 1.1 listed in Section 7.1.4.1.6.

4.2.4.3 Patient Reported Outcomes

As part of an exploratory analysis, subjects will provide information regarding their health-related quality of life (HRQoL) via the following European Organisation for Research and Treatment of Cancer (EORTC) assessment tools: EORTC QLQ-C30, QLQ-HCC18, and EuroQol-5D-3L (EQ-5D-) questionnaires. These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

EORTC QLQ-C30 and EORTC QLQ-HCC18

The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functioning dimensions (physical, role, cognitive, emotional, and social), 3 symptom items (fatigue, nausea/vomiting, pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and quality of life scale [47]. This instrument has been translated and validated into 81 languages and used in more than 3000 studies worldwide.

The EORTC QLQ-HCC18 is a disease-specific questionnaire developed and validated to address measurements specific to HCC [48]. It is one of multiple disease-specific modules developed by the EORTC QLG (Quality of Life Group) designed for use in clinical trials, to be administered in addition to the QLQ-C30 to assess disease-specific treatment measurements. It consists of 18 items containing 6 scales and 2 single items.

EuroQoL-5D

The EQ-5D is a standardized instrument for use as a measure of health outcome. The EQ-5D will provide data for use in economic models and analyses including developing health utilities or quality adjusted life years (QALYs). The 5 health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a three point scale from 1 (extreme problem) to 3 (no problem). The EQ-5D also includes a graded (0 to 100) vertical visual analog scale on which the subject rates his or her general state of health at the time of the assessment. The EQ-5Dwill always be completed by subjects first before completing the EORTC QLQ-C30 and QLQ-HCC18 and is to be completed at various time points as specified in the Trial Flow Chart, beginning with Cycle 1 until 30 days post-treatment discontinuation.

See flow chart for Patient Reported Outcome (PRO) administration schedule (Section 6.1).

4.2.4.4 Safety Endpoints

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with previously systemically treated HCC. The primary safety analysis will be based on subjects who have toxicities as defined by NCI-CTCAE, version 4.0 (see Section 12.6).

The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including, but not limited to, all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 7.2.3.2.

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 anti-neoplastic 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 anti-neoplastic therapy, whichever occurs first. All SAEs that occur within 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, should be followed and recorded.

4.2.4.5 Biomarker Research

Introduction: Cancer immunotherapies are an important novel class of anti-tumor agents. However, much remains to be learned about how cancer immunotherapies work and how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapies, as well as determinants of AEs in the course of our clinical trials. To that end we seek to define novel predictive/pharmacodynamic biomarkers and the best strategies of combination therapy with immuno-oncology drugs. To fully leverage the clinical data collected in this trial, we will also collect biospecimens (blood components, tumor material, etc.) to support biomarker analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) DNA analyses (e.g., single nucleotide polymorphism analyses, whole exome sequencing, whole genome sequencing):

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. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Tumor DNA analyses:

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, and microsatellite instability). Key molecular changes of interest to immuno-oncology drug development are 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) is one of the major mechanisms of neo-antigen presentation in the context of a tumor. The increased presence of foreign-like peptides on the cell surface due to somatic mutations in the DNA of the tumor increases the chances that the tumor will be 'visible' to the adaptive immune system through the MHC-I antigen presentation mechanism.

There are a number of mechanisms by which a tumor can have increased mutational burden, such as defects in key genes related to DNA mismatch repair mechanisms or environmental induced factors such as smoking or UV light exposure. Additionally, a DNA tetrapeptide neo-antigen mutational signature can also be obtained by use of bioinformatic prediction tools of HLA-restricted mutated peptide binding to MHC class I and to the T-cell. There is a potential that in the hyper-mutated state, the presence of neo-antigen mutational patterns and the detection of increased T-cell clonality, both of which can be determined by use of next-generation sequencing methods, may correlate with response to pembrolizumab therapy and/or that the converse, the 'hypomutated' state (the absence of neo-antigens) may correlate with non-response. 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 (e.g., from germline blood DNA).

Tumor and blood RNA analyses:

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., interleukin-10). MicroRNA profiling may also be pursued.

Proteomics and Immunohistochemistry (IHC) using Blood or Tumor:

Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level, as assessed by IHC in tumor sections, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and a PD-L1 IHC diagnostic is marketed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., triple-negative breast cancer, head and neck, and gastric). Additional tumor- or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic profiling using a variety of platforms that could include but are not limited to immunoassay, and/or liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other Blood Derived Biomarkers

In addition to expression within the tumor tissue, tumor-derived proteins (e.g., PD-L1) or tumor-derived DNA can be shed from tumor and released into the blood. In the case of proteins, enzyme-linked immunosorbent assay can measure such proteins in serum and plasma and correlate this expression with response to pembrolizumab therapy, as well as levels of protein in the tumor. DNA can be analyzed using next generation sequencing or polymerase chain reaction-based technologies. Advantages to this method are that blood is a less invasive compartment from which tumor derived protein or nucleic acid biomarkers may be measured.

4.2.4.6 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details

of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to 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, experience with this drug approved in other indications, as well as with similar drugs in HCC suggests that study subjects may receive a clinical benefit (see Section 4.1.1).

The benefit-risk profile for pembrolizumab in HCC population is unknown since these subjects were not previously studied. The safety and efficacy data generated to date provide a favorable risk-benefit assessment for the continued use of pembrolizumab as a treatment for advanced/metastatic melanoma and NSCLC, and as an investigational medicinal product in subjects with triple negative breast cancer, squamous cell carcinoma of the head and neck, urothelial tract cancer, colorectal cancer, adenocarcinoma of the stomach/gastroesophageal junction, renal cell carcinoma, hematologic malignancies, multiple myeloma, and other advanced solid tumors. Based on pembrolizumab data from other indications and from data in HCC patients from other agents in the class, a favorable benefits-risk profile is anticipated. No unexpected risks have been reported in HCC with other immune check point inhibitors other than transient elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST).

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

Male and female subjects with advanced HCC after progression on sorafenib or intolerance of sorafenib with no curative option will be enrolled in this trial.

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 ≥18 years of age on day of signing informed consent.

3. Have a HCC diagnosis confirmed by radiology, histology, or cytology (fibrolamellar and mixed hepatocellular/cholangiocarcinoma subtypes are not eligible).

   Radiologic confirmation diagnosis is provided by the study site. Definition of radiological confirmation: Clinical findings consistent with the diagnosis of liver cirrhosis and a liver mass measuring at least 2 cm with characteristic vascularization (intense enhancement seen in the hepatic arterial-dominant phase and contrast washout in the late portal venous phase) seen in either triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI).

4. 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 12.8).
5. Have a Child-Pugh class A liver score within 7 days of first dose of study drug (see Section 12.7).
6. Have a predicted life expectancy of >3 months.
7. Have at least one measurable lesion based on RECIST 1.1 as confirmed by the blinded central imaging vendor.

   Note: the same image acquisition and processing parameters should be used throughout the study for a given subject.

8. Have a performance status of 0 or 1 using the ECOG Performance Scale within 7 days of first dose of study drug.
9. Have documented objective radiographic progression during or after treatment with sorafenib or intolerance to sorafenib.

   Sorafenib intolerance definition:

   Any Grade ≥2 drug-related AE which

   1) despite supportive therapy, recurred after sorafenib treatment interruption of at least 7 days and dose reduction, resulting in the subject requesting, or the physician recommending, discontinuation due to toxicity.

      OR

   2) required discontinuation of sorafenib due to toxicity, recommended by the physician with no rechallenge.

10. Subjects with chronic infection by HCV who are treated (successfully or treatment failure) or untreated are allowed on study. In addition, subjects with successful HCV treatment are allowed as long as there are ≥4 weeks between achieving sustained viral response (SVR_{12}) and start of study drug.

    Successful HCV treatment definition: SVR_{12}.

11. Has been treated with anti-Hepatitis B therapy.

    Controlled (treated) hepatitis B subjects will be allowed if they meet the following criteria:

    Antiviral therapy for HBV must be given for at least 12 weeks and HBV viral load must be less than 100 IU/mL prior to first dose of study drug. Subjects on active HBV therapy with viral loads under 100 IU/mL should stay on the same therapy throughout study treatment.

    Subjects who are anti-HBc (+), negative for HBsAg, and negative or positive for anti-HBs, and who have an HBV viral load under 100 IU/mL, do not require HBV anti-viral prophylaxis.

12. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication (Cycle 1, Day 1). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

13. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception for the course of the study, starting with the first dose of study medication through at least 120 days or longer based on local regulation after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

14. Male subject of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2 - Contraception, starting with the first dose of study medication (Cycle 1, Day 1) through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

15. Demonstrate adequate organ function as defined in Table 1.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1200/μL
Platelets	≥60,000/μL
Hemoglobin	≥8 g/dL without transfusion or EPO dependency within 7 days.
Renal	
Creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or creatinine clearance)	≤1.5×ULN **OR** ≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN *Note: Creatinine clearance should be calculated per institutional standard*
Hepatic	
Total bilirubin	≤2 mg/dL, or direct bilirubin ≤ULN for those with total bilirubin >2 mg/dL
AST (SGOT) and ALT (SGPT)	≤5×ULN
Albumin	≥3.0 g/dL *Note: No albumin supplement (or BCAA) allowed within the last 14 days.*
Coagulation	
International normalized ratio (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

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating, or has participated, in a study of an investigational agent and received study therapy, herbal/complementary oral or IV medicine, or used an investigation device within 4 weeks of the first dose of treatment. Subjects must also have recovered from associated therapy (i.e., to Grade ≤1 or baseline) and from AEs due to any prior therapy.
2. Has received sorafenib within 14 days of first dose of study medication.
3. 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.
4. Has clinically apparent ascites on physical examination.

   Note: ascites detectable on imaging studies only are allowed.
5. Portal vein invasion at the main portal (Vp4), inferior vena cava, or cardiac involvement of HCC based on imaging.

6. Has had clinically diagnosed hepatic encephalopathy in the last 6 months. Subjects on rifaximin or lactulose to control their hepatic encephalopathy are not allowed.
7. Had a solid organ or hematologic transplant.
8. Had prior systemic therapy for HCC in the advanced (incurable) setting other than sorafenib, prior to start study drug.
9. Has a known severe hypersensitivity (≥ Grade 3) to pembrolizumab, its active substance and/or any of its excipients. (Refer to the respective Investigator's Brochure for a list of excipients.)
10. Has active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

    Physiologic dose of corticosteroid definition: ≤10 mg/day prednisone or equivalent.
12. Has received locoregional therapy to liver (transcatheter chemoembolization [TACE], transcatheter embolization [TAE], hepatic arterial infusion [HAI], radiation, radioembolization, or ablation) within 4 weeks prior to the first dose of study drug.

    Subject is not eligible if aforementioned treatments were administered between last dose of sorafenib and first dose of study medication.
13. Has had major surgery to liver or other site within 4 weeks prior to the first dose of study drug.
14. Has had a minor surgery (i.e., simple excision, tooth extraction) ≤7 days prior to the first dose of study treatment (Cycle 1, Day 1).
15. Has not recovered adequately (i.e., Grade ≤1 or baseline) from the toxicity and/or complications from any intervention prior to starting therapy.
16. Has a diagnosed additional malignancy within 3 years prior to first dose of study treatment with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or curatively resected in situ cancers.
17. Has a known history of, or any evidence of, central nervous system (CNS) metastases and/or carcinomatous meningitis as assessed by local site investigator.
18. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
19. Has an active infection requiring systemic therapy.

20. 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.
21. Has a known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.
22. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the first dose of study medication through 120 days or longer based on local regulation after the last dose of trial treatment.
23. Has received prior immunotherapy including anti–PD-1, anti–PD-L1, or anti–PD-L2 agents, or if the subject has previously participated in Merck pembrolizumab clinical trials.
24. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
25. Has dual active HBV infection (HBsAg (+) and /or detectable HBV DNA) and HCV infection (anti-HCV Ab (+) and detectable HCV RNA) at study entry.
26. 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.

5.2 Trial Treatment(s)

Study medication to be used in this trial is outlined below in Table 2. Best supportive care (BSC) will vary with local treatment practices.

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Experimental
Placebo	0.90% w/v NaCl	Q3W	IV infusion	Day 1 of each 21-day cycle	

Note: Both treatment arms will also receive best supportive care.

Trial treatment should begin within 3 days of randomization. However, every effort should be made to begin trial treatment on the day of randomization.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor 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 the Sponsor.

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.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of the dose of pembrolizumab to be used in this trial is provided in Section 4.0, Background and Rationale. Details on preparation and administration of study drug are provided in the Pharmacy Manual.

Administration of BSC should follow local treatment guidelines.

5.2.1.2 Dose Interval Modification for Non-Hepatic Drug-Related Adverse Events

Adverse events 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 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial 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, or 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 non-hepatic irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Non-hepatic Immune-related AEs Associated with Pembrolizumab

Dose modification, diagnosis, and management guidance for hepatic events of clinical interest is provided in Section 5.2.1.3.

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.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**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		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	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 discontinue[1]		
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 discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent), followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AEs	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and are not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** 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).				

Dosing interruptions are permitted in the case of medical/surgical events or for logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. 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 (ECIs)

In addition to overdose, hepatic ECIs will include any of the following events. All of these events will require holding study treatment and notification of the Sponsor within 24 hours. A hepatology consultation may also be considered. Refer to Section 7.2.3.2 for reporting guidelines and the definition of hepatic ECIs.

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

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

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

Immediate assessment

All subjects

- All subjects should be considered for evaluation according to the directions below within 72 hours of the alert for a non-overdose ECI.
- Procedures:
  - Consider obtaining 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 gastrointestinal bleeding
  - Repeat ALT, AST, total bilirubin (Tbil), direct bilirubin (Dbil), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (GGT), INR, and complete blood count (CBC) with differential
  - Other laboratories or imaging studies as clinically indicated
  - Consider liver biopsy if indicated by hepatologist

Hepatitis C-Infected Subjects (including subjects who previously achieved SVR_{12})

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

Hepatitis B-infected Subjects

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

Permanent Discontinuation Criteria for Subjects with Non-overdose Hepatic ECI

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

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

Diagnosis and Management of Non-Overdose Hepatic ECIs

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. Immune-related hepatitis has been observed in ~1% of subjects who received pembrolizumab. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC subjects in this study.

a. Hepatitis B Flare

Hepatitis B flares are characterized by rapid elevations of ALT and AST to >5×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 3-5 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.
- For subjects who have detectable HBV DNA, re-institute anti-viral therapy.
- If the subject is clinically stable, study treatment dosing may be interrupted for up to 12 weeks. Subjects should undergo weekly laboratory tests including: AST, ALT, ALP, Tbil, Dbil, INR, HBsAg, HBV DNA (if detected at the onset of the flare). Obtain anti-HBe, anti-HBs, and HBV DNA levels (if not detected at the onset of the flare) every 2-3 weeks.
- If ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and subjects are clinically stable, subjects may restart study treatment. If these conditions are not met, then study treatment should be permanently discontinued.

b. Hepatitis C Recurrence or Flare

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

Among subjects with uncontrolled hepatitis C, virologic flares are possible. Hepatitis C flares are characterized by rapid elevations of ALT and AST to >5×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 3-5 weeks.

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

i. Recurrent HCV infection:

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

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

ii. HCV Flare:

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

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

c. Immune-related hepatitis

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

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

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

ii. Management

- Interrupt study treatment and alert the Sponsor as per ECI criteria above for ALT, AST, bilirubin, and hepatic decompensation.
- Start IV corticosteroid (methylprednisolone 125 mg or equivalent) followed by oral corticosteroid.
- 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. Study treatment may be restarted after steroid treatment has been tapered to prednisone ≤10 mg/day (or equivalent dose of another agent). Treatment and laboratory results must be reported on a case report form (CRF).
- If laboratory abnormalities do not resolve within 3 weeks, or steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks, or subjects show evidence of decompensation to CP C status or have esophageal or variceal bleeding at any point, treatment must be permanently discontinued. This must be reported on a CRF.

d. Other Hepatic Events of Clinical Interest

- Infection needs to be ruled out with cultures of blood, urine, and ascites (if possible), as well as chest X-ray and abdominal imaging if relevant. If an infection is found, antibiotics should be started.
- If Tbil is elevated above baseline, imaging 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 study treatment if they are clinically stable after appropriate therapy or discontinue the causative agent, as long as laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade within 3 weeks.
- Treatment must be permanently discontinued if the subject is off study treatment for infection, obstruction, or drug/alcohol-related toxicity for more than 3 weeks, or if they have esophageal bleeding, or become CP C at any point.

5.2.2 Timing of Dose Administration

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

For all additional cycles of study treatment, treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment.

All study treatments will begin on Day 1 of each cycle after all pre-dose study procedures and assessments have been completed as detailed on the Trial Flow Chart –Section 6.0

Study treatment will be administered as a 30 minute IV infusion every 3 weeks. 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 min and +10 min is permitted (i.e., infusion time is 30 minutes: –5 min/+10 min).

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

All trial treatments will be administered on an outpatient basis.

5.2.3 Trial Blinding

A double-blinding technique with in-house blinding will be used. Pembrolizumab and placebo will be packaged identically by the site pharmacy so that the blind is maintained. The subject, the investigator and Sponsor personnel or delegate(s) who are involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.5.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted**.**

5.3 Randomization

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 2:1 ratio to pembrolizumab and placebo, respectively.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Geographic region (Asia without Japan, Non-Asia with Japan)
2. Macrovascular invasion (Yes, No)
3. α-Fetoprotein (ng/mL) (<200, ≥200)

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination 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, the Sponsor and the subject.

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), and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date should be included on the CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and is NOT administered for tumor control. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded on the CRF.

All medications received within 30 days before the first dose of trial treatment and within 30 days after the last dose of trial treatment should be recorded. Medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 7.2.3.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-CR relapse) 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 for tumor control.
    - Note: Radiation for pain or palliation is acceptable (see Section 5.5.1).
- 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, chickenpox, yellow fever, rabies, bacille Calmette-Guerin (BCG) vaccine, and typhoid (oral) vaccine. The killed virus vaccines used as seasonal influenza vaccines for injection are allowed; however live attenuated intranasal influenza vaccines (e.g., FluMist®) are not allowed.
- Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/chronic obstructive pulmonary disease are permitted) for any purpose other than to modulate symptoms from an adverse event suspected of having an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., IV contrast dye) is permitted.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be discontinued from study treatment. 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 should be avoided 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/Alternative Medicines

- No herbal supplements or alternative medicines are allowed during the Screening and Treatment Phase of this trial.

The exclusion criteria describe other medications that are prohibited in this trial.

There are no prohibited therapies during the post-treatment follow-up phase.

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 adverse events with potential immunologic etiology are outlined in Table 3. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary, as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to study treatment.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance. Refer to Section 5.2.1 for dose modification.

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

Guidance for the diagnosis and management of hepatic events of clinical interest is in Section 5.2.1.3.

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

Table 4 shows treatment guidelines for subjects who experience an infusion reaction associated with study drug administration.

Table 4 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5 h (±30 minutes) prior to infusion of study treatment with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing

Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

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

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

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug, starting with the first dose of study medication through at least 120 days or longer based on local regulation, after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) starting with the first dose of study medication (or 14 days prior to the initiation of study medication for oral contraception) through at least 120 days or longer based on local regulation, after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

For countries or sites that follow the Clinical Trial Facilitation Group guidance, please use the following:

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if these therapies have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the Clinical Trial Facilitation Group (CTFG) Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle-stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient), or 3) not heterosexually active for the duration of the study. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- IUD
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- Sexual abstinence

Subjects should be using birth control starting with the first dose of study medication through at least 120 days or longer based on local regulation after the last dose of study medication.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.2.2 – Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on study treatment, the subject will immediately be removed from the study 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 the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.2 (Reporting of Pregnancy and Lactation to the Sponsor).

5.7.4 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 breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond 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 treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.6.3 – Post-Treatment Visits.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.5 – Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject is lost to follow-up.
- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Unacceptable adverse events as described in Section 7.2.

- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the subject at unnecessary risk from continued administration of study drug
- Completed 35 treatments with study drug

  Note: 35 treatments (approx. 2 years) are calculated from the first dose. Subjects who stop study treatment after receiving 35 treatments may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.6. Subjects may be retreated in the Second Course Phase with up to 17 (approx. 1 year) additional trial treatments.
- Confirmed radiographic disease progression outlined in Section 7.1.4 (exception if the Sponsor approves treatment continuation).
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Recurrent Grade 2 pneumonitis

5.8.1.1 Discontinuation from Study Therapy after Complete Response

Discontinuation of treatment may be considered for subjects who have attained a centrally confirmed CR that have received at least 8 study treatments (approximately 6 months) and had at least 2 treatments beyond the date when the initial CR was declared. Subjects who stop treatment then experience radiographic PD may be eligible for up to 17 additional treatments (approximately 1 year) with the initial study treatment in the Second Course Phase at the discretion of the investigator if:

- No cancer treatment was administered since the last dose of study drug
- The subject meets the parameters listed in the Inclusion/Exclusion criteria
- The trial is ongoing

Subjects will resume therapy at the same treatment and schedule as at the time of initial discontinuation. Additional details are provided in Section 7.1.6.2. Response or progression in this Second Course Phase will not count towards the primary endpoint in this trial.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive trial treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the trial site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 5.8 – Subject Withdrawal/Discontinuation.

5.8.3 Lost to Follow Up

If a subject fails to return to the clinic for a required trial visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (eg, phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject. The missing data for the subject will be managed via the pre-specified statistical data handling and analysis guidelines.

5.9 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. 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).

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1) Quality or quantity of data recording is inaccurate or incomplete
2) Poor adherence to protocol and regulatory requirements
3) Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4) Plans to modify or discontinue the development of the study drug.

In the event of Sponsor decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Initial Treatment with Study Drug

Trial Period:	**Screening Phase**	**Treatment Cycles (3-Week Cycles)**								**End of Treat-ment**	**Post-Treatment**		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[a]**
										At Time of Discon	**30 Days Post Last Dose**	**Every 12 Weeks Post Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
Administrative Procedures													
Informed consent	X												
Informed consent for future biomedical research (optional)	X												
Inclusion/exclusion criteria	X												
Subject identification card	X												
Demographics and medical history (including smoking and alcohol use)	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
Survival status[a]		<----------										---------->	X
Clinical Procedures/Assessments													
Review adverse events [c]	X	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination	X									X	X		

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treat-ment	Post-Treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[a]**
										At Time of Discon	**30 Days Post Last Dose**	**Every 12 Weeks Post Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
Directed physical examination		X	X	X	X	X	X	X	X				
Child-Pugh Score [d]	X [e]												
Height, weight, and vital signs (T, P, RR, BP) [f]	X	X	X	X	X	X	X	X	X	X			
12-Lead electrocardiogram	X												
Upper endoscopy	X [g]												
ECOG performance status	X [e]	X	X	X	X	X	X	X	X	X			
EQ-5D, EORTC QLQ-C30, EORTC QLQ-HCC18 [h]		X	X	X	X	X		X	X[g]	X	X		
Pembrolizumab/placebo administration		X [b]	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments													
Pregnancy test [i]	X	X [j]	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT[y]	X [e,y]		X	X	X	X	X	X	X	X	X		
CBC with differential [k]	X [e]		X	X	X	X	X	X	X	X	X		
Chemistry panel and liver panel [k]	X [e]		X	X	X	X	X	X	X	X	X		
Urinalysis [l]	X [e]		X		X		X		X	X			
T3, FT4, and TSH [l, m]	X [e]		X		X		X		X	X	X		
AFP [m, n]	X		X	X	X	X	X	X	X	X	X		

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treat-ment	Post-Treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[a]**
										At Time of Discon	**30 Days Post Last Dose**	**Every 12 Weeks Post Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
C-Reactive protein [m, o]		X	X			X				X			
CENTRAL Laboratory Assessments													
Pembrolizumab pharmacokinetics [r, s]		X	X		X		X		X		X		
Pembrolizumab anti-drug antibodies [r]		X	X		X		X		X		X		
Anti-HCV	X												
If Anti-HCV positive:													
• HCV genotype [p]	X												
• HCV viral load [q]	X	X	X	X	X	X	X	X	X		X		
Anti-HBc (total and IgM), anti-HBs, HBV viral load, HBsAg	X												
If (1) HBsAg+ or (2) anti-HBc+, anti-HBs-, HBsAg- and viral load <100 IU/mL:													
• Anti-HDV [p]	X												
• Anti-HBe and HBeAg	X												
• HBsAg, and HBV viral load [q]		X	X	X	X	X	X	X	X		X		

Trial Period:	**Screening Phase**	**Treatment Cycles (3-Week Cycles)**								**End of Treat-ment**	**Post-Treatment**		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[a]**
										At Time of Discon	**30 Days Post Last Dose**	**Every 12 Weeks Post Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7
• Anti-HBc (total), anti-HBe, anti-HBs, and HBeAg [q]						X			X		X		
Blood for genetic analyses [t]		X											
Blood for biomarker studies (serum and plasma) [o]		X	X			X				X			
Blood for ctDNA (plasma) [o]		X											
Blood for RNA Analysis [o]		X	X			X				X			
Tumor tissue for biomarker analysis [u]	X												
Efficacy Measurements													
Tumor imaging	X [v]	← X [w] →								X [x]		X	

a. In subjects who experience PD or start a new anti-cancer therapy, contact should be made (by telephone or visit) approximately every 12 weeks to assess for survival status. 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 who have a death event previously recorded).
b. Cycle 1 treatment must be given within 3 days of randomization. The window for each visit is ±3 days unless otherwise noted.
c. 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. All protocol specific hepatic ECIs will be collected throughout the study as listed in Section 7.2.3.2. If any of the hepatic ECI criteria are met, collect the Child-Pugh score until the hepatic ECIs resolve.
d. If any of the hepatic ECI criteria are met, document the Child Pugh score with each visit until the hepatic ECIs resolve.
e. ECOG Performance Status, Child-Pugh Score, and laboratory tests for screening and determining eligibility are to be performed within 7 days prior to the first dose of trial treatment except hepatitis and thyroid tests, which may be performed within 28 days.
f. Height will be measured at Visit 1 only.
g. Upper endoscopy to be performed at any time within 12 months before the first dose of study drug.
h. See Section 4.2.4.3 for details regarding administration of Patient Reported Outcomes (PROs). All PROs are to be performed at Cycle 1, Cycle 2, Cycle 3, Cycle 4,

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treat-ment	Post-Treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[a]**
										At Time of Discon	**30 Days Post Last Dose**	**Every 12 Weeks Post Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7

Cycle 5 and Cycle 7. After Cycle 7 (Week 18), PROs are to be performed every 9 weeks (e.g., Week 27, Week 36, Week 45). PROs are to be performed up to a year or End of Treatment, whichever comes first, at treatment discontinuation, and at the 30-day post-treatment discontinuation follow-up visit. A visit window of ±7 days will apply to PRO visit assessment. See Section 7.1.2.7 for timing and order of PROs at each visit.

i. 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. 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 result. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.

j. Not necessary if screening evaluation performed within 72 hours.

k. CBC with differential, chemistry panel, and liver panel to be performed every cycle. Liver panel to include albumin, ALT, AST, total bilirubin, alkaline phosphatase, direct bilirubin, GGT, and total protein.

l. While on treatment, UA and thyroid function tests will be performed every other cycle.

m. At Cycle 1, subjects may be dosed even if CRP evaluation is not available prior to dosing. After Cycle 1, subject will be dosed even if AFP, thyroid, and CRP evaluations are not available prior to dosing; however, the results must be available and reviewed before the next scheduled visit.

n. AFP will be measured every 3 weeks (21±7 days) calculated from the date of randomization, or earlier if clinically indicated.

o. Whole blood samples for serum, plasma, and RNA should be collected pre-dose at Cycle 1, Cycle 2, Cycle 5, and again at discontinuation or progression of disease. Plasma for ctDNA should be collected pre-dose at Cycle 1. These samples can be taken up to 72 hours prior to dosing.

p. Subject may be randomized if results are pending and the subject meets all other eligibility criteria.

q. At screening, subjects must have results within 28 days of first dose; at each subsequent visit, the values must be evaluated before the next visit (3 weeks later). HBsAg, HBV viral load, and HCV viral load are to be performed every 3 weeks during treatment, or earlier if clinically indicated. Anti-HBc (total), anti-HBe, anti-HBs, and HBeAg are to be performed every 12 weeks during treatment, or earlier if clinically indicated. Additional tests to be performed for ECIs are described in Section 5.2.1.3. If the viral load results are not reported in IU/mL, the site should provide the conversion factor specific for the assay method used to convert the assay units of measure to IU/mL. For HBsAg, quantitative and/or qualitative results are submitted.

r. Both PK and anti-pembrolizumab antibody samples: pre-dose (trough) PK and anti-pembrolizumab antibody samples will be collected within 24 hours before infusion at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy).

s. PK Samples: additional post-dose (peak) PK samples will be drawn within 30 minutes after end of study treatment infusion at Cycles 1 and 8. Additional PK samples should be drawn at 24 hours (Day 2), between 72 and 168 hours (Days 4–8), and 336 hours (Day 15) after Cycle 1 dosing.

t. Details for collection of blood for genetic testing can be found in Section 7.1.3.6 Planned Genetic Analysis Sample Collection.

u. Tissue is not required for enrollment, but is strongly encouraged to be submitted if available. Newly obtained tissue is preferred (after sorafenib treatment); formalin-fixed, paraffin-embedded block specimens are preferred to slides. Leftover tumor tissue will be stored for future biomedical research if the subject signs the FBR consent.

v. Screening tumor imaging will be performed within 21 days prior to randomization. Confirmation of baseline measurable disease per RECIST 1.1 by the central imaging vendor is required prior to subject randomization. Imaging at screening should include the chest, abdomen, and pelvis, as detailed in the Site Imaging Manual.

w. The first on-study imaging time point will be performed at 6 weeks calculated from the date of randomization and will continue to be performed Q6W (42±7 days), or

Trial Period:	Screening Phase	Treatment Cycles (3-Week Cycles)								End of Treat-ment	Post-Treatment		
Treatment Cycle/Title:	**Screening**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**≥8**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up[a]**
										At Time of Discon	**30 Days Post Last Dose**	**Every 12 Weeks Post Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]	-28 to -1		±3	±3	±3	±3	±3	±3	±3	±3	±7	±7	±7

earlier if clinically indicated. Imaging details can be found in the Site Imaging Manual.

x. In subjects who discontinue study therapy without confirmed PD by the site per irRECIST, tumor imaging should be performed at the time of treatment discontinuation. If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.

y. Activated partial prothrombin time is to be assessed at screening only.

6.2 Second Course Treatment

Trial Period:	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 and Beyond**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up [a]**
									At Time of Discon	**30 Days Post-Discon**	**Every 12 Weeks Post-Discon**	**Approx. Every 12 Weeks**
Scheduling Window (Days) [b]		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures												
Eligibility criteria	X											
Concomitant medication review	X	X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments												
Review adverse events [c]	X	X	X	X	X	X	X	X	X	X	X	
Full physical examination	X								X			
Directed physical examination		X	X	X	X	X	X	X				
Child-Pugh Score [d]	X [e]											
Weight, and vital signs (T, P, RR, BP)	X	X	X	X	X	X	X	X	X			
ECOG performance status [e]	X	X	X	X	X	X	X	X	X			
Post-study anticancer therapy status										X	X	X
Survival status[a]	<----------										---------->	X
Trial Treatment Administration												
Pembrolizumab/placebo administration	X	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments												
Pregnancy test [f]	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT[m]	X [e,m]	X	X	X	X	X	X	X	X	X		
CBC with differential [g]	X [e]	X	X	X	X	X	X	X	X	X		
Chemistry and liver panels [g]	X [e]	X	X	X	X	X	X	X	X	X		
Urinalysis [g]	X [e]		X		X		X	X	X			
T3, FT4, and TSH [g, h]	X [e]		X		X		X	X	X	X		
AFP [h]	X [e]	X	X	X	X	X	X	X		X		

Trial Period:	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 and Beyond**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up [a]**
									At Time of Discon	**30 Days Post-Discon**	**Every 12 Weeks Post-Discon**	**Approx. Every 12 Weeks**
CENTRAL Laboratory Assessments												
Anti-HCV [i]	X											
If Anti-HCV positive:												
• HCV viral load [j]	X	X	X	X	X	X	X	X		X		
• HCV genotype	X											
If (1) HBsAg+ or (2) anti-HBc+, anti-HBs-, HBsAg- and viral load <100 IU/mL:												
• HBsAg and HBV viral load [j]	X	X	X	X	X	X	X	X		X		
• Anti-HBc (total), anti-HBe, anti-HBs, and HBeAg [j]					X			X		X		
Efficacy Measurements												
Tumor imaging	X [k]	X [k] ⟷							X [l]		X	

a. In subjects that experience site assessed PD or starts a new anti-cancer therapy contact should be made (by telephone or visit) approximately every 12 weeks to assess for survival status. 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 who have a death event previously recorded).
b. In general, the window for each visit is ±3 days unless otherwise noted.
c. 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. All protocol specified hepatic ECIs will be collected throughout the study as listed in Section 7.2.3.2. If any of the hepatic ECI criteria are met, collect the Child Pugh score with each visit until the hepatic ECIs resolve.
d. If any of the hepatic ECI criteria are met, collect the Child Pugh score until the hepatic ECIs resolve.
e. Laboratory and ECOG tests for determining eligibility are to be performed within 7 days prior to the first retreatment dose of study drug.
f. 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 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 result. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
g. After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. CBC, chemistry, and liver panel to be performed every cycle. Liver panel to include albumin, ALT, AST, total bilirubin, alkaline phosphatase, GGT, direct bilirubin, and total protein.
h. After Cycle 1, subject will be dosed even if AFP and thyroid evaluations are not available prior to dosing; however the results must be available and reviewed before the next scheduled visit.
i. If anti-HCV was negative prior to retreatment in the Second Course Phase, anti-HCV must be performed.
j. At each visit, the values must be evaluated before the next visit (3 weeks later). HBsAg, HBV viral load, and HCV viral load are to be performed every 3 weeks during

Trial Period:	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 and Beyond**	**Discon**	**Safety Follow-up**	**Follow-up Visits**	**Survival Follow-up [a]**
									At Time of Discon	**30 Days Post-Discon**	**Every 12 Weeks Post-Discon**	**Approx. Every 12 Weeks**

treatment, or earlier if clinically indicated. Anti-HBc (total), anti-HBe, and anti-HBs, and HBeAg are to be performed every 12 weeks during treatment, or earlier if clinically indicated. Additional tests to be performed for ECIs are described in Section 5.2.1.3. If the viral load results are not reported in IU/mL, the site should provide the conversion factor specific for the assay method used to convert the assay units of measure to IU/mL. For HBsAg, quantitative and/or qualitative results can be submitted.

k. Tumor imaging should be performed within 21 days prior to starting or restarting study treatment and continue to be performed every 6 weeks (42±7 days) calculated from the first dose of retreatment, or more frequently if clinically indicated.

l. Tumor imaging should be performed at the time of treatment discontinuation. If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not mandatory.

m. Activated partial prothrombin time is to be assessed at screening only.

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 the investigator and or the Sponsor 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 Future Biomedical Research. 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 informed consent form, any subsequent revised written informed consent form 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 Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research 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

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include smoking and alcohol use, all active conditions, and any condition diagnosed within the prior 10 years that is considered to be clinically significant by the investigator. Disease details regarding the subject's HCC 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. Any autoimmune disorders, regardless of onset date, should be recorded.

7.1.1.5 Disease Details

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

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 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 30 days of the first dose of trial medication, including alternative/complementary medications. Prior anti-cancer treatment for HCC will be recorded separately and not listed

as a prior medication. In addition, for all subjects with a history of hepatitis B or hepatitis C, information on past and /or present anti-viral treatment will be collected.

7.1.1.6.1.1 Prior Treatment Details for HCC

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

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial from the time of signing the informed consent form until the Safety Follow-up Visit. In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up Visit should be recorded.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.7 Subsequent Anti-Cancer Status

The investigator or qualified designee will review all new anti-cancer 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. Details regarding survival status follow-up are outlined in 7.1.6.3.3 – Survival Follow Up.

7.1.1.8 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.

7.1.1.9 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

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

Interruptions from the protocol-specified treatment plan for greater than 12 weeks between doses for non–drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

The total volume of study treatment infused will be compared to the total volume prepared to determine compliance with each dose administered. The instructions for preparing and administering study treatment are provided in the Pharmacy Manual.

Administration of trial treatment will be witnessed by the investigator and/or trial staff or qualified designee per institutional guidelines and procedures.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event 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 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 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with study treatment exposure should be evaluated to determine if it is possibly an event of a potentially immunologic etiology; see Section 5.6.2.

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams should be performed as specified in the Trial Flow Chart - Section 6.0. Assessment for possible ascites and hepatic encephalopathy should be noted on every examination. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart - Section 6.0, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. Assessment for possible ascites and hepatic encephalopathy should be noted on every examination. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Height, Weight, and Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in the Trial Flow Chart - Section 6.0 - Height will be measured at Visit 1 only.

Vital signs should include temperature, pulse, respiratory rate, blood pressure, height, and weight.

7.1.2.4 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed one time during screening using local standard procedures. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.2.5 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess ECOG Performance Status (see Section 12.5) at Screening, prior to dosing on Day 1 of each treatment cycle, and at discontinuation of trial treatment as specified in the Trial Flow Chart – Section 6.0.

7.1.2.6 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. The score considers 5 factors, 3 of which assess the synthetic function of the liver (i.e., Tbil level, serum albumin, and coagulation parameters [INR or PT]) and 2 of which are based on clinical assessment (i.e., degree of ascites and degree of hepatic encephalopathy).

7.1.2.7 Patient Reported Outcomes (PROs)

It is strongly recommended that PROs are administered prior to drug administration, adverse event evaluation, and disease status notification starting with the EQ-5D, followed by EORTC QLQ-C30 and EORTC QLQ-HCC18; an exception to this recommendation may occur at the treatment discontinuation visit where patients may have already been notified of their disease status or an AE evaluation is known prior to them arriving to the clinic. All PROs are to be performed as specified in the Trial Flow Chart – Section 6. If the subject does not complete the PROs, the MISS_MODE form must be completed to capture the reason the assessment was not performed. A visit window of ±7 days will apply to PRO visit assessments.

If, at the time of first dose of study treatment, the translated version of the HCC18—one of the PRO measures—is not available for that language/country, and it cannot be completed by the subject at Cycle 1, Day 1, then the HCC18 will not be required for this subject at any point of the study. The other study PRO measures must be completed as scheduled. Note: for some sites, the translated HCC18 might become available after study startup and should be administered to subjects at their time of first dose of study treatment; for some sites the HCC18 translation might not be available for the entire duration of the study.

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 Laboratory Procedures Manual. Refer to the Trial Flow Chart - Section 6 for the schedule 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 5.

Table 5 Laboratory Tests

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

a Perform on women of childbearing potential 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. Activated partial thromboplastin time is to be assessed at screening only.

c. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.

d. T3 is preferred; if not available free T3 may be tested.

e. If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Laboratory Procedure Manual.

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

g. All hepatitis tests (including HBsAg) will be done centrally.

Laboratory tests for screening should be performed within 7 days prior to the first dose of study treatment. An exception is hepatitis, AFP, and thyroid test, which may be performed within 28 days prior to first dose. Subjects eligible for study retreatment should have imaging performed within 21 days and laboratory tests performed within 7 days prior to the first dose of study treatment in the Second Course Phase. After Cycle 1, in both the Initial Treatment Phase and the Second Course Phase, pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

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, unless otherwise specified in the flow chart. 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.

7.1.3.2 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.

7.1.3.3 Central Laboratory Assessments

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

7.1.3.4 Pharmacokinetic (PK) /Pharmacodynamic Evaluations

To evaluate the immunogenicity of and exposure to pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in Section 6.1 . Blood samples collected for PK and ADA may be stored. Analysis will be performed only if required. If ongoing PK and/or ADA sampling is deemed unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.4.1 Blood Collection for PK

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. PK samples should be drawn according to the PK collection schedule for all subjects. Every effort should be taken to collect samples at 30 days after end of study treatment.

7.1.3.4.2 Blood Collection for Anti-pembrolizumab Antibodies

Sample collection, storage and shipment instructions for serum samples will be provided in the procedure manual. Anti- pembrolizumab antibody samples should be drawn according to the ADA collection schedule for all subjects (Section 6.1). Every effort should be taken to collect samples at 30 days after end of study treatment for ADA. Simultaneous PK sampling is required for interpretation of ADA analysis.

7.1.3.5 Blood Samples for RNA Analysis, and Biomarker Studies

Information about sample collection, storage and shipment for blood, plasma, and serum is provided in the Laboratory Procedure Manual. Any leftover samples from the RNA analysis and biomarker studies will be stored for future biomedical research if the subject signs the FBR consent.

7.1.3.6 Tumor Tissue

Supplying tumor tissue for biomarker analysis is strongly encouraged but is not required for study enrollment. Biopsies should not be performed for the sole purpose of biomarker analysis for this protocol. Newly obtained tissue is preferred (after sorafenib treatment) to an older archival sample if available. Formalin-fixed, paraffin-embedded (FFPE) block specimens are preferred to slides. If only slides can be sent, they should be sent within 7 days of cutting from the block. If the subject signs the FBR consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

7.1.3.7 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Laboratory Procedures Manual. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. 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 analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

7.1.3.8 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of Future Biomedical Research:

- DNA for future research.
- Leftover tumor for future research
- Leftover RNA
- Leftover plasma and serum from biomarker studies

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the blinded central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging in the brain. However, when MRI is the standard of care at a site, MRI may be used whether or not CT is contraindicated. 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 the blinded central imaging vendor at screening will be used to determine subject eligibility. Confirmation of measurable disease by the central imaging vendor per RECIST 1.1 is required prior to subject randomization. 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 for all study subjects from the sites will be submitted to the central imaging vendor. In addition, additional imaging (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 submitted to the central imaging vendor as well.

After the local site investigator-assessed first radiologic evidence of PD, the central imaging vendor will verify PD during the study. Expedited verification of radiologic PD by the central imaging vendor will be communicated to the study site and sponsor.

7.1.4.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 21 days prior to the date of randomization. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. Prior to randomization, the screening images must be submitted to the blinded central imaging vendor for review 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 21 days prior to the date of randomization, and can be assessed by the central imaging vendor.

7.1.4.1.2 Tumor Imaging During the Trial

The first on-study imaging assessment should be performed at 6 weeks (42±7 days) from the date of randomization. Subsequent tumor imaging should be performed Q6W (42±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 is verified by the blinded central imaging vendor (unless site principal investigator [PI] elects to continue treatment and follow irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor,

whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1 partial response (PR) and CR should be confirmed by a repeat tumor imaging assessment ≥4 weeks from the date the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (i.e., 6 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 6 weeks, 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 irRECIST (Section 7.1.4.1.7), disease progression on subjects treated with trial treatment should be confirmed by the site at least 4 weeks after central verification of 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 7.1.4.1.7. 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 if clinically stable. Subjects who have confirmed disease progression as assessed by the site will discontinue the treatment. Exceptions are detailed in Section 7.1.4.1.7.

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. 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 12 weeks (84±7 days) to monitor disease status until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

7.1.4.1.4 Second Course (Retreatment) Tumor Imaging

A scan must be performed within 21 days prior to restarting study treatment. Local reading (investigator assessment with site radiology reading) will be used to determine eligibility. Imaging should be submitted to the blinded central imaging vendor for retrospective review.

The first on-study imaging assessment should be performed 6 weeks (42±7 days) after the restart of treatment. Subsequent tumor imaging should be performed every 6 weeks (42±7 days) or more frequently if clinically indicated.

Per irRECIST 1.1 (Section 7.1.4.1.7), if tumor imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtained a

confirmation scan do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating progressive disease in clinically stable subjects.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation. 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 radiologic imaging every 12 weeks (84±7 days) until the start of new anti-cancer treatment, disease progression, death, or the end of the study, whichever occurs first.

7.1.4.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the blinded central imaging vendor 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 (e.g., discontinuation of study therapy). Initial tumor imaging showing site-assessed PD should be submitted to the central imaging vendor immediately. The site will be notified if the central imaging vendor verifies PD using RECIST 1.1. Figure 2 illustrates the imaging flow involving verification of PD for clinically stable subjects.

7.1.4.1.6 Modified RECIST (mRECIST) Assessment of Disease

Modified RECIST for HCC allows evaluation of treatment effects that are not reflected in simple total size changes of lesions. RECIST 1.1 by the blinded central imaging vendor will still be the primary measure of the tumor response. Details are fully described in [46]. Extrahepatic lesion assessment, as well as response categories and definitions, are identical to RECIST 1.1. Key differences from RECIST 1.1 include:

- Lesions within the liver parenchyma are measured so as to include only the portion showing increased contrast enhancement in the arterial phase.
- New lesions in the liver must meet one of the following conditions to be considered indicators of progression:
    - At least 10 mm in longest diameter, and showing typical HCC enhancement (enhancement during the arterial phase and washout during the portal venous phase)
    - At least 10 mm in longest diameter with atypical enhancement, but showing at least 10 mm of growth on a subsequent scan

- Porta hepatis lymph nodes should never be selected as target lesions, and should only be followed as non-target lesions if their short axis measurement at screening is ≥20 mm.

7.1.4.1.7 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by the blinded central imaging vendor review will be evaluated retrospectively.

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment. 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. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In subjects who have shown initial evidence of radiological PD by RECIST 1.1 as verified by the central imaging vendor, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (using irRECIST for subject management, see Table 6 and Figure 2).

This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥4 weeks later to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values,
2) No decline in ECOG performance status,
3) Absence of rapid progression of disease, and
4) Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Any subject deemed clinically unstable should be discontinued from trial treatment at central verification of site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Target lesion sum of diameters is <20% or <5 mm absolute increase compared to nadir,
- Non-target disease resulting in initial PD is qualitatively stable or improved,
- New lesion resulting in initial PD is qualitatively stable or improved,
- No incremental new lesion(s) since last evaluation, and
- No incremental new non-target lesion progression since last evaluation.

If repeat imaging does not confirm PD by irRECIST as assessed by the local site investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Target lesion sum of diameters remains ≥20% and at least 5 mm absolute increase compared to nadir,
- Non-target disease resulting in initial PD is qualitatively worse,
- New lesion resulting in initial PD is qualitatively worse,
- Additional new lesion(s) since last evaluation,
- Additional new non-target lesion progression since last evaluation.

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy.

NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease [first PD also verified by the central imaging vendor]) per irRECIST, but the subject is achieving a clinically meaningful benefit and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Sections 6.1 and 6.2; consultation with the Sponsor is also necessary after each subsequent site assessment of irPD for treatment to be continued. All images must be submitted to the blinded central imaging vendor.

Additional details about irRECIST are referenced in the Merck Tip Sheet for RECIST 1.1 and irRECIST.

Table 6 Imaging and Treatment after First Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 which has been verified by the blinded central imaging vendor	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site 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 image should occur according to the regular imaging schedule outlined in the protocol

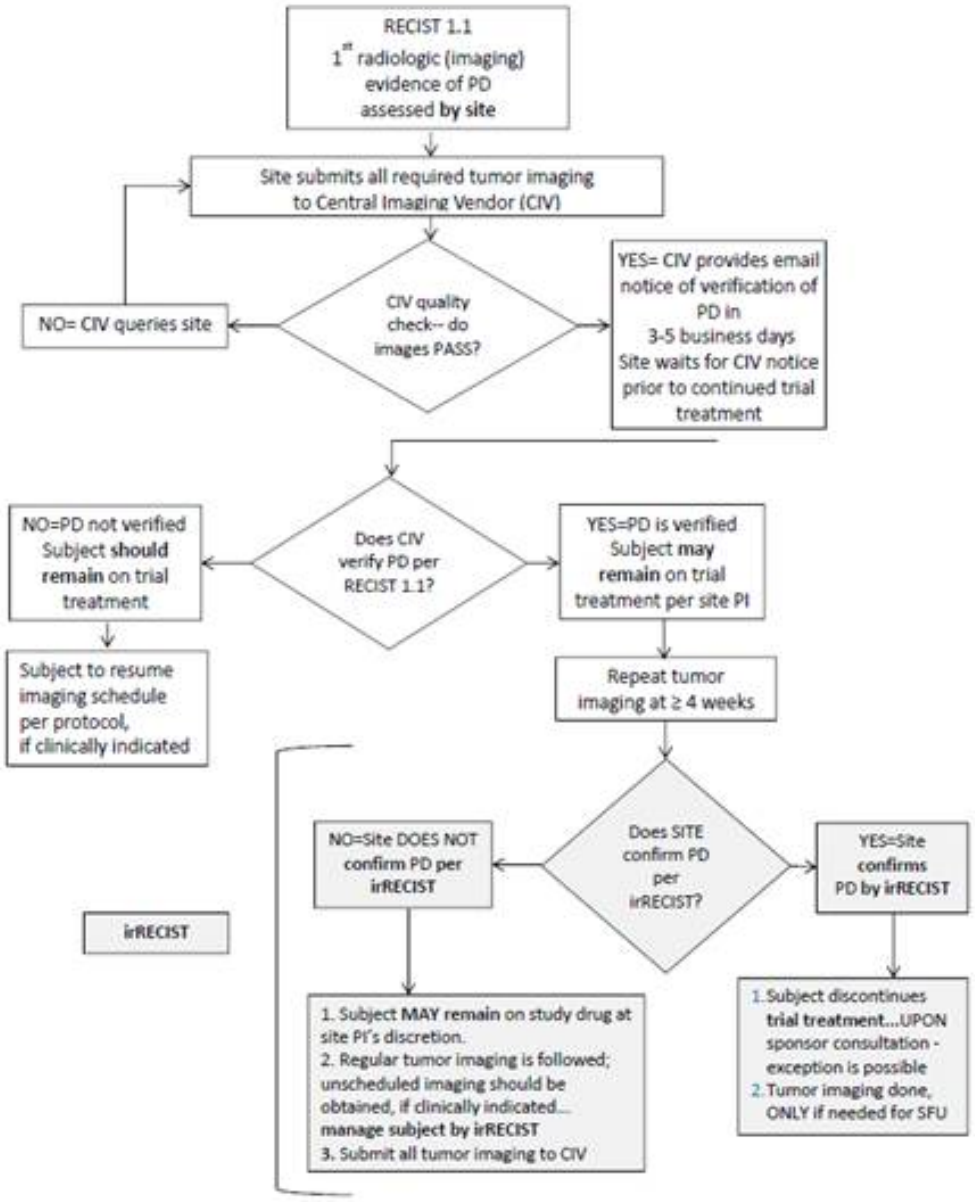


Figure 2 Imaging and Treatment for Clinically Stable Subjects after First Radiologic Evidence of Progressive Disease Assessed by Site

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment visit should be performed at the time of discontinuation. Any adverse events 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. Subjects who attain a CR or complete 35 trial treatments (approximately 2 years) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.6.2. After discontinuing treatment following assessment of a CR or the 35 trial treatments, subjects should return to the site for a Safety Follow-up visit (Section 7.1.6.3.1) and then proceed to the Follow-up Period of the study (Section 7.1.6.3.2).

7.1.5.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.1.5.2 Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE SUBJECT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND THE SUBJECT UNLESS NECESSARY.

For emergency situations where the investigator or delegate needs to identify the drug used by a subject and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant’s treatment assignment, the investigator or delegate should make reasonable attempts to enter the intensity/toxicity grade of the AEs observed, the relation to study drug, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call

center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

Study treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

Adverse event information should be entered in the participant's chart, if possible, before the investigator or delegate contacts the emergency unblinding call center to request unblinding of a participant's treatment assignment. Unblinding should not be delayed if this information cannot be recorded in the chart before unblinding takes place.

At the end of the trial, unblinding logs are to be returned to the Sponsor or designee.

7.1.5.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or 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.

See protocol-specified guidance in the Trial Administrative Binder, Procedures Manual, and Site Imaging Manual.

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

Approximately 28 days prior to treatment, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated.

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.

Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Laboratory tests and ECOG performance status (PS) are to be performed within 7 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.
- 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.

7.1.6.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided above in Trial Procedures (Section 7.0).

Subjects who stop study drug with SD or better may be eligible for up to 17 additional trial treatments (approximately 1 year) if they progress after stopping study treatments. Retreatment with study drug is termed the Second Course Phase and is only available if the trial remains open and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with study treatment after attaining an investigator-determined CR according to RECIST 1.1
        - Was treated with at least 8 trial treatments (approximately 6 months) before discontinuing therapy
        - Received at least two study treatments beyond the date when the initial CR was declared

    OR

    - Had stable disease (SD), PR or CR and stopped study treatment after 35 treatments (approximately 2 years) for reasons other than disease progression or intolerability
- **AND**
    - Experienced an investigator-determined confirmed radiographic disease progression after stopping their initial study treatment
    - Did not receive any anti-cancer treatment since the last dose of study treatment
    - Has a performance status of 0 or 1 on the ECOG Performance Scale
    - Demonstrates adequate organ function as detailed in Section 5.1.2
    - Female subject of childbearing potential should have a negative serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication (Cycle 1, Day 1).

- Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of study medication through at least 120 days or longer based on local regulation, after the last dose of study medication.
    - *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*
- Male subjects of child bearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, and not to donate sperm starting with the first dose of study therapy through at least 120 days or longer based on local regulation, after the last dose of study therapy.
    - *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might 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.

Subjects who enter the Second Course Phase will be retreated with the same treatment as when they last received study treatment. Study treatment will be administered for up to an additional 17 trial treatments (approximately 1 year).

Visit requirements for the second course phase are outlined in the Second Course Phase Trial Flow Chart (Section 6.2).

7.1.6.3 Post-Treatment Visits

7.1.6.3.1 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 anti-cancer 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 anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

Subjects who are eligible for retreatment may have up to two safety follow-up visits, one after the Initial Treatment Period and one after the Second Course Treatment Phase.

7.1.6.3.2 Follow-up Visits

Subjects who discontinue trial treatment for reasons other than disease progression will move into the Follow-up Phase and should be assessed Q12W by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of a new anti-cancer therapy, disease progression, death, or the end of the study.

Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment according to the criteria in Section 7.1.4.1.4 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression.

7.1.6.3.3 Survival Follow-up

Subjects, who experience disease progression (by site assessment) or start a new anti-cancer therapy, will move into the Survival Follow-Up Phase. Subjects should be contacted (by telephone or visit) approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Post-study anti-cancer therapy will be collected during survival follow-up.

7.1.6.4 Survival Status

To ensure current and complete survival data are available at the time of database locks, updated survival data may be requested during the course of the trial by the Sponsor. 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 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 who have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

An adverse event 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 adverse event can therefore be any unfavourable 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 (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor’s product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. 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.

Sponsor'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 the Sponsor 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 adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization 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 time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the Electronic Data Capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than ≥1000 mg (5 times the protocol defined dose) of pembrolizumab. No specific information is available on the treatment of over dose of pembrolizumab. In the event of overdose, study treatment should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy,

whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 7 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor 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/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, other than progression of the cancer under study (reference Section 7.2.3.3 for additional details) whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry

guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor 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/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. Hepatic ECIs include any of the following events. All of these events will require holding study treatment, notification of the event(s) to the Sponsor within 24 hours via electronic media or paper, and a hepatology consultation. These hepatic ECIs must be reported to the Sponsor within 24 hours, even if they are considered due to progression of the cancer under study.

For dose interval modification, refer to Section 5.2.1.2. For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 5.2.1.3.

   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 mg/dL
    ii. Among subjects with Baseline levels that are ≥1.5mg/dL: a value ≥2× the Baseline level
    iii. Total bilirubin >3.0 mg/dL regardless of baseline level

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor 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 global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. . Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 7 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Sponsor's product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
No, there is not a reasonable possibility of Sponsor's product relationship	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 Trial Governance and Oversight

7.3.1 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external data monitoring committee (eDMC) regarding the trial.

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an eDMC will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The voting members of the eDMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The eDMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of eDMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the eDMC. The eDMC will monitor the trial at an appropriate frequency, as described in the detailed eDMC charter. The eDMC will also make recommendations to the sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, 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 the conduct of any analysis, will be documented in a supplemental (sSAP) and referenced in the Clinical Study Report (CSR) for the study. There will be a separate PK analysis plan as well as biomarker analysis plan. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 8.2 through 8.12.

Study Design Overview	A Phase III Study of Pembrolizumab (MK-3475) vs. Best Supportive Care (BSC) as Second-Line Therapy in Subjects with Previously Systemically Treated Advanced Hepatocellular Carcinoma
Treatment Assignment	Subjects will be randomized in a 2:1 ratio to receive pembrolizumab plus BSC or placebo plus BSC (control arm). This is a double-blind study. Treatment allocation/randomization will be stratified according to the following factors: 1. Geographic region (Asia without Japan, Non-Asia with Japan) 2. Macrovascular invasion (Yes, No) 3. α-Fetoprotein (ng/mL) (<200, ≥200)
Analysis Populations	Efficacy: Intention to Treat (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoints/Hypotheses	1. Pembrolizumab + BSC improves progression-free survival (PFS) per RECIST 1.1 assessed by blinded central imaging vendor compared to placebo + BSC. 2. Pembrolizumab+ BSC improves overall survival (OS) compared to placebo + BSC.
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab to the control on PFS and OS using a stratified log-rank test. Estimation of the hazard ratio will be done using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. Stratified Miettinen and Nurminen's method [49] with weights proportional to the stratum size will be used for comparison of the objective response rates (ORR) between the treatment arms.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There are no Tier 1 events in this trial. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters. The 95% confidence intervals for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method, an unconditional, asymptotic method [49].

Interim Analyses	Two interim analyses will be performed in this study. Results will be reviewed by an external data monitoring committee. Details are provided in Section 8.7. • Interim Analysis (IA) o Timing: To be performed when approximately 183 OS events (67% of expected total OS events) are observed. With 16 months enrollment, the IA is expected approximately at Month 22, at which time approximately 183 OS events (67% of expected total OS events) and 331 PFS events are expected to have been accumulated. o Purpose: Primary efficacy hypothesis testing for PFS (a single analysis) and interim efficacy analysis for OS . Only if PFS or OS are significant, the analysis of the secondary endpoint of ORR (a single analysis) will also be performed. • Second Interim Analysis o Timing: To be performed when approximately 232 OS events (85% of expected total OS events) have been observed, projected to occur at approximately Month 28. o Purpose: Second efficacy IA for OS (assuming not declared successful at the first IA). • Final analysis (event-driven trial) o Timing: when approximately 273 OS events have been observed, estimated to be 35 months after study start. o Purpose: Final efficacy analysis for OS (assuming not declared successful at either of the 2 interim analyses).
Multiplicity	The multiplicity strategy in this study will be applied to the 2 primary hypotheses (superiority of pembrolizumab in PFS and superiority of pembrolizumab in OS) and the secondary hypothesis of superiority of pembrolizumab in ORR. The overall Type I error across the 3 hypotheses above is strongly controlled at 2.5% (one-sided). The multiplicity strategy will follow the graphical approach of Maurer and Bretz [50] as described in Section 8.8, with initially 0.2% allocated to PFS hypotheses and 2.3% allocated to OS hypotheses. Within the OS hypothesis that is analyzed following a group sequential approach, the Type I error rates for the interim and final analyses will be controlled through the alpha-spending functions specified for this endpoint as described in Section 8.8. The PFS analysis and the ORR analysis do not use the group sequential approach. The PFS hypothesis is tested using only the PFS data collected at the time of the first interim OS analysis. Similarly, the secondary ORR hypothesis is tested using only the ORR data collected at the time of the first interim OS analysis, whenever the Type I error becomes available for the ORR analysis.

Sample Size and Power	The sample size is approximately 408. The analysis of the OS endpoint is event driven. The testing of the OS hypothesis is conducted upon accumulating a preset number of events. The study is designed and will be conducted to accumulate approximately 273 OS events (unless superiority in OS is proven at an interim analysis). For the primary endpoint PFS, the trial is anticipated to have approximately 94% power at the time of the testing of the primary PFS hypothesis to demonstrate that pembrolizumab is superior to the control at a one-sided 0.2% alpha-level, if the underlying hazard ratio of PFS is 0.60. For the primary endpoint OS, the trial has approximately 92% power to demonstrate that pembrolizumab is superior to the control at a one-sided 2.3% alpha-level, if the underlying hazard ratio of OS is 0.65.

8.2 Responsibility for Analyses/In-House Blinding

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

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

Since the trial is double-blinded, analyses or summaries generated by randomized treatment assignment, and actual treatment received will be limited and documented. In addition, the blinded central imaging vendor will perform the central imaging review without knowledge of treatment group assignment.

The eDMC will serve as the primary reviewer of the unblinded results of the interim analyses and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the Sponsor. An external unblinded statistician and statistical programmer will be responsible for generating unblinded data summaries and presenting them to the eDMC. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee and limited additional Sponsor personnel may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

8.4.1.1 Primary

Progression-Free Survival (PFS) – RECIST 1.1 by Blinded Central Imaging Vendor Review

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded central imaging vendor review or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

Overall Survival (OS)

OS is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

8.4.1.2 Secondary

Objective Response Rate (ORR) – RECIST 1.1 by blinded central imaging vendor review

ORR is defined as the proportion of the subjects in the analysis population who have a CR or PR per RECIST 1.1.

Disease Control Rate (DCR) - RECIST 1.1 by blinded central imaging vendor review

DCR is defined as the proportion of subjects who have achieved CR, PR, or stable disease (SD) after ≥5 weeks (the start of the window for the first scheduled scan) based on assessments by the blinded central imaging vendor per RECIST 1.1.

Time to Progression (TTP) - RECIST 1.1 by blinded central imaging vendor review

TTP is defined as the time from randomization to the first documented disease progression per RECIST 1.1. See Section 8.6.1 for definition of censoring.

Duration of Response (DOR) - RECIST 1.1 by blinded central imaging vendor review

For subjects who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR per RECIST 1.1 until disease progression per RECIST 1.1 or death due to any cause, whichever occurs first. See Section 8.6.1 for definition of censoring.

8.4.2 Safety Endpoints

Safety endpoints are described in Sections 4.2.4.4 and 7.2.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The Intention-to-Treat (ITT) population will serve as the population for primary efficacy analysis. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 8.6 Statistical Methods.

8.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study medication for one cycle but receives the correct treatment for all other cycles will be analyzed according to the correct treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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.

Details on the approach to handling missing data for safety analyses are provided in Section 8.6 Statistical Methods.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the sSAP.

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

8.6.1.1 Progression-free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The hypotheses of treatment difference in PFS will be tested by the stratified log -rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. Due to the small number in the stratum of presence of macrovascular invasion, subjects from any geographic region or with any level of α-fetoprotein will be combined in this stratum. Thus, the following 5 strata will be used in the stratified log-rank test and the stratified Cox model:

- Macrovascular invasion (No) + Geographic region (Asia without Japan) + α-fetoprotein (ng/mL) (<200)

- Macrovascular invasion (No) + Geographic region (Non-Asia with Japan) + α-fetoprotein (ng/mL) (<200)
- Macrovascular invasion (No) + Geographic region (Asia without Japan) + α-fetoprotein (ng/mL) (≥200)
- Macrovascular invasion (No) + Geographic region (Non-Asia with Japan) + α-fetoprotein (ng/mL) (≥200)
- Macrovascular invasion (Yes) + Geographic region (Asia without Japan or Non-Asia with Japan) + α-fetoprotein (ng/mL) (<200 or ≥200)

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by blinded central imaging vendor review, regardless of discontinuation of study drug. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment and PFS analysis for PD per irRECIST by the blinded central imaging vendor review.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by the blinded central imaging vendor review, 2 sensitivity analyses will be performed with a different set of censoring rules. The first sensitivity analysis is the same as the primary analysis except that (1) the date of documented PD or death will be the progression date, regardless of whether or not new anti-cancer treatment is initiated and (2) it censors at the last disease assessment, regardless of whether or not new anti-cancer treatment is initiated if no PD and no death occur. The second sensitivity analysis is the same as the first sensitivity analysis, except that it considers discontinuation of treatment due to reasons other than complete response or initiation of an anti-cancer treatment subsequent to discontinuation of study-specified treatment, whichever occurs later, to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 8.

Table 8 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤ 1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented after ≥ 2 consecutive missed disease assessments or after new anti-cancer therapy	Censored at last disease assessment prior to the earlier date of ≥ 2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anti-cancer therapy is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study or completed study therapy
No PD and no death; new anti-cancer therapy is initiated	Censored at last disease assessment before new anti-cancer therapy	Censored at last disease assessment	Progressed at date of new anti-cancer therapy

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log [-log] of the survival function vs. time for PFS will be plotted for the comparison between pembrolizumab and the control arm. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies: for example, using Restricted Mean Survival Time method [51], parametric method [52], etc. Further details of sensitivity analyses will be described in supplemental SAP.

The main PFS analysis will be conducted according to the hypotheses testing plan as described in Section 8.7 Interim Analyses and Section 8.8 Multiplicity. The supportive analysis of the PFS data available at the time of the final OS analysis will be also conducted.

8.6.1.2 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The hypotheses of treatment difference in survival will be tested by the stratified log -rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization will be applied to both the stratified log-rank test and the stratified Cox model. The same 5 strata defined for the PFS analysis (see Section 8.6.1.1) will be used for the OS analysis.

Subjects in the control arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm, and may switch to another anti PD-1 treatment following the verification of progressive disease by blinded central imaging vendor review. Exploratory analyses to adjust for the effect of treatment switching to other PD-1 therapies on OS may be performed based on recognized methods, e.g. the Rank Preserving Structural Failure Time model proposed by Robins and Tsiatis [53], two-stage model, etc., based on an examination of the appropriateness of the data to the assumptions required by the methods.

8.6.1.3 Objective Response Rate

Stratified Miettinen and Nurminen's method [49] with weights proportional to the stratum size will be used for comparison of the objective response rates between the treatment arms. A 95% confidence interval for the difference in response rates between the pembrolizumab arm and the control arm will be provided. The stratification factors used for randomization will be applied to the analysis. The same 5 strata defined for the PFS analysis (see Section 8.6.1.1) will be used for the ORR analysis.

The ORR analysis will be conducted according to the hypotheses testing plan as described in Section 8.7 Interim Analyses and Section 8.8 Multiplicity.

8.6.1.4 Disease Control Rate

Stratified Miettinen and Nurminen's method [49] with weights proportional to the stratum size will be used for comparison of the DCR between the treatment arms. A 95% confidence interval for the difference in response rates between the pembrolizumab arm and the control arm will be provided. The stratification factors used for randomization will be applied to the analysis. The same 5 strata defined for the PFS analysis (see Section 8.6.1.1) will be used for the DCR analysis.

8.6.1.5 Time to Progression

The non-parametric Kaplan-Meier method will be used to estimate the TTP curve in each treatment group. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to estimate the magnitude of the treatment difference (i.e., hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4) will be applied to both the stratified log-rank test and the stratified Cox model. The same 5 strata defined for the PFS analysis (see Section 8.6.1.1) will be used for the TTP analysis.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the analysis, for the subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by blinded central imaging vendor review, regardless of discontinuation of study drug. Unlike in PFS analysis, death is not considered as an event. Censoring rules for TTP are summarized in Table 9.

Table 9 Censoring Rules for TTP

Situation	Primary Analysis
Death only	Censored at date of randomization or date of last non-PD disease assessment, whichever is later
No PD and no death; new anticancer treatment is not initiated	Censored at last non-PD disease assessment
No PD and no death; new anticancer treatment is initiated	Censored at last non-PD disease assessment before new anticancer treatment
PD documented after ≤1 missed disease assessment	Progressed at date of documented PD
PD documented after ≥2 missed disease assessments	Censored at last disease assessment prior to the ≥2 consecutive missed disease assessments

8.6.1.6 Duration of Response

Subjects who achieved CR or PR and are alive, have not progressed, have not initiated new anti-cancer treatment, have not missed ≥2 consecutive missed disease assessments, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.

The non-parametric Kaplan-Meier method will be used to estimate the DOR curve in each treatment group; estimates and 95% CIs at specific duration time points will be provided.

Censoring rules for DOR are summarized in Table 10.

Table 10 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 disease assessments or after new anti-cancer therapy.	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed adequate disease assessments and before new anti-cancer therapy, if any	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, have not missed ≥2 consecutive disease assessments, and have not been determined to be lost to follow-up.

Table 11 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

Analyses of the DCR, TTP, and DOR data will be performed at the time of the interim and final analysis of OS.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 8.7 Interim Analyses and in Section 8.8 Multiplicity.

Table 11 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis #1			
PFS per RECIST 1.1 by blinded central imaging vendor review	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 8)
Primary Hypothesis #2			
OS	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Secondary Hypothesis #1			
ORR per RECIST 1.1 by blinded central imaging vendor review	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization (see Section 5.4) will be applied to the analysis model.
‡ Miettinen and Nurminen method [49]

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, vital signs, etc.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. For this protocol, there are no Tier 1 events.

Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

AEs (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, vital signs, that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug related AE, any Grade 3-5 AE, any serious AE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints.

The 95% confidence intervals will be provided for between- treatment differences in the percentage of subjects with Tier 2 events; these analyses will be performed using the Miettinen and Nurminen method [49], an unconditional, asymptotic method.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death		
	Specific AEs, SOCs, or PDLCs (incidence ≥4 of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs or PDLCs‡ (incidence <4 of subjects in all of the treatment groups), AEOSI		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X

AE = adverse event; AEOSI = adverse events of special interest; ECG = electrocardiogram; PDLC = pre-defined limit of change; SOC = system organ class.

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

There are 2 planned interim analyses in this trial in addition to the final analysis. Results will be reviewed by an eDMC.

8.7.1 Efficacy Interim Analyses

The purpose of the first interim analysis is to conduct the main testing for efficacy on the PFS and ORR endpoints and to conduct an interim testing for efficacy on the OS endpoint. It will be performed when approximately 183 OS events (67% of expected total OS events) are observed. With approximately 16 months enrollment, the IA1 is expected approximately at Month 22, at which time approximately 331 PFS events are expected to have been accumulated.

The purpose of the second interim analysis is to conduct the efficacy testing on the OS endpoint if the result of OS endpoint is not successful at the first IA. The second IA will be performed when approximately 232 OS events (85% of expected total OS events) are observed, which is expected at approximately Month 28.

The final analysis (FA) will be performed when approximately 273 OS events are observed which is expected at Study Month 35.

The operating characteristics of conducting the IA for testing the OS hypothesis at 67% and 85% expected total OS information are shown in Table 14. A detailed description of the multiplicity adjustment and hypotheses testing plan is provided in Section 8.8 Multiplicity.

8.7.2 Safety Interim Analyses

As noted in Section 7.3.3 – Data Monitoring Committee, the DMC will be responsible for periodic interim safety reviews as specified in the DMC charter.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the two primary hypotheses (superiority of pembrolizumab on PFS or OS) and the secondary hypothesis of superiority of pembrolizumab in ORR.

The overall Type I error across the testing of the OS, PFS, and ORR hypotheses is strongly controlled at α=2.5% (one-sided). The multiplicity strategy will follow the graphical approach of Maurer and Bretz [50]. Figure 3 provides the multiplicity strategy diagram of the study.

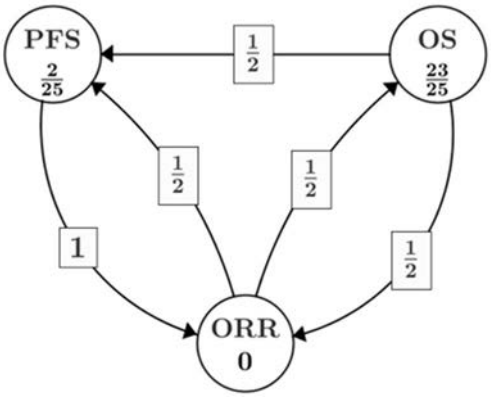


Figure 3 Multiplicity Strategy

In the diagram shown in Figure 3, when a particular null hypothesis is rejected, the arrows leading to it are removed, and the Type I error allocated to the null hypothesis that was rejected is re-distributed to the other two hypotheses. The arrows on the diagram show how the Type I error allocated to a hypothesis that was successfully tested will be re-distributed for the testing of the other two hypotheses. Initially, α=2.3% (23/25 of the overall total α=2.5% for testing the OS, PFS, and ORR) is allocated to the OS hypothesis and α=0.2% is allocated to the PFS hypothesis.

The testing of the PFS, OS, and ORR will proceed as follows.

PFS Hypothesis: The testing of the primary PFS hypothesis will be conducted at the time of the first OS IA. The testing of the PFS hypothesis will be based on a PFS test statistic calculated only from study data available at the time of the main PFS analysis at the first OS IA. The PFS hypothesis will initially be tested at Type I error α=0.2%. Depending on the result of the initial testing of the PFS hypothesis and the results of testing of the OS and ORR hypotheses, the PFS hypothesis can be tested at Type I error levels of α=0.2%, =1.35%, or =2.5%. Table 13 shows the boundary thresholds corresponding to a successful testing of the PFS hypothesis at each of these Type I error levels. From Table 13, to declare success on the PFS hypothesis at Type I error α=0.2%, the nominal calculated p-value should be ≤0.002, and the PFS hazard ratio should be ≤0.71. At the time of the main PFS analysis at approximately Month 22, it is expected that 331 PFS events would have been accumulated under assumptions specified in Section 8.9 - Sample Size and Power Calculations.

Table 13 Efficacy Boundaries for Testing the PFS Hypothesis

Analysis	Study Calendar Time	N[b]	Events	Information Fraction	Efficacy Boundary Crossing		
					Type I Error (α)	Hazard Ratio	Power[c]
Primary	Month 22[a]	408	331	1.0	0.20%	0.71	99.00%
					1.35%	0.77	>99%
					2.50%	0.80	>99%

[a] The main analysis of PFS will occur based on PFS data at this time. Per the multiplicity adjustment scheme, it is possible for the main analysis PFS test statistic (based on PFS data at this time) to be used again at the time of the second interim OS analysis (Month 28) and end-of-study time point (Month 35) for a re-testing of the PFS hypothesis.

[b] Expected number of subjects randomized into the study at the time of analysis.

[c] The power calculation is based on the assumptions in Section 8.9.

OS Hypothesis: The OS hypothesis will be tested following a group sequential approach. The testing of the OS hypotheses will be first conducted at approximately Month 22 of the study (i.e., the first IA time point when approximately 183 OS events would have been accumulated). If unsuccessful at the first IA, the OS hypotheses will be tested at the second IA time point when approximately 232 OS events would have been accumulated at approximately Month 28 of the study, and if unsuccessful at the second IA, the OS hypotheses will be tested at the final analysis time point when 273 events will be accumulated at Month 35, approximately. The nominal Type I error rates for the 2 interim analyses and final analysis that will allow tight control of the overall Type I error for testing the OS hypothesis will be derived using the alpha-spending function approach based on the overall Type I error allocated to the OS hypothesis. The group sequential testing of the OS hypothesis will be conducted using the Lan-DeMets spending function that approximates an O'Brien-Fleming boundary. The OS hypothesis will initially be tested at the overall Type I error α=2.3%. If both the PFS and ORR null hypotheses have been rejected at the α=0.2% level, the OS hypothesis will be tested at a Type I error level of α=2.5%.

Table 14 shows the boundary thresholds corresponding to a successful group sequential testing of the OS hypothesis at each of these Type I error levels. From Table 14, with an overall Type I error α=2.3%, the first interim OS hypothesis testing with 183 events at Type I error α=0.55% has an associated power of 60% following a group sequential approach under assumptions specified in Section 8.9. For example at overall Type I error α=2.3%, to declare success on the OS hypothesis at Type I error α=0.55% at the first IA, the OS hazard ratio should be $\leq$0.67; to declare success on the OS hypothesis at Type I error α=1.20% at the second IA, the OS hazard ratio should be $\leq$ 0.73; and to declare success on the OS hypothesis at Type I error α=1.87% at the final analysis, the OS hazard ratio should be $\leq$0.77. Conducting the OS hypothesis testing with 273 events at the final analysis at overall Type I error α=2.3% has an associated power of 91%. The projected interim analyses information fraction of 0.67 and 0.85 will be adjusted according to the proportion of the 273 final planned OS events actually available at the time of the interim analyses. Table 14 shows the example of the hazard ratio boundaries that will be applied if 0.67 and 0.85 of required OS events are observed by the time of the first and second IA, respectively. If the final OS events vary from 273, a minor adjustment in the final bound may be required as well.

The spending function planned to be used for the testing of the OS hypothesis satisfies the requirements laid out in Maurer and Bretz [50].

Table 14 Efficacy Boundaries for Testing the OS Hypothesis

Type I Error (Overall α)	Analysis	Study Calendar Time	N§	Events	Information Fraction	Efficacy Boundary Crossing†		
						Nominal α	Hazard Ratio	Power
2.3%	Interim1	Month 22	408	183	0.67	0.55%	0.67	60%
	Interim2	Month 28	408	232	0.85	1.20%	0.73	82%
	Final	Month 35	408	273	1.00	1.87%	0.77	91%
2.5%	Interim1	Month 22	408	183	0.67	0.62%	0.68	62%
	Interim2	Month 28	408	232	0.85	1.32%	0.73	83%
	Final	Month 35	408	273	1.00	2.02%	0.77	92%

† Based on O'Brien-Fleming spending function. The power calculation is based on the assumptions in Section 8.9.
§ Expected number of subjects randomized into the study at the time of analysis.

ORR Hypothesis: The testing of the secondary ORR hypothesis will be conducted at the time of the first OS IA. The testing of the ORR hypothesis will be based on an ORR test statistic calculated only from study data available at the time of the main ORR analysis at the first OS IA from all randomized subjects. The ORR hypothesis is initially allocated a Type I error α=0% and thus, cannot be tested unless one or both of the PFS or OS null hypotheses have been rejected. Depending on the results of the OS and PFS hypotheses testing, the ORR hypothesis can be tested at Type I error levels of α=0.2%, 1.15%, or 2.5%.

Table 15 shows the boundary thresholds corresponding to each of three possible Type I error levels. To declare success on the ORR hypothesis at overall Type I error α=0.2%, the nominal calculated p-value should be ≤0.2% (i.e. the Type I error level), and the ORR percentage point difference (pembrolizumab–control) should be ≥8.5%.

Table 15 Efficacy Boundaries for Testing the ORR Hypothesis

Analysis	Study Calendar Time	N‡	Efficacy Boundary Crossing		
			Type I Error (α)	ORR Δ§	Power
Primary	Month 22†	408	0.20%	8.5%	84%
			1.15%	5.8%	97%
			2.50%	5.0%	98%

‡ Expected number of subjects randomized into the study at the time of analysis.
§ Δ = ORR in pembrolizumab group – ORR in control group. The assumed expected ORR in pembrolizumab and control groups are 15% and 3%, respectively.
† Per the multiplicity adjustment scheme, it is possible for the main analysis ORR test statistic (based on ORR data at this time) to be used again at the second IA (i.e., Month 28) and end-of-study time point (i.e., Month 35) for a re-testing of the ORR hypothesis.

8.9 Sample Size and Power Calculations

The study will randomize subjects in a 2:1 ratio into pembrolizumab arm and the control arm. Approximately 408 subjects are required to be enrolled in order to test the OS hypothesis at the desired study requirements.

The analysis of the OS endpoint is event driven. The testing of the OS hypothesis is conducted upon accumulating a preset number of events. The study is designed and will be conducted to accumulate approximately 273 OS events.

PFS Analysis: As described in Section 8.7 Interim Analysis, the main PFS analysis will be conducted at the same time as the first OS IA at approximately Month 22 of the study. It is projected that approximately 331 PFS events will be accumulated at this time. With 331 PFS events, the testing of the PFS hypothesis at Type I error α=0.2% has 94% power to demonstrate that pembrolizumab is superior to the control with respect to PFS if the underlying PFS hazard ratio (pembrolizumab/control) is 0.60.

The power calculation is based on the following assumptions: 1) PFS follows an exponential distribution with a median of 2.5 months in the control arm; 2) An enrollment period of 16 months; 3) a minimum follow-up of approximately 6 months; and 4) A yearly drop-out rate of ~10%.

OS Analysis: A total of 273 OS events are required to test the OS hypothesis at Type I error α=2.3% with ~92% power (see Table 14) if the underlying OS hazard ratio (pembrolizumab/control) is 0.65. A total of 408 subjects are needed to be enrolled into the study in order to accumulate 273 OS events at approximately Month 35 of the study.

The sample size and power calculation is based on the following assumptions: 1) OS follows a piece-wise exponential distribution with zero hazard during the first month and a median of 10 months in the control arm; 2) An enrollment period of 16 months; 3) a minimum follow-up of 19 months; and 4) A yearly dropout rate of ~2%.

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% confidence interval [CI]) for the dual primary endpoints will be estimated and plotted within each category of the following classification variables:

- Geographic region (Asia without Japan, Non-Asia with Japan)
- Macrovascular invasion (Yes, No)
- α-Fetoprotein (ng/mL) (<200, ≥200)
- Etiology (HCV, HBV, and uninfected)
- Reason for discontinuation of sorafenib (progressive disease, intolerance)
- ECOG performance status (0, 1)
- Age (<65 years, ≥65 years)
- Extrahepatic spread (Yes, No)

- Gender (Male, Female)
- Current disease overall BCLC stage (B, C)

Country-specific populations may also be analyzed per local regulatory requirements.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

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 will be provided by the Sponsor as summarized in Table 16.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 16 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab 100 mg/4 mL	Solution for infusion	Provided centrally by the Sponsor

All supplies indicated in Table 16 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 16 will be provided by the trial site, subsidiary or designee. Every attempt should 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 the Sponsor.

9.2 Packaging and Labeling Information

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

Site pharmacies will receive open label vials of study drug. No kitting is required.

9.3 Clinical Supplies Disclosure

This trial is blinded but provided open label; therefore, an unblinded pharmacist or qualified trial site personnel will be used to blind supplies. Treatment identity (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.5.2). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Only the principal investigator or delegate and the respective subject's code should be unblinded. Trial site personnel and Sponsor personnel directly associated with the conduct of the trial should not be unblinded to treatment assignment.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

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 Discard/Destruction/Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators 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 the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, 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, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

10.1.4 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC 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 US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor'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 the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor 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 the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor 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 the Sponsor.

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 the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor 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 the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

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/case report forms, 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. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor 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 the Sponsor 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 the Sponsor 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 Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor 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 the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor 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, as the Sponsor, 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, the Sponsor 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 [Clinical Study Report (CSR) CI]. The Sponsor 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 Food and Drug Administration Amendments Act (FDAAA) of 2007, and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. 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.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

10.5 Quality Management System

By signing this protocol, the Sponsor 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.

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at www.clinicaltrials.gov if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main

paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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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 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

b. Informed Consent

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

4. Confidential Subject Information for Future Biomedical Research

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

7. Retention of Specimens

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Subjects

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for FBR (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

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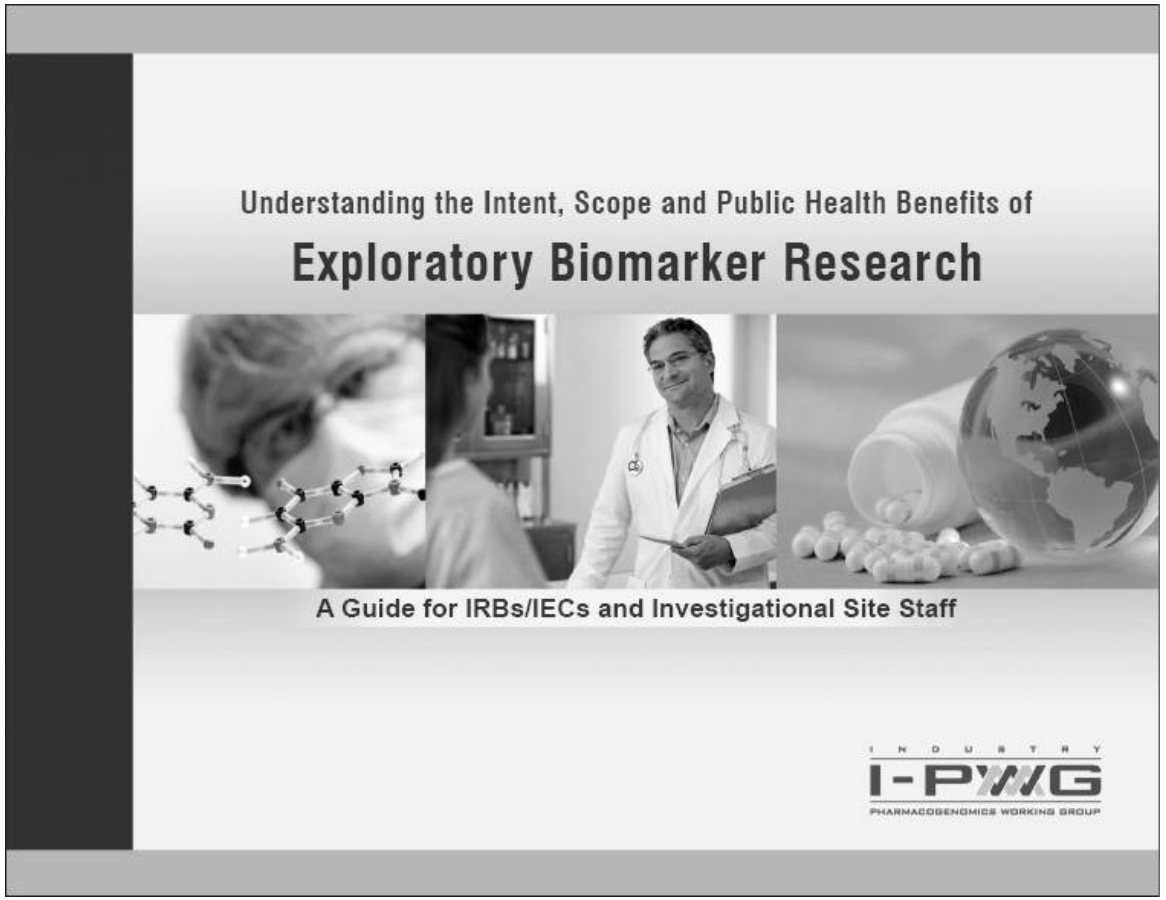
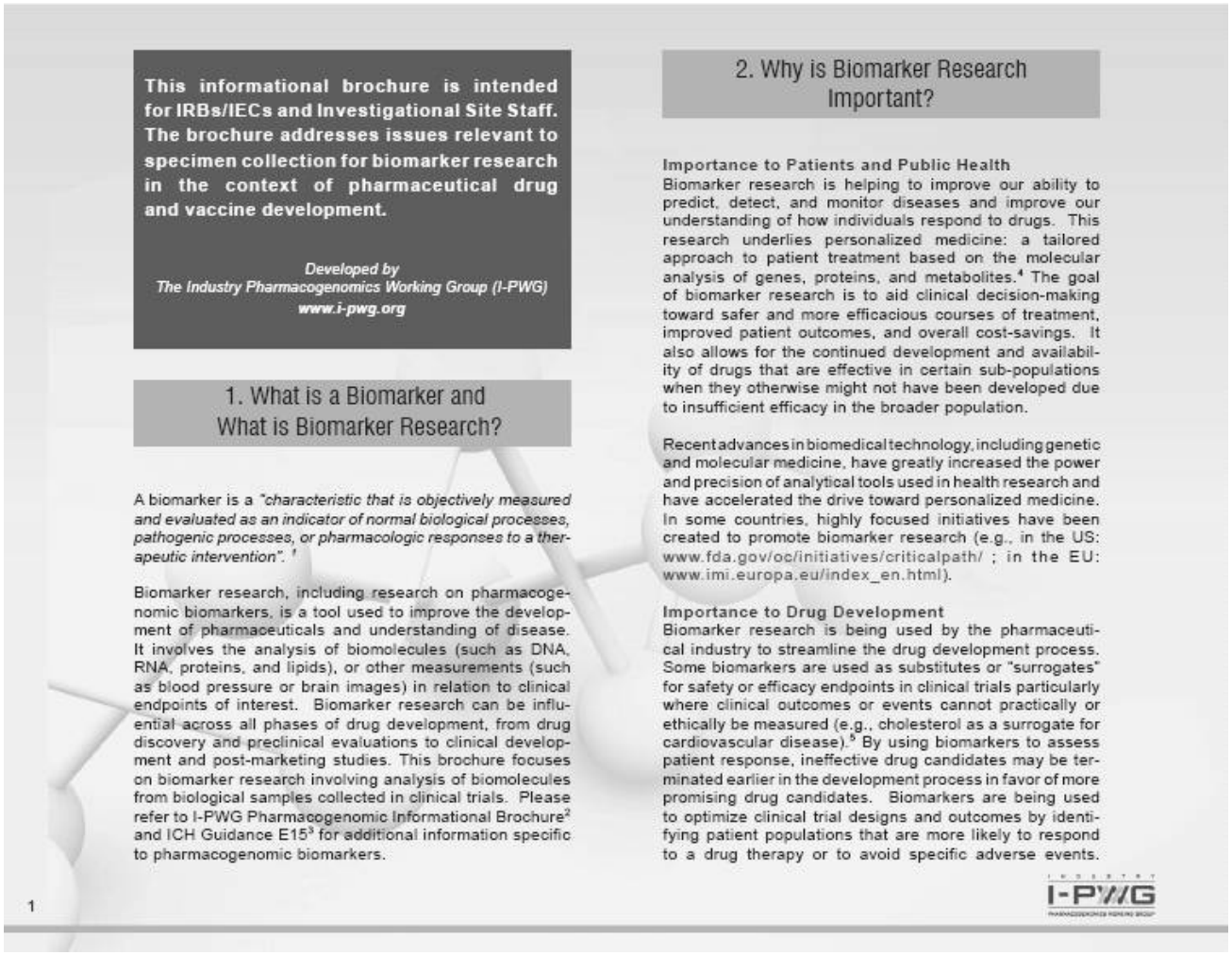
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

1. What is a Biomarker and What is Biomarker Research?

A biomarker is a *"characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".* [1]

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure[2] and ICH Guidance E15[3] for additional information specific to pharmacogenomic biomarkers.

2. Why is Biomarker Research Important?

Importance to Patients and Public Health
Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.[4] The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: www.fda.gov/oc/initiatives/criticalpath/ ; in the EU: www.imi.europa.eu/index_en.html).

Importance to Drug Development
Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).[5] By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

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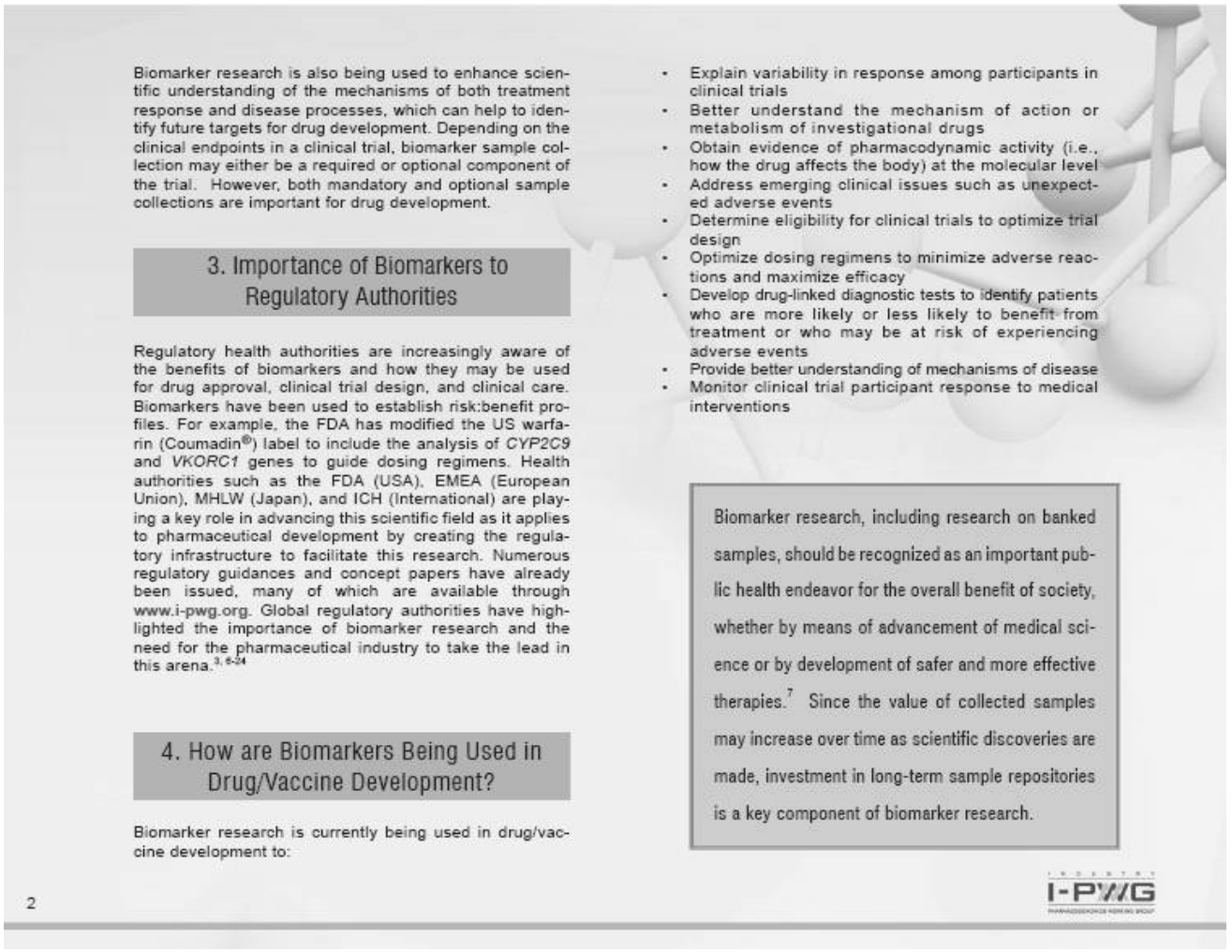
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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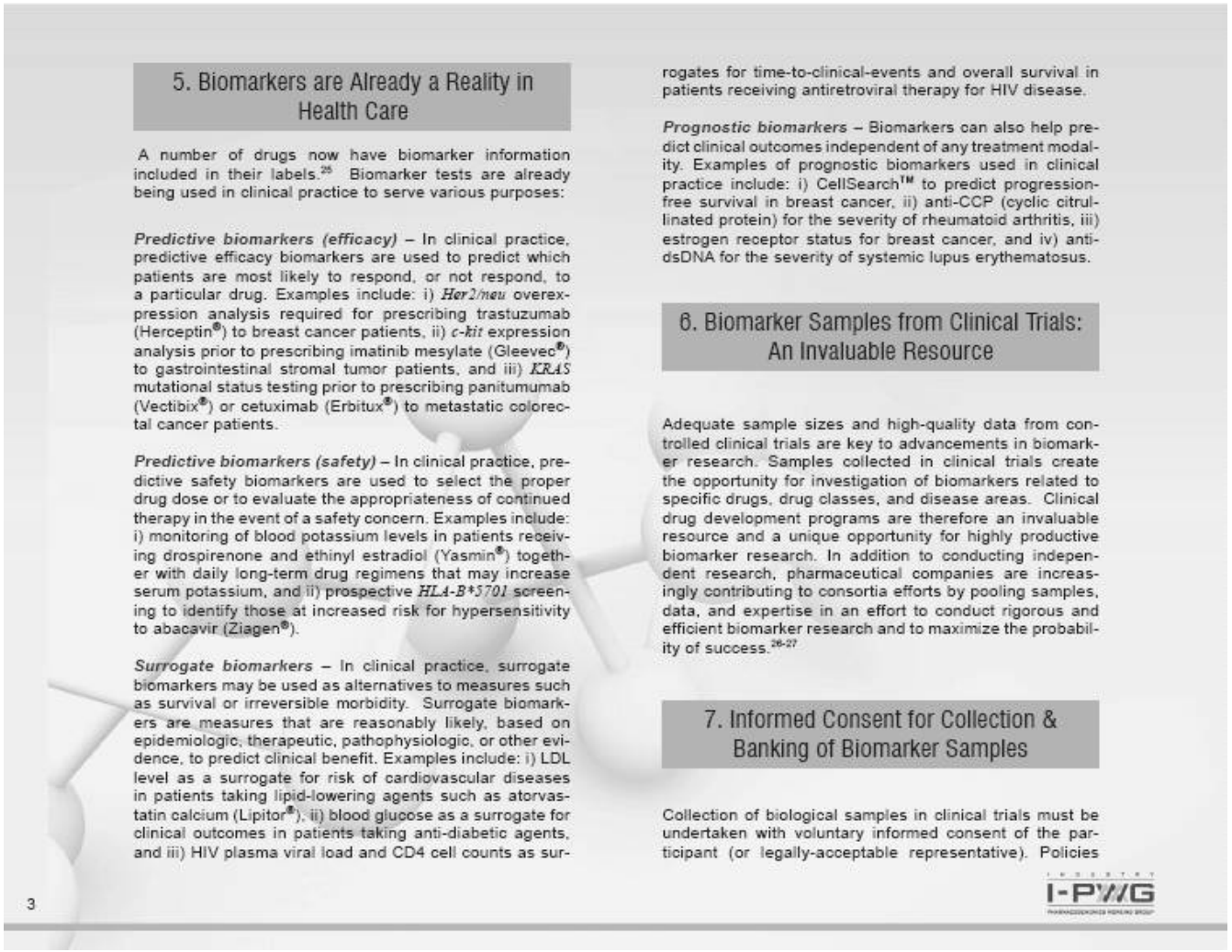

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

Predictive biomarkers (efficacy) – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin®) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec®) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix®) or cetuximab (Erbitux®) to metastatic colorectal cancer patients.

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

Surrogate biomarkers – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor®), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as surrogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.[26-27]

7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

Consent for Future Research Use

While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.[3, 31] Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

The scope of research – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[38]

The duration of storage – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.

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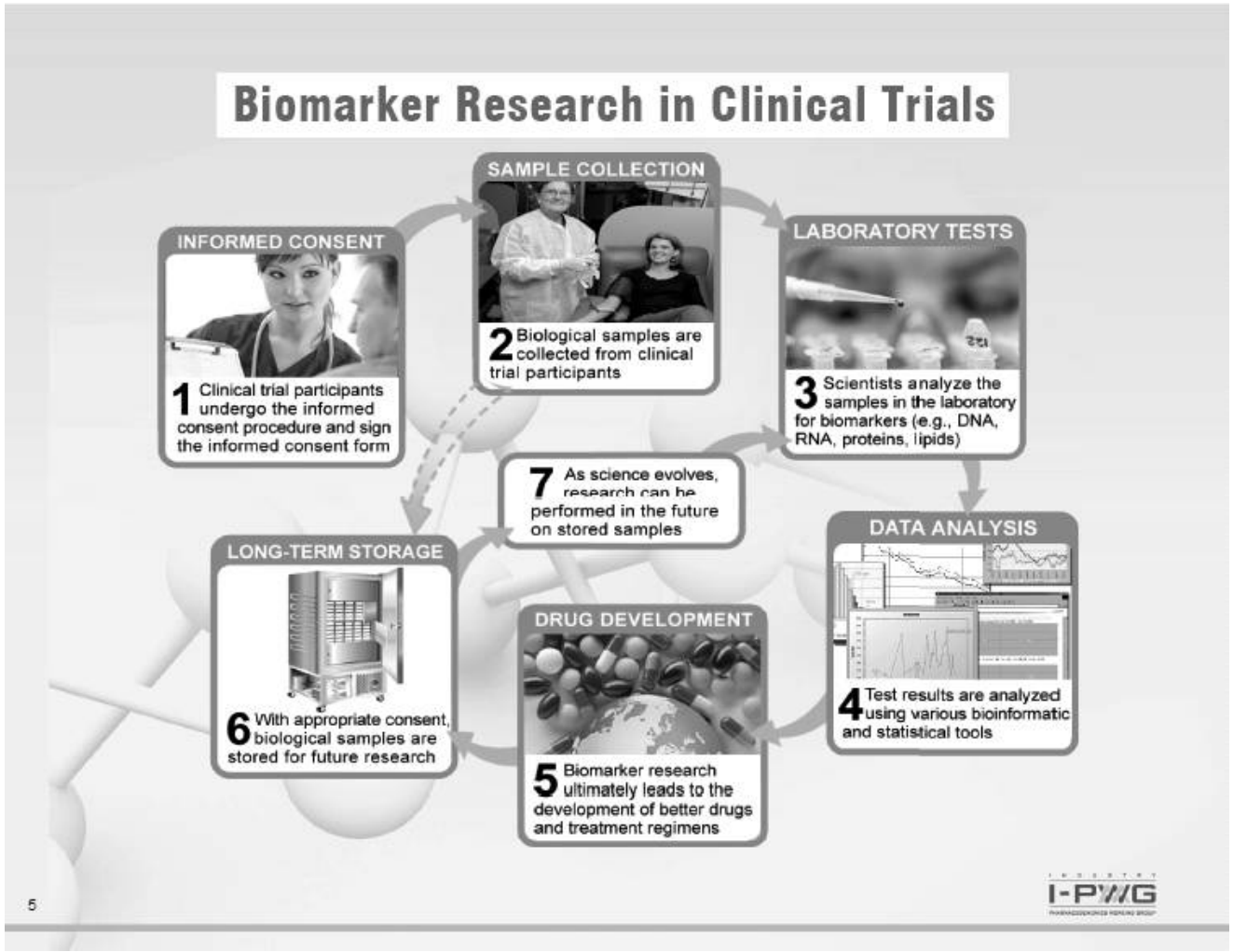
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbitux®) and panitumumab (Vectibix®) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

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other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

"...provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: www.i-pwg.org.

13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-

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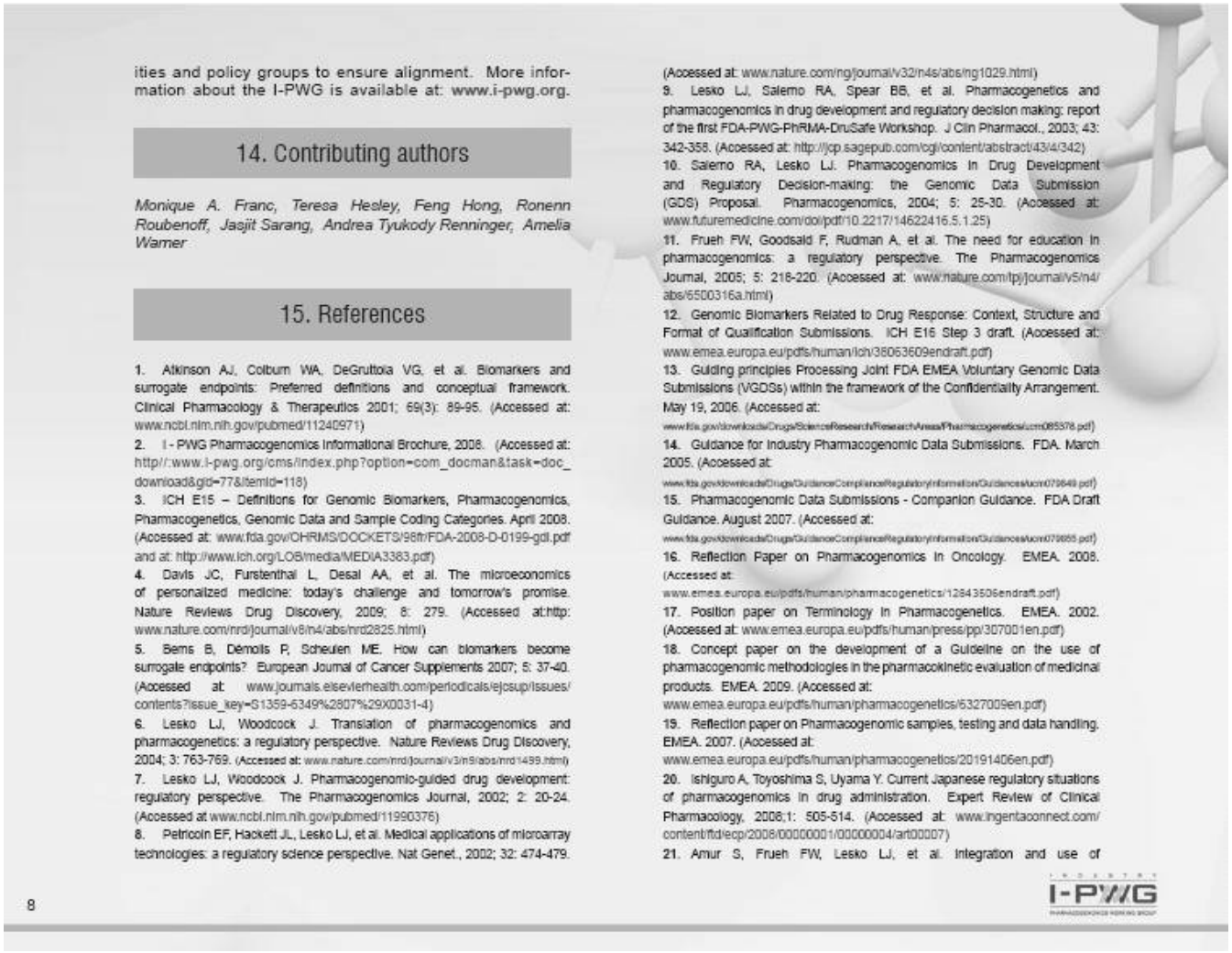

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

Monique A. Franc, Teresa Hesley, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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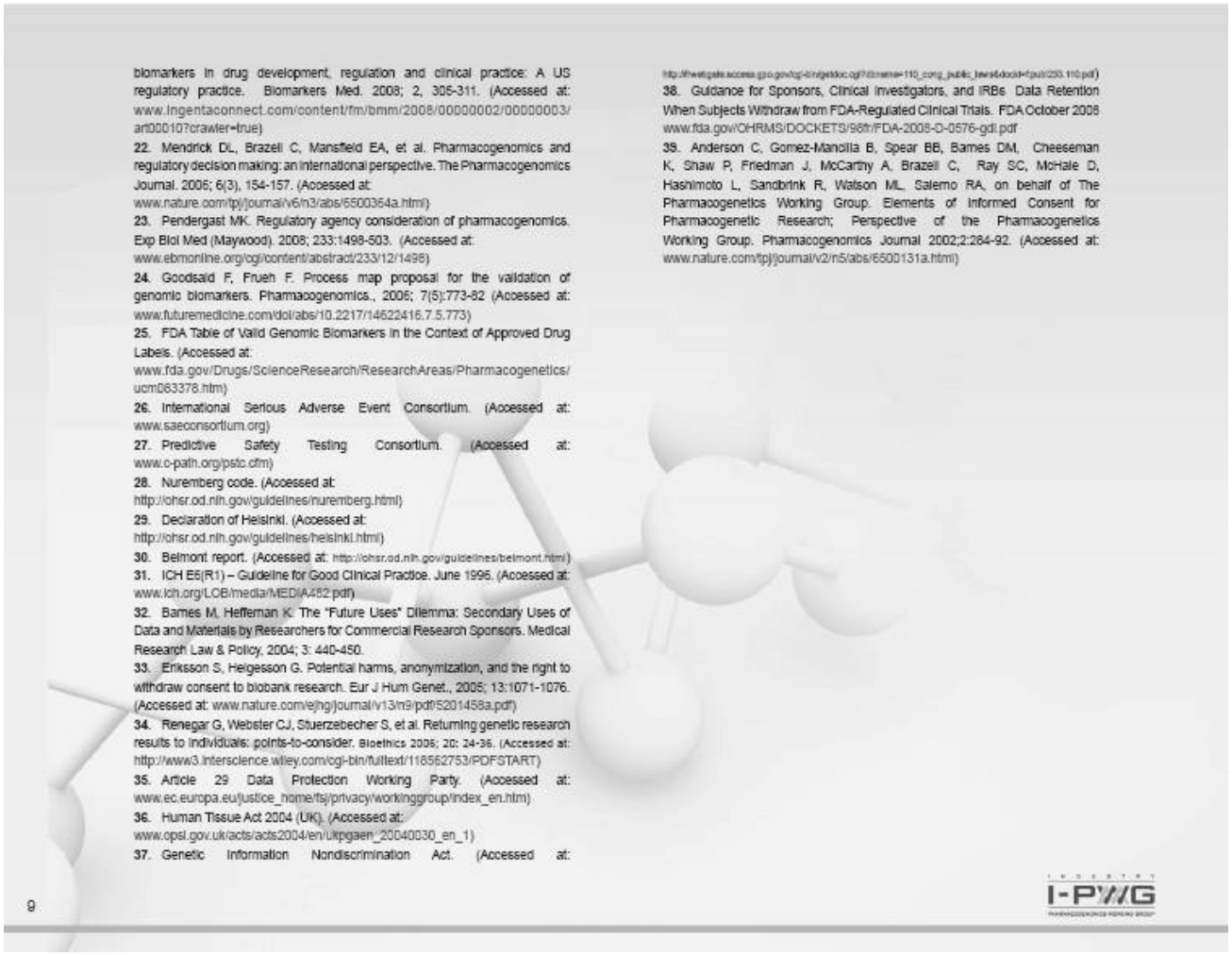

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12.4 Hepatitis B Definitions and Treatment Considerations

Table 17 describes the various definitions of treatment considerations and eligibility for study participation, along with the definitions of hepatitis B.

Table 17 Hepatitis B Definitions and Treatment Considerations

Test	Patient Status	Eligible for KN-240?	Any HBV Treatment Needed?
HBsAg (–) Total anti-HBc (+) HBsAb (+)	Immune after natural infection	Yes	No
HBsAg (–) Total anti-HBc (–) HBsAb (+)	Immune after vaccination	Yes	No
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (+) HBsAb (–)	Acute infection	No	—
HBsAg (+) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–)	Chronic infection	Yes	Yes, need to be on a HBV treatment for at least 12 weeks prior to start of study treatment without evidence of a flare during that period Exclude if: (a) <12 weeks of therapy; (b) HBV viral load 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 viral load (negative)	Unclear. Could be: (1) Resolved infection (2) False positive anti-HBc (3) Low level infection (4) Resolving acute infection	Yes	No
HBsAg (–) Total anti-HBc (+) IgM anti-HBc (–) HBsAb (–) HBV viral load (+)	(1) Low level infection (2) Resolving acute infection	Yes	Yes (as above)

12.5 ECOG Performance Status

Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.*

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

12.6 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).

12.7 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.

Measure	1 point	2 points	3 points
Total bilirubin[1] (mg/dL)	<2.0	2.0 to 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR[2] Or Prothrombin time, prolongation (seconds)	<1.7 <4.0	1.7 to 2.3 4.0-6.0	> 2.3 >6.0
Ascites	None	Mild (easily controlled by medication)	Moderate to Severe (poorly controlled)
Hepatic encephalopathy[3]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

[1]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).

[2] Different textbooks and publications use different measures. Some older reference works substitute PT prolongation for INR

[3] Hepatic encephalopathy graded according to West Haven Criteria for Semi-quantitative Grading of Mental Status: *Adapted from: Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.*

- Grade I: Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade II: Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior
- Grade III: Somnolence to semi-stupor, but responsive to verbal stimuli
  Confusion; Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

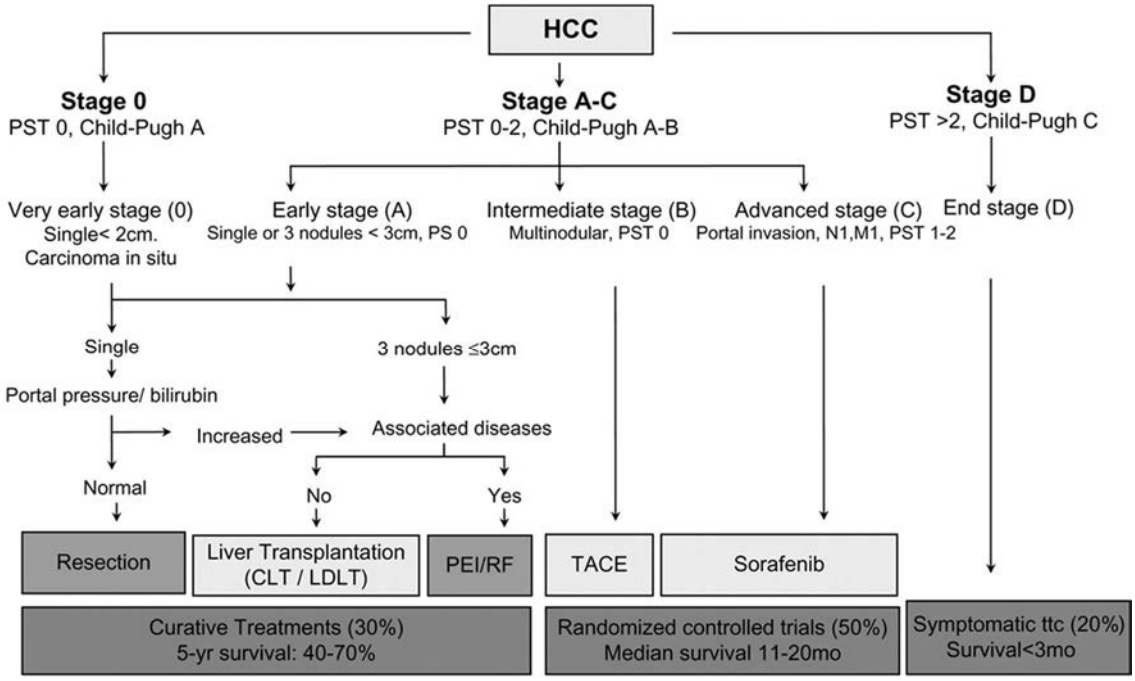
Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Points	Class	One-year survival	Two-year survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

12.8 Barcelona Clinic Liver Cancer Staging System

The Barcelona Clinic Liver Cancer staging system is shown in Figure 4 below [54].



CLT = cadaveric liver transplantation; LDLT = living donor liver transplantation; PEI = percutaneous ethanol injection; RF = radio frequency (ablation); TACE = transarterial chemoembolization.

Figure 4 Barcelona Clinic Liver Cancer staging system

12.9 List of Abbreviations

Abbreviation/Term	Definition
ADA	Anti-drug antibodies
AE	Adverse event
AFP	Alpha fetoprotein
ALC1	Antibodies to liver cytosol antigen
ALKM-1	Antibodies to liver/kidney microsomes
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antibodies to nuclei
aPTT	Activated partial thromboplastin time
ASaT	All subjects as treated
ASMA	Antibodies to smooth muscle
AST	Aspartate aminotransferase
BCAA	Branched chain amino acids
BCG	Bacille Calmette-Guerin (tuberculosis)
BCLC	Barcelona Clinic Liver Cancer scale
BID	Twice daily
BSC	Best supportive care
CI	Confidence interval
CL	Clearance
C_{max}	Serum maximum concentration
CNS	Central nervous system
CR	Complete response
CRF	Case Report Form
CRP	C-Reactive protein
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
C_{trough}	Serum minimum concentration
Dbil	Direct bilirubin
DCR	Disease control rate
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECI	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
eDMC	External data monitoring committee
ELISA	Enzyme-linked immunosorbent assay
EOC	Executive Oversight Committee
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—Core 30
EORTC QLQ-HCC18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire—HCC 18
EQ-5D	EuroQol EQ-5D (EuroQol EQ-5 Dimension 3 Level)
ER	Emergency room
ERC	Ethics review committee
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act

Abbreviation/Term	Definition
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed, paraffin-embedded
FOLFOX	Chemotherapy regimen containing: folinic acid, 5-fluorouracil, and oxaliplatin
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GEP	Gene expression profile
Anti-HBc	Hepatitis B core antibody, Total
Anti-HBc, IgM	Hepatitis B core antibody, IgM
HBeAg	Hepatitis B early antigen
Anti-HBe	Hepatitis B early antibody
Anti-HBs	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
Anti-HCV	Hepatitis C antibody
HDV	Hepatitis D virus
Anti-HDV	Hepatitis D antibody
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International normalized ratio
irPD	radiographic progression of disease
irRECIST	Immune related RECIST (modification of RECIST 1.1)
IRB	Institutional Review Board
ITT	Intent-to-treat
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system (IUS)
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Integrated web response system
mAb	Monoclonal antibody
miRNA	Micro RNA
mRECIST	Modified RECIST for HCC
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed death ligand 1

Abbreviation/Term	Definition
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PR	Partial response
PRO	Patient Reported Outcome
PS	Performance status
QD	Once daily
RECIST	Response Evaluation Criteria in Solid Tumors
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q12W	Every 12 weeks
QALY	Quality adjusted life years
QLG	Quality of Life Group
RNA	Ribonucleic acid
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Stable disease
SIM	Site Imaging Manual
SOP	Standard operating procedures
sSAP	Supplemental SAP
SVR_{12}	Sustained virologic response for 12 weeks
SVR_{24}	Sustained virologic response for 24 weeks
Tbil	Total bilirubin
TACE	Transcatheter chemoembolization
TAE	Transarterial embolization
TIL	Tumor infiltrating lymphocytes
TTP	Time to progression
ULN	Upper limit of normal
V	Volume of distribution

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – TRIAL PROCEDURES (Assessing and Recording Adverse Events). I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	