UCSF Helen Diller Family Comprehensive Cancer Center

Phase II Trial of Pembrolizumab (MK-3475) with GM-CSF Induction in Advanced Biliary Cancers

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Version Number	Version Date
7.0	10/01/2019
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1.0 TRIAL SUMMARY

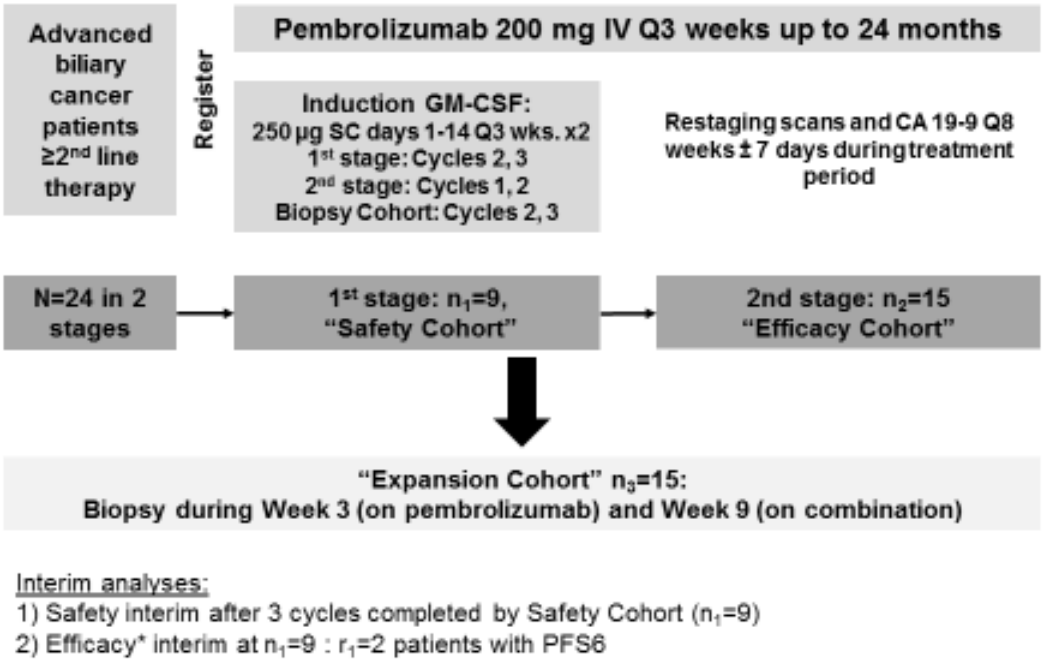
Abbreviated Title	Pembrolizumab plus GM-CSF Induction in Advanced Biliary Cancers
Trial Phase	II
Clinical Indication	Advanced biliary cancers including unresectable intrahepatic or extrahepatic cholangiocarcinoma and gall bladder carcinoma
Trial Type	Open label, single arm phase II therapeutic clinical trial
Type of control	None
Route of administration	Intravenous (pembrolizumab) and subcutaneous (GM-CSF)
Trial Blinding	N/A
Treatment Groups	N/A (not randomized)
Number of trial subjects	Total enrollment of 42 subjects for expected PFS6-evaluable n=40 and overall response evaluable n=37, combined between the following three cohorts: Stage 1: n=9 (completed) Stage 2: n=18 (completed) Expansion Cohort: n=15
Estimated enrollment period	Stages 1 and 2: 16 months (completed); Expansion Cohort: 12 months
Estimated duration of trial	52 months for accrual plus up to 2 years on treatment from start of treatment of last enrolled patient in the Expansion Cohort, with potential for up to 2 additional years of survival follow up in event that last patient has prolonged stable disease and discontinues without progression after 24 months or 35 cycles
Duration of Participation	Expect median time on pembrolizumab treatment of 6 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label phase II trial to examine efficacy and safety of a novel combination of pembrolizumab plus induction GM-CSF in patients with advanced biliary cancers treated at UCSF.

2.2 Trial Diagram



Interim analyses:
1) Safety interim after 3 cycles completed by Safety Cohort (n_1=9)
2) Efficacy* interim at n_1=9 : r_1=2 patients with PFS6

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective & Hypothesis

(1) **Objective:** Determine overall response rate (ORR) by RECIST 1.1[1] in the overall study population.

Hypothesis: The ORR by RECIST 1.1 in overall study population will be 20% which is a meaningful proportion with response compared to a null hypothesis response rate of approximately 5% for no treatment in 2nd line advanced biliary cancers, noting that there is no current FDA-approved therapy after failure of 1st line gemcitabine-based regimens and uncontrolled and retrospective studies show that responses to standard cytotoxic therapies are modest and transient.[2-4] ORR on treatment with single-agent pembrolizumab in unselected ≥ 2nd line biliary cancer patients has not yet been reported from KEYNOTE-158 (unpublished data, Merck).

3.2 Secondary Objective(s) & Hypothesis (es)

(1) **Objective**: Measure safety (NCI CTCAE v.4.0) for the novel combination overall and according to anatomic subtype.

Hypothesis: The combination is safe and feasible with ≤ 50% related ≥ grade 3 toxicity rate (Common Terminology Criteria for Adverse Events (CTCAE) version 4.0) during first 3 cycles (completion of Induction Phase plus 1 additional cycle).

(2) **Objective:** Determine proportion PD-L1+ overall.

Hypothesis: Approximately 40% of tumors will be PD-L1+ overall based upon PD-L1+ rates observed in KEYNOTE-028 biliary cohort.[5]

(3) **Objective:** Determine overall response rate (ORR) by RECIST 1.1[1] according to PD-L1 status.

Hypothesis: The ORR by RECIST 1.1 will be higher in PD-L1+ biliary cancers compared to PD-L1- tumors.

(4) **Objective:** Determine proportion with progression-free survival at 6 months (%PFS6) overall and according to PD-L1 status.

Hypothesis: In advanced biliary tract cancer patients after failure of 1st-line chemotherapy, pembrolizumab plus induction GM-CSF will achieve proportion with PFS at 6 months of 40% (H_1), a meaningful proportion compared to 20% (H_0) in historical controls treated with conventional 2nd line chemotherapy.

(5) **Objective:** Measure median duration of response (DOR), PFS, and OS in overall cohort and according to PD-L1 status.

Hypothesis: The median OS in overall cohort will be improved compared to historical control OS of approximately 6.7 months from start of treatment with 2nd line chemotherapy for advanced biliary cancer.[6]

3.3 Exploratory Objective(s)

(1) Describe clinical outcomes according to anatomic subtype of biliary tract cancer.

(2) Explore proportion PD-L1+ on tumor cells and tumor infiltrating immune cells (TIIC) in archival tumor samples according to anatomic subtype of biliary tract cancer.

(3) Measure proportions with CA19-9 decline ≥ 25% and ≥ 50% at best response from baseline overall and according to PD-L1 status.

(4) Characterize serial peripheral blood mononuclear cells (PBMC) (at baseline, on treatment, and at progression) for immune cell profiles by methods which may include multiparameter flow cytometry and/or Cytof, gene expression profiling, and T cell repertoire by T cell receptor sequencing.

(5) Characterize TIIC quantity and profile and T cell repertoire in archival pre-treatment tumor tissue.

(6) Explore for associations between ORR by RECIST 1.1 and irRC, PFS, OS, and PD-L1 status with clinically-available tumor genotyping results including common mutations, MSI/MMR status, and TMB.

(7) Measure Re-induction (r) PFS (rPFS and rPFS6), safety, response rate (rRR), and CA 19-9 response for any patients who undergo re-induction with GM-CSF for progression after response or stabilization post first induction.

(8) Measure Second Course (s) PFS (sPFS and sPFS6), safety, response rate (sRR), and CA 19-9 response for any patients who receive Second Course of treatment with pembrolizumab for progression post discontinuation.

3.4 Additional Exploratory Objectives in Expansion Biopsy Cohort Only:

(1) Measure proportions PD-L1+ in tumor cells and TIICs in pre-treatment archival samples and in research biopsy samples 1) on pembrolizumab monotherapy and 2) in combination with GM-CSF.

(2) Quantify total tumor infiltrating immune cells (TIICs) in pre-treatment archival samples and in research biopsy samples 1) on pembrolizumab monotherapy and 2) in combination with GM-CSF.

(3) Characterize immune cell profiles in pre-treatment archival samples and in research biopsy samples 1) on pembrolizumab monotherapy and 2) in combination with GM-CSF

4.0 BACKGROUND & RATIONALE

4.1 Background on Indication

Cancers of the biliary tract are a family of epithelial cancers which include intra- and extrahepatic cholangiocarcinoma (CCA) and gall bladder carcinoma (GBC). Biliary cancers represent the second most common primary cancer of the liver after hepatocellular carcinoma (HCC) and their incidence, particularly for intrahepatic CCA, has risen significantly over the past decade.[7] Though the risk factors for biliary cancers are not well understood, conditions associated with chronic inflammation including hepatitis B virus (HBV) or hepatitis C virus (HCV), chronic cholangitis, or a history of liver fluke infection are associated with higher rates of CCA.[7,8]

In patients with advanced biliary cancers including CCA and gall bladder adenocarcinoma not amenable to resection, the "Advanced Biliary Cancer-02" (ABC-02) trial established the combination of gemcitabine plus cisplatin as the global standard for 1st-line therapy, showing significantly improved survival compared to gemcitabine alone.[9] Though the ABC-02 regimen achieved significant survival benefit, overall outcomes remain grim, with median overall survival of 11.7 months for patients treated with the combination of gemcitabine plus cisplatin compared to 8.1 months for patients treated with gemcitabine alone.[9]

There is no standard 2nd-line chemotherapy for advanced biliary cancers, though 5-fluorouracil-based regimens are commonly used.[2] A retrospective study of 2nd line therapy with the combination of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) after 1st-line gemcitabine plus oxaliplatin among 34 patients with advanced cholangiocarcinoma treated at a single-center in France between 2005-2013 reported median 2nd-line PFS of 2.9 months.[4] Another retrospective analysis of outcomes from 603 patients treated with 1st-line gemcitabine plus platinum across 17 centers in France between 2002-2013 showed that 32% of patients received 2nd-line chemotherapy

after progression on 1st-line therapies.[2] For those who received 2nd-line chemotherapy, the median PFS was 3.2 months and median OS was 6.7 months in the 2nd-line setting, without significant differences by regimen. The ORR was 12%. A retrospective registry analysis of 198 advanced biliary tract cancer patients treated with 2nd line chemotherapy at UCSF, Memorial Sloan Kettering Cancer Center, and Vanderbilt University Cancer Center after failure of 1st-line gemcitabine plus platinum regimens showed median time on treatment of only 2.2 months, supporting %PFS6 as a meaningful endpoint.[10]

There is an urgent need for more effective treatments for this grim family of cancers, across lines of therapy but particularly post failure of standard 1st line therapy, after which there are no established treatments.

4.2 Background on Compounds

Pembrolizumab and GM-CSF are both approved by the United States Food and Drug Administration (FDA) for multiple indications. Please refer to the Investigator's Brochures (IB) and approved FDA labeling for additional detailed background information on MK-3475 and GM-CSF.

4.2.1 Pharmaceutical and Therapeutic Background on Pembrolizumab

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems 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, also known as an immune "checkpoint." 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). The structure of murine PD-1 has been resolved. 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. 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. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. 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. 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 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. 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. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

Nivolumab is another humanized IgG4 mAb inhibitor of ligand activation of the PD-1 receptor which is being studied in multiple tumor types, including hepatocellular carcinoma (HCC) associated with underlying viral hepatitis,[11] and has been approved in the United States for treatment of patients with metastatic melanoma or advanced squamous, non-small cell lung cancer.

4.2.2 Pharmaceutical and Therapeutic Background on GM-CSF (Sargramostim)

GM-CSF is a cytokine that regulates the survival, proliferation, differentiation, and function of granulocytes and macrophages. GM-CSF has also been demonstrated to enhance the functional activities of effector cells including dendritic cells (DC), neutrophils, and monocytes. Increased class II MHC expression on DC as a result of exposure to GM-CSF leads to increased antigen presentation to T cells, stimulating T cell responses. Additionally, increased co-stimulatory molecule expression on DC with GM-CSF enhances T cell response. In vitro, GM-CSF is among the principal adjuvants used for production of DC from monocytes. In a phase 1 study of neoadjuvant granulocyte colony stimulating factor (GM-CSF) before prostatectomy for localized prostate cancer, GM-CSF subcutaneously for 2-4 weeks resulted in CD8+ T cell recruitment to tumors, in addition to increases in circulating dendritic cells, CD4+ T cells, and proliferative CD8+ T cells.[12]

GM-CSF at a dose of 250 µg/m2 daily is approved in the United States to promote neutrophil recovery following induction chemotherapy for acute myelogenous leukemia and for myeloid reconstitution post autologous or allogeneic peripheral blood progenitor cell or bone marrow transplantation (see FDA package insert). The pleiotropic immunological effects described above also have resulted in the investigation of GM-CSF using various schedules and doses in multiple immunotherapeutic anti-tumor strategies. GM-CSF has shown single-agent anti-tumor activity in clinical trials in prostate and ovarian carcinomas.[13-15]

4.2.3 Preclinical and Clinical Trial Data for Pembrolizumab and GM-CSF

Please refer to the Investigator's Brochures for preclinical and clinical data on pembrolizumab and GM-CSF.

4.3 Rationale

This phase II study will examine the efficacy and safety of the novel combination of pembrolizumab plus induction GM-CSF in advanced biliary cancer patients with the hypotheses that the combination may increase proportion of patients with PFS6 compared to contemporary historical controls, with acceptable safety.

4.3.1 Rationale for the Trial and Selected Subject Population

Cancers associated with infectious etiologies[16-18] and cancers with chromosomal instability[19,20] have shown higher response rates to immune checkpoint inhibitors such as anti-PD-1 or anti-CTLA-4 monoclonal antibodies. Chronic infections and inflammatory conditions are well-established risk factors for biliary cancers.[7,8,21] Gene expression profiling has identified an inflammatory subclass of CCA, including a transcriptome signature unique to prior fluke infection.[22-25] Chromosomal instability and defects in DNA repair pathways, including a small subset of patients with microsatellite instability, also occur in CCA.[22,25,26] These characteristics provide a theoretical rationale for the study of checkpoint inhibition in biliary cancers.

Early clinical data also provide a strong signal for efficacy of checkpoint inhibition in biliary cancer patients. As part of the KEYNOTE-028 (NCT02054806) phase Ib basket trial of pembrolizumab in 20 tumor types, a biliary cancer cohort of 23 patients with PD-L1+ tumors was enrolled (including 3 patients from UCSF). Approximately 40% of the biliary cancer patients screened for KEYNOTE-028 had tumors which were PD-L1+ as defined by at least 1% PD-L1 expression on a proprietary immunohistochemistry (IHC) assay.[5] The overall response rate for the biliary cancer cohort was approximately 17% in the KEYNOTE-028 trial and was notable for several patients with profound and prolonged responses, some of which remain ongoing. One example is a UCSF patient with metastatic intrahepatic CCA and rapid progression on 1st-line gemcitabine plus cisplatin therapy who experienced a confirmed PR on KEYNOTE-028, with RECIST 1.1 decrease by approximately 14% after 2 months, 23% after 4 months, and eventually achieving complete response (CR) which remains ongoing now over 36 months since enrollment on KEYNOTE-028 and approximately 16 months since discontinuation of pembrolizumab after 2 years of treatment per protocol (confidential, unpublished data from RKK). Multiple dermal and muscle metastases including a cardiac intraventricular septum metastasis have decreased in size and/or become clinically and radiographically occult on treatment, without any significant toxicity. Further supporting that biliary cancers may be susceptible to immune-mediated anti-cancer effects, a case of near complete response to mutation-specific (ERBB2IP) tumor infiltrating lymphocyte adoptive transfer[27] and spontaneous tumor regressions[28] have also been described in CCA patients.

This study permits inclusion of patients with underlying viral hepatitis, a common risk factor in biliary cancers. Though viral hepatitis was an exclusion factor for prior pembrolizumab studies, studies of other checkpoint inhibitors in HCC patients with viral hepatitis have not demonstrated an increased risk of hepatic decompensation or fulminant hepatitis. In a large phase I/II study in

HCC patients, nivolumab demonstrated a promising overall response rate of 23% with prolonged duration of responses, very mild toxicity, and no evidence of reactivation of viral hepatitis nor fulminant inflammatory responses in HCC cohorts defined by HBV, HCV, and nonviral etiologies.[11] The CTLA-4 inhibitor tremelimumab also showed a favorable PR rate of almost 18% without any events of hepatic decompensation in advanced HCC patients with underlying HCV cirrhosis (though transient and reversible grade 3 and 4 transaminitis was observed in approximately 45% of cases, without hepatic decompensation).[29]

4.3.2 Rationale for Pembrolizumab Dose and Schedule

An open-label phase I trial (Protocol 001) was conducted to evaluate the safety and clinical activity of single agent MK-3475. 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) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W was the highest dose tested in PN001. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as

assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

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 optimal duration of therapy with PD-1 inhibition in patients with radiographic response or stable disease after prolonged therapy is not known. Ongoing responses to pembrolizumab and nivolumab have been demonstrated, continuing in many cases for over a year post final dose of therapy. For this study, treatment with pembrolizumab will be continued until documented disease progression or other reason for study discontinuation (such as unacceptable toxicity or withdrawal of consent) until completing approximately 24 months of treatment (up to 35 doses) or after attaining confirmed CR (see Section 5.8.1) at which time treatment will be discontinued. In eligible cases of progression within 6 months after discontinuation of pembrolizumab after prior CR, PR, or SD with evidence for clinical benefit (see Section 7.1.5.2), retreatment with a "Second Course" of pembrolizumab may be considered on a case-by-case basis with approval from Study Chair and Merck (see Section 7.1.5.2). Second Course (s) PFS (sPFS and sPFS6), response rate (sRR), and CA 19-9 response will be described in these cases.

4.3.3 Rationale for GM-CSF in Combination with Pembrolizumab

In preclinical models, the addition of GM-CSF-secreting tumor vaccines to checkpoint blockade by a CTLA-4 inhibitor is synergistic.[30] The GM-CSF-secreting whole cell pancreas cancer vaccine GVAX has been shown to induce PD-1 and PD-LI expression in pancreatic tumors and/or in tumor-associated lymphoid cells or monocytes,[31] and the combination of anti-PD-1 therapy and GM-CSF-secreting tumor cell immunotherapy shows synergy in mouse models of colon cancer and melanoma.[32]

There are multiple clinical studies which demonstrate safety and preliminary efficacy of GM-CSF in combination with CTLA-4 inhibition. In a phase I trial of patients (n=24) with advanced prostate cancer conducted at UCSF, addition of granulocyte macrophage colony stimulating factor (GM-CSF) to checkpoint inhibition by the anti-CTLA4 antibody, ipilimumab, resulted in prostate specific antigen (PSA) decline, along with expansion of tumor antigen-specific T cells, specific tumor antibody response (to NY-ESO-1 and TP53), and activation of effector T cells.[33] The correlative analyses for this study were conducted in the laboratory of Dr. Larry Fong at UCSF. Building from this data, a recent phase II randomized clinical trial examined the efficacy of the combination of ipilimumab 10 mg/kg IV every 21 days with fixed doses of GM-CSF (250 µg) administered subcutaneously (SC) daily on days 1-14 every 21 days, compared to ipilimumab alone, in 245 patients with advanced melanoma.[34] This study showed significantly improved OS

in patients treated with the combination (68.9% vs. 52.9% at 1 year, p=0.01), while rates of grade 3-5 adverse events were lower in the combination arm (44.9% vs. 58.3% for ipilimumab alone, p=0.04). In pancreatic cancer, a cancer closely related to biliary cancers both anatomically and biologically, a phase 1b study of the combination of ipilimumab and GM-CSF-secreting whole cell vaccine (GVAX) in 30 patients showed acceptable safety of the combination compared to ipilimumab alone, higher rates of CA 19-9 decline, and higher absolute 1-year OS rate of 27% in the combination arm, compared with 7% in the ipilimumab arm.[35]

To date, there are no published clinical data on the combination of PD-1 inhibition and GM-CSF or GVAX. A multicenter phase 2 trial of GVAX, nivolumab, and CRS207 (an attenuated listeria vaccine expressing the tumor antigen, mesothelin) is underway in advanced pancreatic cancer patients (NCT02243371).

Interim and ongoing analyses of safety and efficacy of Stage 1 and 2 of this study showed acceptable safety without any unexpected adverse events along with promising response rate as described below in Section 4.3.5.1, Rationale for Expansion Cohort.

4.3.4 Rationale for GM-CSF Induction Dose and Schedule

GM-CSF may enhance antigen presentation, in which case a priming dose of GM-CSF prior to checkpoint inhibitor administration could be sufficient to enhance T cell activation. Alternatively, GM-CSF may increase the numbers of Fc receptor bearing antigen-presenting cells to enhance the activation of T cells by providing a cellular scaffold for a checkpoint inhibitor. With this mechanism, GM-CSF may need to be administered simultaneously with a checkpoint inhibitor in order to potentiate T cells.

We hypothesize that any potential contribution of GM-CSF will be most important during a priming or "induction" phase of treatment. This study will examine the efficacy of a novel induction regimen of GM-CSF administered at a fixed dose of 250 μg SC once daily on days 1-14 every 21 days for 2 cycles (6 weeks), in combination with pembrolizumab at fixed dose of 200 mg IV every 21 days as above, based upon the observed efficacy of this GM-CSF dose and schedule in combination with ipilimumab in metastatic melanoma, and in similar combinations in prostate cancer and pancreatic cancer.[33-35]

For the initial Safety Cohort (Stage 1) of 9 patients, pembrolizumab was initiated as a single agent on Cycle 1, Day 1, and GM-CSF was administered days 1-14 in Cycles 2 and 3. A planned interim safety analysis showed that the incidence of ≥ Grade 3 adverse events adjudicated as at least possibly treatment-related to the combination of GM-CSF plus pembrolizumab met criteria to continue with study enrollment (see Section 8.5.1). Enrollment to Efficacy Cohort (Stage 2) was subsequently completed with 18 additional patients. In the Efficacy Cohort, GM-CSF was initiated concurrently with pembrolizumab starting Cycle 1, Day 1 for two induction cycles, based upon the rationale that priming by GM-CSF is optimized if administered in advance or concurrently with PD-1 inhibition.

Acknowledging that the optimal duration and schedule of GM-CSF induction is unknown, re-induction with GM-CSF for 2 additional cycles is allowed in patients who demonstrate CR, PR, or prolonged SD with evidence of clinical benefit after the Induction Phase and within 12 months from enrollment, but who subsequently progress on single-agent pembrolizumab between

approximately 6-12 months (corresponding to Cycle 8-16) after enrollment (after the primary endpoint of PFS6 has been ascertained for that patient) (see Section 7.1.5.1). Repeat GM-CSF induction requires approval on a case-by-case basis from the Study Chair. Re-induction (r) PFS (rPFS and rPFS6) and response rate (rRR) will be described in these cases.

If ≥5 patients (approx. 20%) undergo GM-CSF re-induction and demonstrate restored CR or PR within 6 months after re-induction, the study team will consider whether to amend the protocol to allow for prolonged GM-CSF treatment or serial re-induction depending on the observed outcomes.

4.3.5 Rationale for Expansion Cohort

The Safety and Efficacy Cohorts (Stages 1 and 2) of this study completed enrollment as of 18-SEP-2017. After completion of accrual and follow up to the Safety Cohort (n=9), the UCSF Data and Safety Monitoring Committee (DSMC) conducted planned safety and efficacy analyses and determined that the target safety and efficacy thresholds were reached, enabling continuation of study enrollment to the Efficacy Cohort (Stage 2) (n=18 additional patients). The Safety Cohort interim safety analysis did not identify any unexpected toxicity of the combination. Related grade 3-4 toxicity occurred in 2/9 (22%): 1 event grade 4 hyperglycemia/ketoacidosis, 1 event grade 3 alkaline phosphatase. An additional grade 2 serious adverse event (SAE) of grade 2 hyperthyroidism with ophthalmopathy resolved after a course of prednisone. The interim efficacy analysis indicated PFS6 in 4/9 (44%), along with 2 partial responses (PR), 1 confirmed and 1 preceded by prolonged minor regression and achievement of PFS6. Minor regression and prolonged CA 19-9 decline >50% occurred in 2 additional Safety Cohort patients, both of whom achieved PFS6 and one who remains on treatment as of 18-SEP-2017 now with prolonged stable disease over 1.5 years, sustained CA 19-9 tumor marker decline >50% from baseline, and resolution of prior abdominal pain and anorexia since starting treatment.

As of 18-SEP-2017, the Efficacy Cohort (Stage 2) has completed enrollment with an additional 18 patients. Ongoing safety analyses are consistent with the known safety profile of pembrolizumab, without any unexpected events. Preliminary ORR results show 3 additional cases with unconfirmed + confirmed PR out of 13 evaluable cases, as well as another case with prolonged minor regression, resolution of pain, and > 50% CA 19-9 decline ongoing over 12 months since start of treatment. PFS6 results are not yet mature in this cohort.

Based upon the promising preliminary ORR (5/21 evaluable cases, 23.8%) and additional durable clinical responses observed in a meaningful subset of patients enrolled to Stages 1 and 2 of the study coupled with acceptable safety, the protocol will be amended to enroll an additional Expansion Cohort (n=15) in order to improve confidence on ORR and PFS endpoints as well as to obtain additional biospecimens for correlative analyses.

4.3.5.1 Rationale for Expansion Cohort Schedule and Biopsies

An important exploratory objective of the Expansion Cohort is to obtain paired biopsy samples from patients while on treatment with pembrolizumab monotherapy and in combination with GM-CSF, in addition to archival pre-treatment samples. Correlative analyses of tumor and TIIC PD-L1 expression, TIIC profiles, and PBMC profiles will explore for changes associated with

pembrolizumab alone and with addition of GM-CSF to better understand the differential contributions of each study drug to the observed clinical and radiographic responses in this study.

To enable comparisons of pembrolizumab monotherapy and in combination with GM-CSF, the schedule for the Expansion Cohort will be the same as the Safety Cohort, starting with 1 cycle of pembrolizumab monotherapy before adding induction GM-CSF during Cycles 2 and 3. The observed safety and efficacy of the Safety Cohort and Efficacy Cohort are similar, though limited by small sample sizes, supporting the choice of the Safety Cohort schedule for the Expansion Cohort. Biopsies will be planned during Week 3 of pembrolizumab monotherapy and Week 9 after addition of GM-CSF and after first restaging imaging has been obtained. PMBC profiles will be compared between the Safety and Expansion Cohorts (expected n=23) and the Efficacy Cohort (n=18), enabling further characterization of the impact of GM-CSF on immune cell profiles in a larger group of subjects.

4.3.6 Rationale for Endpoints

4.3.6.1 Primary Efficacy Endpoint: Overall Response Rate (ORR)

Based upon results from Stages 1 and 2 indicating a promising proportion of patients with durable radiographic and clinical responses, the primary endpoint for this study will be changed to overall response rate (ORR) by locally-assessed RECIST 1.1,[1] previously a key secondary endpoint, and %PFS6 will be changed to a key secondary endpoint. In advanced biliary cancer patients treated with standard 2nd-line chemotherapies, the historical response rate is approximately 10% with short duration of response,[2,4] and there is no standard therapy approved by the FDA in this context owing to limited efficacy. In unselected advanced biliary cancer patients treated with pembrolizumab monotherapy in KEYNOTE-158, the response rate has not yet been reported. A target ORR of 20% (H_1) on treatment with pembrolizumab plus induction GM-CSF would represent a meaningful improvement in this population, with H_0 5% as null hypothesis in the absence of any established effective standard 2nd line therapy in advanced biliary cancers.

4.3.6.2 Secondary Efficacy Endpoints

Proportion with PFS at 6 months (%PFS6) %PFS6 will be a key secondary endpoint for the overall study. In advanced biliary cancers treated with standard ≥ 2nd line systemic chemotherapies, retrospective studies report median PFS of only approximately 2 to 3 months (corresponding to %PFS6 of approximately 20% (H_0) assuming normal distribution).[2,4,10] A target %PFS6 of 40% (H_1) on treatment with pembrolizumab plus induction GM-CSF would represent a clinically meaningful improvement. Locally-assessed RECIST 1.1[1] will be used to determine progression.

Overall survival will be measured as another key secondary endpoint with the hypothesis that the median overall survival will be increased compared to a historical control median OS of 6.7 months from start of standard second line chemotherapy for advanced biliary cancers.[6]

An additional secondary efficacy endpoint is DOR, defined as time from first RECIST 1.1 response to disease progression in subjects who achieve a PR or better, as a clinically-relevant measure of efficacy. The duration of response or disease stabilization with 2nd line conventional chemotherapy in biliary tract cancers is very short, with median PFS only approximately 2-3

months on standard 2nd line therapies, and the majority of objective responses transient, lasting less than 6 months.[2,37]

Re-induction and Second Course efficacy endpoints will also be described.

4.3.6.3 Safety Endpoints

Safety is a key secondary endpoint for this novel combination. The combination of GM-CSF plus ipilimumab showed an improved toxicity profile compared to ipilimumab alone with significantly lower rates of treatment-related grade 3-5 adverse events (44.9% versus 58.3%, p=0.04),[34] but the safety of pembrolizumab in combination with induction GM-CSF has not been studied in humans. The interim safety analysis after 9 patients in the Safety Cohort completed 3 cycles of therapy (1 cycle of pembrolizumab followed by 2 cycles with GM-CSF induction plus pembrolizumab, for total of 9 weeks in the Safety Cohort) or been removed for related toxicity events showed acceptable safety to continue enrollment to the Efficacy Cohort (see Section 4.3.5). The interim safety analysis showed that related ≥ Grade 3 toxicity rate during the first 3 cycles did not exceed 50%, a target set based upon the safety profile of standard chemotherapy in biliary tract cancers, and based upon the reported rate of related Grade 3-5 toxicity of approximately 45% for the combination of ipilimumab plus GM-CSF in advanced melanoma.[9,34] The all-cause Grade 3 or 4 toxicity rate was approximately 70% in advanced biliary cancer patients treated with combination of standard 1st line chemotherapy with gemcitabine plus cisplatin in the ABC-02 trial,[9] while the rate of Grade 3 or 4 toxicity was reported as 32% for 2nd line chemotherapy (predominantly 5-fluorouracil-based combinations) in a multicenter, retrospective AGEO analysis.[6]

Re-induction and Second Course safety will also be described at completion of study.

4.3.6.4 Biomarker Research

4.3.6.4.1 Tumor and TIIC PD-L1 Expression by Immunohistochemistry (IHC)

Tumor and/or TIIC PD-L1 expression by IHC are associated with an increased likelihood of response to immune checkpoint inhibition with PD-1 inhibitors in some cancer types.[38] A pooled analysis of 20 trials including 1475 patients with melanoma, non-small cell lung cancer (NSCLC), and genitourinary cancer showed a significant interaction between PD-L1 expression and response overall, with overall RR 34.1% vs. 19.9% (p<0.0001).[38] Response rates were significantly higher in PD-L1+ melanoma and NSCLC but no significant difference in response rate was observed according to PD-L1 status for genitourinary cancers, and a significant proportion of patients with PD-L1-negative tumors achieved tumor response to PD-1 inhibition across tumor types.

It is not known whether tumor PD-L1 expression is a predictive biomarker for response in biliary cancers, as the KEYNOTE-028 biliary cohort required PD-L1 expression for eligibility[5] and the unselected KEYNOTE-158 biliary cohort results have not been reported. Intra-tumoral spatial and temporal heterogeneity in PD-L1 expression may also confound interpretation of tumor PD-L1 expression in archival pre-treatment samples which, in some cases, may have been harvested long before start of treatment.

Priming by an induction course of GM-CSF could also induce expression of PD-L1 in tumors or in TIIC such as tumor-associated lymphoid cells or monocytes, as has been demonstrated with administration of GVAX in pancreatic tumors.[31]

Based upon these findings which suggest that pre-treatment tumor PD-L1 expression may not be essential for response to treatment with the combination of pembrolizumab plus induction GM-CSF, tumor PD-L1 expression by IHC is not required as an integral biomarker for eligibility but will be tested as an integrated biomarker and secondary objective. Archival tumor biopsy or resection samples will be accessioned and tested centrally in batch at end of study for PD-L1 expression using an approved IHC assay (QualTek Laboratories). It is expected that the majority of samples will have been obtained pre-treatment. Treatment history at time of tumor sampling for each case will be documented in case report forms (CRFs), and an exploratory analysis may be conducted to compare proportion with PD-L1 expression based upon whether sample was obtained pre-treatment or after treatment with prior chemotherapy. An exploratory analysis will also be performed to compare tumor PD-L1 status in primary versus metastatic sites and according to anatomic location of the primary biliary cancer (e.g., intrahepatic CCA, extrahepatic CCA, GBC) or the metastatic site (e.g., liver vs. non-liver).

Paired primary and metastatic site tumor samples from the same patient will be tested and described when available. On-treatment or post-treatment tumor samples will also be analyzed if available in cases for which tumor resection or biopsy is required for clinical care (e.g. palliative metastatectomy, biopsy of an equivocal lesion to confirm progression, or if fiducial placement is required for palliative radiotherapy). PD-L1 expression will also be measured in on-treatment tumor biopsy samples obtained on pembrolizumab therapy and on combination therapy in patients enrolled to the Expansion Cohort.

4.3.6.4.2 Peripheral Blood Mononuclear Cell (PBMC) Immune Cell Subsets, TCR Clonotype Frequency and Diversity, and Other Analyses

Research blood samples will be collected from all patients at baseline, at multiple time points during treatment, and at progression (see Section 6.0 – Study Flow Chart). Whole blood will be processed into PBMC and cryopreserved at the UCSF Immune Monitoring Core for future analyses in batch at completion of study, pending funding and if warranted based upon clinical outcomes.

PBMC samples may be used to characterize immune cell subsets and T cell receptor (TCR) sequencing. . Other analyses including immune cell gene expression profiling may be performed depending on adequacy of samples available, funding, and evolving biomarker data from other immune checkpoint inhibitor studies. Dr. Fong's laboratory has demonstrated that treatment with the combination of CTLA-4 blockade plus GM-CSF results in expansion of activated effector CD8+ T cells as well as expansion of tumor antigen-specific T cells in patients with advanced prostate cancer.[33,39] Dr. Fong's laboratory and collaborators also have shown that checkpoint blockade by treatment with CTLA-4 inhibition in patients with metastatic prostate cancer and melanoma can increase T cell clonotype repertoire and diversity.[33,40] Circulating immune cell subsets will be measured using flow cytometry and Cytof as has been previously described.[33,39] The frequency of individual clonotypes, and the diversity of overall clonotype repertoire, will be measured by next-generation sequencing.[40] Baseline and changes on treatment in PBMC immune

cell subsets, TCR clonotype frequency and diversity, and gene expression profiles may be examined for relationship to clinical outcomes including PFS, RR, DOR, OS, and CA 19-9 response.

In the initial Safety Cohort (n=9) and the Expansion Cohort (n=15), PBMC samples for TCR analyses are collected before and after pembrolizumab alone in Cycle 1, followed by after the combination of pembrolizumab plus GM-CSF in Cycles 2 and 3. In the Efficacy Cohort (n=18), PBMC samples are collected before and after start of combination pembrolizumab plus induction GM-CSF, then on pembrolizumab monotherapy after completion of 2 cycles of GM-CSF. The variation in schedules of GM-CSF administration will enable intra-patient and inter-patient comparisons of immune cell profiles, TCR clonotype frequency and diversity, and other analyses pre-treatment, after pembrolizumab alone, and after the combination of pembrolizumab plus GM-CSF, as well as inter-patient comparisons between pembrolizumab and the combination of pembrolizumab plus GM-CSF after the first cycle, to better understand the relative impact of pembrolizumab alone and in combination with GM-CSF in this non-randomized study.

4.3.6.4.3 Tumor Infiltrating Immune Cell (TIIC) Numbers and Profiles Pre-Treatment and On-Treatment

Preexisting tumor immune infiltration is associated with increased likelihood of tumor response to checkpoint inhibition.[41,42] This association between tumor immune infiltration and increased response to immunotherapy may be due to preexisting tumor-specific T cell clones within the tumor which have been primed by tumor antigens but attenuated by checkpoint signaling, which are then activated upon checkpoint inhibition.

To explore the impact of tumor immune infiltration in biliary cancers treated with the combination of pembrolizumab plus induction GM-CSF, archival pre-treatment tumor core biopsy or resection samples (primary and/or non-nodal metastatic site depending on availability) will be obtained when available. Pending funding and adequate sample size, the samples may be examined in batch for immune cell infiltrates (TIIC) and T cell subset composition in batch at study completion in the laboratory of Dr. Larry Fong at UCSF as has been previously described.[33,39,43] The presence of TIIC and immune cell subset composition will be explored for association with clinical outcomes including PFS, ORR, DOR, OS, and CA 19-9- response.

If available from a standard of care tissue sampling event, , such as in cases for which an on-treatment or post-treatment tumor resection or biopsy is required for clinical care (e.g. palliative metastatectomy/debulking, biopsy of an equivocal lesion, or if fiducial placement is required for palliative radiotherapy), paired archival on-treatment or post-treatment tumor samples will also be analyzed in comparison to the baseline/pre-treatment specimen.

In the Expansion Cohort, paired biopsies will be obtained on pembrolizumab and on pembrolizumab plus GM-CSF to ascertain the relative impact of pembrolizumab alone compared to pre-treatment archival sample, then the impact of addition of GM-CSF to pembrolizumab compared to pre-treatment and compared to pembrolizumab monotherapy. It is expected that GM-CSF effect will be apparent after 2 weeks of exposure based upon tumor tissue analyses showing increased tumor T cell infiltration in prostate cancer patients treated with GM-CSF prior to radical prostatectomy.[12]

In Expansion Cohort biopsy samples, TIIC studies will be performed in batch at conclusion of study, pending additional grant funding. TIIC in tumor tissue will be compared descriptively to paired PBMC from the same patient (Section 4.3.5.3.2).[33] TIIC will be quantified and individual immune cell subsets profiled by IHC and other methods in paired FFPE biopsy specimens including but not limited to: cytotoxic CD8+, helper CD4+FOXP3-, and regulatory CD4+FOXP3+ T cells. The proportion of activated T cells (defined using markers such as PD1+ and Ki67+) will also be analyzed, as will myeloid-derived suppressor cells (using markers such as M2 CD68/Arg-1, M1 CD68/iNOS). Other techniques such as laser capture microdissection may be used if needed to isolate tumor from microenvironment, pending funding and depending on standard IHC results.

In Expansion Cohort biopsy samples, tumor infiltrating T cell TCR clonotypes, gene expression profiles, and/or other analytes may also be analyzed by next generation sequencing and other methods, pending funding and adequate sample availability. If performed, these analyses will be performed on pre-treatment archival tumor samples if adequate material is available as well as from fresh frozen or FFPE core biopsy samples 1) on pembrolizumab monotherapy and 2) in combination with GM-CSF.

4.3.6.4.4 Tumor Genotype and Association with Response Outcomes, PD-L1 status, T-cell Infiltration, and TCR Repertoire

Higher tumor mutation burden (TMB) and genomic instability are associated with increased likelihood of response to pembrolizumab in non-small cell lung cancers.[19,20] It is thought that increased mutational burden overall, as well as certain specific mutations, may be immunogenic.

Multiple clinical trials are now available for genotype-defined populations in cholangiocarcinoma, including *FGFR2* fusions and *IDH1* or *IDH2* mutations.[44] It is expected that the majority of patients enrolled on this study will have had targeted tumor next generation tumor sequencing such as FoundationOne (http://foundationone.com) performed as standard of care prior to enrollment, based upon emerging evidence for targeted therapies in advanced biliary cancers.

For patients with available tumor sequencing results performed as part of clinical care, specific mutations, pathways, TMB, and presence of genomic instability-related mutations will be explored for association with clinical outcomes including PFS, RR, DOR, and OS. The tumor mutation profile and TMB will also be explored for association with PD-L1 status and presence of immune infiltrates, based upon emerging evidence that specific tumor mutations can impact T cell infiltration and activation.[19,45]

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial for All Cohorts

1. Histologically- or cytologically-diagnosed advanced or locally-advanced biliary cancer not eligible for resection or other curative therapies, including:

    a. Intrahepatic (peripheral) cholangiocarcinoma;

b. Extrahepatic cholangiocarcinoma including hilar/perihilar (Klatskin), middle, and distal locations;

c. Gallbladder carcinoma (GBC);

d. Mixed/combined hepatocellular-cholangiocarcinoma;

e. Ampullary carcinoma and pancreas ductal adenocarcinoma are NOT eligible.

2. Clinical and/or radiographic progression on ≥ 1 prior systemic treatment regimen with cytotoxic chemotherapy, targeted therapy, and/or investigational therapy for advanced biliary cancer. Cumulative toxicity or intolerability (such as progressive cytopenias, neuropathy, or asthenia on a 1st line regimen of gemcitabine plus cisplatin) requiring treatment discontinuation of ≥ 1 prior systemic treatment regimen is also sufficient for eligibility. There is no maximum eligible prior number of lines of therapy provided all eligibility criteria are met. Adjuvant chemotherapy including gemcitabine and/or fluoropyrimidine after prior surgical resection of CCA or GBC will be considered as 1 line of prior therapy if relapse/recurrence with incurable disease occurred within ≤ 6 months of last dose.

5.1.2 Subject Inclusion Criteria for All Cohorts

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.

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

3. Have a performance status of 0 or 1 on the ECOG Performance Scale.

4. Demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 28 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,000 /mcL
Platelets	≥60,000 / mcL (≥ 75,000/mcL in Expansion Cohort, see below)
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN

AST (SGOT) and ALT (SGPT)	≤ 5 X ULN
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

5. Patients with known hepatitis B or C virus (HBV or HCV) infection are eligible provided liver function parameters meet laboratory eligibility criteria in Table 1.

    a. Patients with active HBV infection must have monitoring of viral load and demonstrate adequate treatment with appropriate antiviral therapy according to institutional practice.

    b. Patients with active HCV infection must have monitoring of liver function tests and viral load if indicated according to institutional practice.

6. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

8. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

5.1.3 Additional Expansion Cohort Subject Inclusion Criteria

1. Presence of ≥ 1 target lesion measurable by RECIST 1.1[1] not planned for biopsy.

2. Presence of ≥ 1 tumor lesion accessible for paired on-treatment minimally-invasive percutaneous biopsies (CT, ultrasound or punch), as assessed by investigator and/or radiologist; this lesion may be included as a target or non-target lesion for RECIST 1.1.

3. Platelet count ≥ 75,000/mcL

4. No contraindication to tumor biopsy at time of study enrollment.

5. Consent for on-treatment paired biopsies.

5.1.4 Subject Exclusion Criteria for All Cohorts

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

1) Is currently participating and receiving study therapy or has participated and received study therapy in a study of an investigational agent, or used an investigational device within 4 weeks of the first dose of treatment.

2) Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy for purposes of immunosuppression or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3) Has a known history of active TB (Bacillus Tuberculosis).

4) Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

5) Has untreated active Hepatitis B (e.g., HBsAg reactive).

6) Has an active infection requiring systemic antibiotic therapy at time of enrollment.

    a) Treatment with antibiotic prophylaxis for indwelling biliary stent(s) or peri-procedural antibiotics for uncomplicated biliary stent exchanges is allowed and not an exclusion.

7) Hypersensitivity to pembrolizumab or any of its excipients.

8) Has received treatment with an anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

9) Has received treatment with chemotherapy, targeted small molecule therapy, or radiation therapy to non-liver sites within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent administered more than 2 weeks earlier.

    a) Subjects with ≤ Grade 2 neuropathy or alopecia are an exception to this criterion and may qualify for the study.

    b) If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

10) Has had prior chemoembolization, bland embolization, radioembolization, local ablative therapies, radiation to liver tumors, or major surgery such as liver resection within 4 weeks prior to study enrollment or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to intervention more than 4 weeks earlier.

11) Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

12) Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

13) Has active autoimmune disease that has required systemic treatment in the 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.

14) Has known history of or any evidence of active, non-infectious pneumonitis.

15) Has had prior organ or stem cell transplantation.

16) 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.

17) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

18) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

19) Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

    a) This criterion does not apply to eligibility for Second Course treatment.

20) Has received a live vaccine within 30 days of planned start of study therapy.

    a) Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

5.2.1 Dose Selection

The rationale for selection of doses and schedules to be used in this trial is provided in Section 4.0 – Background and Rationale. The treatment to be used in this trial is outlined below in Table 2. See Study Flow Chart (Section 6.0) for additional information on treatment schedule.

Table 2 Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Treatment Period[1]	Use
Pembrolizumab	200 mg	Once Q3 weeks	IV infusion over 30 minutes	Every 3 week cycle for up to 24 months or 35 cycles (see Section 5.8)	Experimental
GM-CSF	250 µg	Daily on days 1-14 Q3 weeks for 2 cycles	SC**	Two Induction Cycles: Cycles 2 and 3 in Safety Cohort (n=9) and Expansion Cohort (n=15); Cycles 1 and 2 in Efficacy Cohort	Experimental

Key: IV=intravenous; SC=subcutaneous. [1]A subset of patients may be eligible for Second Course pembrolizumab and/or re-induction with GM-CSF (see Section 7.1.5). *Cycle length is 21 days (Q3 weeks) with GM-CSF "induction" in Cycles 2-3 (Safety and Expansion Cohorts) or 1-2 (Efficacy Cohort). **Patients will be instructed on self-injection administration prior to first dose, with re-training each cycle or more often as needed.

5.2.2 Dose Modifications or Interruptions for Toxicity

Toxicity will be assessed according to the NCI CTCAE v4.0. Dose modifications, interruptions, and treatment discontinuation for one or both study drugs will be determined according to the system showing the greatest degree of toxicity and according to the treating investigator's assessment of toxicity attribution. Toxicity will be formally assessed at protocol-defined safety assessment time points well as by investigator review of weekly laboratory testing and, in the interim, by patient contact with the study team. General principles of toxicity management are listed below:

- Laboratory values should be rounded to one significant digit for grade determination according to standard rounding practice.
- Optimal supportive care should be provided for all clinically relevant toxicity.
    - See section 5.6 for guidance on supportive care/rescue medications for specific toxicities.
- Dose interruptions or delays in start of a cycle for any reason (toxicity or non-toxicity) during the Induction Phase (Cycles 1 and 2 in Efficacy Cohort, Cycles 2 and 3 in Safety and Expansion Cohorts) should be applied to both drugs together so that both drugs are restarted on Day 1 of each cycle.

- Doses of GM-CSF which are held during a cycle due to toxicity will not be re-administered.

- Doses of GM-CSF which are missed/skipped (e.g. due to logistical reasons, patient oversight, or other non-toxicity related factors) may be made up at end of cycle, daily for up to 3 doses. Missed/skipped doses >3 will not be re-administered.

- A patient will be removed from protocol therapy if pembrolizumab is permanently discontinued but may continue on pembrolizumab if GM-CSF is discontinued for toxicity before completing induction (2 cycles).

- For any toxicity (regardless of grade), despite optimal supportive care, that is felt by the treating investigator to represent a risk to the patient's safety, additional dose reduction, treatment delay, or treatment discontinuation is permitted at the discretion of the treating investigator.

5.2.2.1 Dose Modifications for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. As toxicity on pembrolizumab has not been shown to be dose related, dose reductions are not thought to ameliorate specific toxicities. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Pembrolizumab-Related Adverse Events

Toxicity	Hold Treatment For Grade		Timing for Restarting* Treatment	Discontinue Subject
Diarrhea/colitis	2-3		Hold until toxicity resolves to Grade 0-1	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4		Permanently discontinue	Permanently discontinue
AST, ALT, or increased bilirubin (despite optimal supportive care including biliary drainage if obstruction is present)	2^1-3^2		Hold until toxicity resolves to Grade 0-1 or baseline grade (if Grade 2 at baseline)[1]	If toxicity does not resolve within 12 weeks of last dose
	3^2-4		Permanently discontinue	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or hyperglycemia	T1DM or 3-4		Hold for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure; resume pembrolizumab when patients are clinically and metabolically stable	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hypophysitis	2-3		Hold until toxicity resolves to Grade 0-1	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4		Permanently discontinue	Permanently discontinue
Hyperthyroidism	3		Hold until toxicity resolves to Grade 0-1	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4		Permanently discontinue	Permanently discontinue
Hypothyroidism	2-4		Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted	Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted
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 AEs	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
Infusion reaction	3-4		Permanently discontinue	Permanently discontinue
Pneumonitis	2		Hold until toxicity resolves to Grade 0-1	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4		Permanently discontinue	Permanently discontinue
Renal failure or nephritis	2		Hold until toxicity resolves to Grade 0-1	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks

Toxicity	Hold Treatment For Grade	Timing for Restarting* Treatment	Discontinue Subject
	3-4	Permanently discontinue	Permanently discontinue
All other drug-related toxicity[3] attributed to pembrolizumab	3 or severe 2	Hold until toxicity resolves to Grade 0-1 or baseline grade if abnormal at baseline	If toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

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

* Dose interruptions or delays in start of a cycle for any reason (toxicity or non-toxicity) during Induction Phase (Cycles 1 and 2 in Efficacy Cohort (Part 2), Cycles 2 and 3 in Safety and Expansion Cohorts (Parts 1 and 3)) should be applied to both GM-CSF and pembrolizumab together so that both drugs are restarted on Day 1 of each cycle.

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, treatment is not required to be held for Grade 2 AST or ALT.

[2] For patients with baseline Grade 2 AST or ALT, Grade 3 AST or ALT does not automatically require treatment discontinuation. If AST or ALT increases by greater than or equal to 50% relative to baseline and is assessed as treatment-related (e.g. no evidence of interval tumor progression or biliary obstruction) and lasts for at least 1 week despite supportive care, then patients should be discontinued.

[3] Patients with intolerable or persistent Grade <3 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose. Patients with mild grade 3 toxicity (e.g. mild or asymptomatic rashes or asymptomatic laboratory abnormalities) may be continue on treatment with augmented supportive care and close monitoring at discretion of treating physician.

5.2.2.2 Dose Modifications for GM-CSF

GM-CSF can induce hematologic effects including variable increases in WBC and/or platelet counts, possibly leading to potential complications of excessive leukocytosis such as hyperviscosity, allergic reactions including anaphylaxis, fluid retention, and respiratory symptoms due to sequestration of granulocytes in pulmonary circulation. Monitoring of blood counts (CBC with differential) is recommended at least twice weekly during GM-CSF administration at standard doses. CBC with differential was checked twice weekly during GM-CSF induction cycles (Cycles 2 and 3) in Safety Cohort. As no increased leukocytosis was observed, weekly testing is performed in the Efficacy and Expansion Cohorts. Liver function and renal function should be monitored at least every 2 weeks on GM-CSF in patients at risk for renal or hepatic dysfunction. Body weight and hydration status should be carefully monitored during GM-CSF administration.

Table 4 Dose Modification Guidelines for GM-CSF-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting*,** Treatment	Discontinue Subject
Leukocytosis	WBC 50,000-100,000/mm^3 and/or ANC > 20,000/mm^3	Hold drug and recheck within 3-7 days; if ANC < 10,000 mm^3 and WBC < 50,000 mm^3 and asymptomatic, re-start with 50% dose reduction (125 µg SQ daily) to complete 14 days; maintain dose reduction for next cycle(s)	If WBC count does not decrease to < 50,000/mm^3 within 3 weeks or recurs >100,000/mm^3 despite 50% dose reduction
	≥ 3 (WBC >100,000/mm^3) and/or hyperviscosity syndrome or complication	Permanently discontinue	Permanently discontinue
Thrombocytosis	Platelet count >500,000/mm^3	Hold drug and recheck within 3-7 days; if platelet count < 500,000/mm^3 and asymptomatic, then re-start with 50% dose reduction (125 µg SQ daily) to complete 14 days; maintain dose reduction for next cycle(s)	If platelet count does not decrease to < 500,000/mm^3 within 3 weeks or recurs >500,000/mm^3 despite 50% dose reduction
	>1,000,000/mm^3 and/or hyperviscosity syndrome or complication	Permanently discontinue	Permanently discontinue
Allergic reactions	3-4	Permanently discontinue	Permanently discontinue
Edema/fluid retention despite optimal supportive care (e.g. elevation, diuretics)	Moderate or severe (e.g. Grade ≥ 2 if obscuring normal contours or interfering with self-care)	Hold until edema recovers to Grade 0-1 or baseline, then re-start with 50% dose reduction (125 µg SQ daily) to complete 14 days; maintain dose reduction for next cycle(s)	If moderate or severe edema does not recover to Grade 0-1 or baseline within 3 weeks or if recurs despite dose reduction
All other drug-related toxicity[3] attributed to GM-CSF	3 or severe 2	Hold until toxicity resolves to Grade 0-1 or baseline, then re-start with 50% dose reduction (125 µg SQ daily) to complete 14 days; maintain dose reduction for next cycle(s)	Toxicity does not recover to Grade 0-1 or baseline within 3 weeks of last dose
	4	Permanently discontinue	Permanently discontinue

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

* Dose interruptions or delays in start of a cycle for any reason (toxicity or non-toxicity) during Induction Phase (Cycles 1 and 2 in Efficacy Cohort (Part 2), Cycles 2 and 3 in Safety and Expansion Cohorts (Parts 1 and 3)) should be applied to both GM-CSF and pembrolizumab together so that both drugs are restarted on Day 1 of each cycle.

**Skipped or missed doses of GM-CSF during a cycle (e.g. due to logistical reasons, patient oversight, or other non-toxicity-related factors) may be made up at end of cycle daily up to 3 doses.

[3] Patients with intolerable or persistent Grade <3 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 3 weeks of the last dose.

5.2.2.3 Dose Interruptions or Delays for Reasons Other than Toxicity

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

5.2.3 Dose Preparation and Timing

GM-CSF and pembrolizumab doses will be prepared by Investigational Pharmacist according to FDA package insert instructions for each drug.

All trial treatments will be administered on an outpatient basis.

5.2.3.1 Timing of Pembrolizumab Administration

Pembrolizumab will be administered on Day 1 of each 21-day cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be adjusted up to 3 days before or after the scheduled Day 1 of each cycle due to administrative or other logistical reasons such as holidays/schedule conflicts.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion on Day 1 of each cycle, 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 approximately -5 minutes and +10 minutes is permitted (i.e., approximate infusion time is 30 minutes: -5 min/+10 min).

5.2.3.2 Timing of GM-CSF Administration

GM-CSF will be administered starting Day 1 of each induction cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0), then continued daily through Day 14 (Days 1-14 Q21 days, in Cycles 2 and 3 for the Safety Cohort (n=9) and Expansion Cohort (n=15). GM-CSF induction is administered in Cycles 1 and 2 in the Efficacy Cohort based upon acceptable safety in the Safety Cohort. Trial treatment may be adjusted up to 3 days before or after the scheduled Day 1 of each cycle due to administrative or other logistical reasons such as holidays/schedule conflicts.

GM-CSF 250 µg will be administered as a SC injection days 1-14 every 3 weeks during the Induction Phase (Cycles 1 and 2). Day 1 injection each cycle will be self-administered (after self-injection teaching by an infusion center RN or another qualified medical provider), after pembrolizumab infusion with additional self-injection training/re-training as needed at each GM-CSF time point. Subsequent injections will be self-administered by patient or family member/friend. Effort should be made to administer GM-CSF at approximately the same time each day (±3 hours from Day 1 dosing time).

Missed/skipped GM-CSF doses (e.g. due to logistical reasons, patient oversight, or other non-toxicity-related factors) may be made up at end of cycle daily up to 3 doses.

5.2.3.3 GM-CSF Patient Diary/Injection Record

Patient diaries will be used to record GM-CSF SC injection compliance, site, and any injection-related symptomatic toxicity (see Appendix 11.2) during induction cycles. The Clinical Research Coordinator (CRC) at each site will collect the completed diary at start of subsequent cycle.

5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, the investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

This is not a randomized trial.

5.4 Stratification

No stratification is planned.

5.5 Concomitant Medications/Vaccinations (Allowed and Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Study Chair and the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

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 case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response 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 and GM-CSF
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.
    - Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from a suspected immune-related AE (irAE) or as premedication for iodinated contrast if not amenable to MRI imaging instead of contrast CT. The use of physiologic/replacement doses of corticosteroids may be approved after consultation with the Study Chair.
- Antiviral therapy for active HCV is not allowed during protocol therapy unless approved by the Study Chair due to unknown potential for toxicity in combination.

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

The Exclusion Criteria section 5.1.3 describes other medications which 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 Supportive Care Guidelines for Pembrolizumab

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

If after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.2.1 for guidance on pembrolizumab dose modifications.

Suggested steroid regimens include:

- Systemic steroids equivalent to prednisone 1-2 mg/kg/day for severe immune-related toxicity requiring immunosuppressive therapy.
- Oral prednisone 0.5 mg/kg/day or other equivalent steroid regimen for mild-moderate immune-related toxicity requiring immunosuppressive therapy.
- Topical corticosteroids for mild-moderate dermatitis.
- Corticosteroid eye drops for ocular immune-related toxicity.
- Once symptoms resolve or return to Grade 1/baseline, initiate slow steroid taper over at least 4 weeks, with close monitoring.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

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

- **Diarrhea/colitis**: Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

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

- **Hypophysitis**:

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

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

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

- **Hepatitis attributed to immune toxicity**: Assessment should be based upon greatest increase in AST, ALT, or total bilirubin. Elevations in alkaline phosphatase alone should not be used to determine treatment-related toxicity grade or supportive care interventions since this marker is commonly elevated in biliary tract cancers and may be an index of biliary obstruction independent of treatment-related toxicity. Evaluation for viral reactivation and antiviral therapy for HBV or HCV should be considered if any evidence hepatotoxicity according to standard institutional practice in HBV/HCV patients receiving anti-cancer therapies

  - For **Grade 2** events (if normal or Grade 1 at baseline), monitor liver function tests more frequently until returned to baseline values (consider weekly) to ensure not progressive.

- For **Grade 4** events and **Grade 3** if increased by greater than or equal to 50% relative to baseline and is assessed as treatment-related (e.g. no evidence of interval tumor progression or biliary obstruction), treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 0-1 or baseline, a steroid taper should be started and continued over no less than 4 weeks.

- **Renal failure or Nephritis**:
  - For **Grade 2** events assessed as treatment-related and despite best supportive care (e.g. oral or IV hydration), treat with oral or systemic corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When creatinine value improves to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Other immune-mediated adverse reactions, including ocular manifestations**
  - Permanently discontinue pembrolizumab if clinically significant or severe immune-mediated adverse reactions (see 5.2.2.1).
  - Initiate systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent for severe immune-mediated adverse reactions.
  - Administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

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

Table 4 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

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 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
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.

5.6.2 Supportive Care for GM-CSF

- **Edema:** Diuretics, dietary sodium restriction, limb elevation, compression stockings, and other standard supportive care interventions may be implemented according to standard of care at investigator discretion.

- **Injection site reactions:** Patients and/or caregivers will receive subcutaneous injection teaching each induction cycle, including instructions to avoid administering near waist or navel and to rotate injection sites.

- See Section 5.2.2.2 for guidance on dose modifications for toxicity attributed to GM-CSF.

5.6.3 General Supportive Care for Biliary Tract Cancer

- Antibiotics for cholangitis or stent/biliary drain prophylaxis: Antibiotics with biliary tract coverage may be administered at discretion of treating investigator for symptoms of cholangitis or prophylactically (such as before/after elective biliary drain or stent exchange or replacement).
- Antiviral therapy: Subjects with active HBV infection should receive appropriate antiviral therapy and close monitoring for reactivation according to institutional practice in patients

receiving potentially immunosuppressive anti-cancer therapies. Evaluation for viral reactivation and antiviral therapy for HBV or HCV should be considered if any evidence hepatotoxicity according to standard institutional practice in HBV/HCV patients receiving anti-cancer therapies. Antiviral therapy for HCV is not permitted during protocol therapy unless approved by Study Chair.

- Diuretics: Diuretics such as furosemide and spironolactone may be used for the management of edema or ascites at the discretion of the treating physician. Severe episodes of edema, such as congestive heart failure, pleural effusion, ascites, pericardial effusion, or pulmonary edema may require additional measures such as percutaneous drainage, hospitalization, and/or discontinuation of protocol therapy.
- Electrolyte supplementation: Electrolytes should be repleted according to standard institutional protocols.
- Esophageal varices management: All patients with history of esophageal varices should be treated with optimal supportive care for this condition such as proton pump inhibitor and propranolol or other non-selective beta-blocker.
- Palliative radiation: Patients who require palliative radiation for worsening symptoms related to underlying malignancy must be removed from study. This may be considered a clinical progression event depending on judgment of treating investigator and clinical context.
- Supplements and alternative therapy: Treatment with non-conventional therapies (e.g., herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with treatment and the study endpoints and there is no known potential for drug interactions, according to assessment by the treating investigator and/or Investigational Pharmacist or designee.
- Topical agents: Topical steroid creams may be used to manage pruritic skin toxicity at the discretion of the treating physician. Non-alcohol-based topical emollients and non-alcohol-based moisturizers may be used for dry skin.
- Treatment of hypersensitivity or allergic reactions: Subjects who experience study drug-associated temperature elevations ≥ 38.5°C or other hypersensitivity symptoms may be treated symptomatically with acetaminophen, steroids, diphenhydramine, meperidine, or other medications at the discretion of the treating investigator.

In addition, optimal standard of care therapies and best supportive care should be provided for other toxicity, comorbidity, or complications of biliary obstruction or liver disease which occur during protocol therapy, according to institutional standards.

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. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods, or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from date of consent throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

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 Phase defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Study Chair and to Merck. 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 treatment with pembrolizumab, the subject will immediately be removed from the study. 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 Study Chair and to Merck without delay and within 24 business hours to the Study Chair and within 2 business days from investigator awareness, to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Study Chair. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Study Chair and to Merck and followed as described above and in Section 7.2.2.

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

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Study Chair if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.5 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Radiographic disease progression by RECIST 1.1.

  Note: A subject may be granted an exception by Study Chair to continue on treatment until another scan time point (approximately 8 more weeks) if scans within first 6 months demonstrate radiographic progression to account for possible delayed responses on immunotherapy,[46] provided the patient is clinically stable or clinically improved (see Section 8.3.1).

  Note: A subject with progression occurring between approximately 6-12 months (Cycles 8-16) on protocol therapy may be eligible for re-induction with GM-CSF if progression occurs after a documented response to prior induction (see Section 7.1.5.1).
- Unacceptable adverse experiences as described in Section 5.2.1.2.
- 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.
- The subject is lost to follow-up.
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab at 24 months may be eligible for up to one year of additional study treatment as Second Course treatment if they progress within 6 months after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.
- Administrative reasons

The End of Treatment and Follow-Up Phase procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of 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 as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have scheduled post-treatment follow-up monitoring for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by chart review, clinic visits, or telephone contact for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with Second Course pembrolizumab at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the original entry criteria in Section 5.1 (except for exclusion 19 which is not applicable to Second Course eligibility) and the trial remains open to enrollment. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details on Second Course are provided in Section 7.1.5.2.

5.9 Subject Replacement Strategy

See Section 8.6 for definition of analysis populations for safety and efficacy. Approximately 10% over-enrollment is planned to account for possible non-evaluability.

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 (see Section 8.2.1 – Interim Safety Analysis and Stopping Rules).

4. Plans to modify or discontinue the development of the study drug. In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 STUDY FLOW CHARTS

6.1 Safety Cohort Flow Chart (Safety Population)

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**											**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment. then every 12 weeks ±28 days	Every 12 weeks ±28 days
Administrative Procedures															
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration[a]		X			X			X	X	X	X	X			
GM-CSF Administration Days 1-14[a,m]					D1-14[m]										
GM-CSF Patient Diary/Injection Record[c,m] (Appendix 11.2)					X[m]			X[m]							
Post-Study Anticancer Therapy Status													X	X	X
Survival Status													X	X	X
Clinical Procedures/Assessments															
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X[d]		
Full Physical Examination	X	X	X	X[o]	X	X	X[o]	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X[o]	X	X	X[o]	X	X	X	X	X	X		
ECOG Performance Status (Appendix 11.4)	X	X			X			X	X	X	X	X	X		
Child Pugh Score (Appendix 11.5)	X														

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**											**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment. then every 12 weeks ±28 days	Every 12 weeks ±28 days
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum β-HCG[e]	X	X			X			X	X	X	X	X			
PT/INR	X	X	X	X	X	X	X	X	X	X	X	X	X		
aPTT	X	X	X	X	X	X	X	X	X	X					
CBC with Differential[n]	X	X	X	X	X[n]	X[n]	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[g]	X	Every 8 weeks from C1D1 ± 14 days											X		
T3, FT4 and TSH[g]	X	Every 8 weeks from C1D1 ± 14 days											X		
Efficacy Measurements															
Tumor Imaging[h]	X	Every 8 weeks from C1D1 (± 7 days for first 6 months of treatment, ±14 days after 6 months until end of treatment)[h]												X[h]	
CA 19-9 Tumor Marker[i]	X	Every 8 weeks from C1D1 ± 14 days											X[i]		
Archival Tissue Collection/Correlative Studies Blood (Appendix 11.6)															
Archival Tumor Tissue Collection[j]	X[j]												X[j]	X[j]	
PBMC Blood Collection[k]	X	X	X	X[o]	X			Every 8 weeks ± 14 days through C9D1					X	X[k]	

a	Cycle length is 21 days, ±3 days. Pembrolizumab is administered IV Q21 days ±3 up to 24 months or 35 cycles (Sections 5.2, 5.8, 7.1.5.2). GM-CSF is administered days 1-14 Q21 days, ±3 days for induction Cycles 2 and 3 only with option for re-induction in cases meeting criteria in Section 7.1.5.1; Day 1 and subsequent doses are self-administered after self-injection teaching by infusion center RN or another qualified medical provider.
b	A 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. Though the Safety Follow-Up Visit and assessments should be performed at UCSF when possible, safety follow up assessments (including administrative, clinical, laboratory, and efficacy assessments) may be extracted from clinical data obtained from a subject's local physician's office visit, during a hospitalization, and/or during any other standard

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles						
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment. then every 12 weeks ±28 days	Every 12 weeks ±28 days

	medical encounter, if travel to UCSF would confer hardship due to distance and/or due to initiation of new therapy. Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 8 weeks (56 ± 28 days) by radiographic imaging to monitor disease status. After 1 year, the Follow Up visits and imaging timepoints will occur approximately every 12 weeks (± 28 days). After 2 years, patients will be followed according to Survival Follow-Up phase.
c	GM-CSF Patient Diary/Injection Record and instructions will be provided to each patient on Day 1 of Cycles 2 and 3 and any subsequent re-induction cycles. The completed diaries will be collected on Day 1 of Cycles 3 and 4 and after any re-induction cycles. See Appendix 11.2.
d	Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to baseline or Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment, whichever occurs first, will also be followed and recorded.
e	Perform on women of childbearing potential only at screening and prior to each pembrolizumab infusion. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
f	See Section 7.1.3 and Table 5 for specific laboratory tests required as part of comprehensive metabolic panel.
g	Or more often if clinically indicated.
h	Cross-sectional imaging with CT or MRI abdomen plus pelvis (including triphasic/multiphase liver preferred) and CT chest with/ or without contrast is required at screening, every 8 weeks (±7 days) during treatment for first 6 months then every 8 weeks (±14 days days) after 6 months on treatment until end of treatment. In subjects without evidence progression at treatment discontinuation, scans should be every 8 weeks ±28 days for up to 1 year during Follow-Up Phase, then every 12 weeks ± 28 days (or more often if clinically indicated). Imaging may be performed more often if clinically indicated to evaluate for progression or toxicity. Imaging should be performed as close to time of Safety Follow-Up visit as possible in cases of discontinuation after confirmed response or completion of 24 months of treatment.
i	CA 19-9 should be checked at same time points as imaging. Note that CA 19-9 may be elevated due to biliary obstruction/stent occlusion independent of progression. CA 19-9 testing may be performed more often if clinically indicated to evaluate for progression.
j	Archival tumor samples (FFPE block when available and/or at least 10 unstained slides of approximately 10 µm thickness plus a paired H&E slide) should be obtained from prior tumor sampling/diagnostic procedure(s) such as prior resection, core biopsy, or cytology/cell button when available. FFPE block or slides should also be obtained from any subsequent tumor sampling which occurs during or after protocol therapy (such as repeat biopsy to confirm progression or palliative metastatectomy surgery). See Appendix 11.6.
k	Blood samples will be obtained in all patients for PBMC immune profiling at Screening, on Day 1, 8, and 15 of Cycle 1, on Cycle 2 Day 1, Cycle 3 Day 1, then Q8 weeks ± 14 days during subsequent cycles through C9D1. Screening sample may be used for Cycle 1, Day 1 if obtained within 3 days. Samples will be obtained at time of Safety Follow-Up visit (PBMC collection at this time-point may be omitted or delayed until next UCSF clinic visit if patient has Safety Follow-Up Visit assessments performed outside of UCSF), and at time of progression if patient discontinued treatment without progression and is identified with progression during Follow-Up. See Appendix 11.6.

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles						
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment. then every 12 weeks ±28 days	Every 12 weeks ±28 days

m	Re-induction GM-CSF will be allowed case-by-case according to Section 7.1.5.1, between approximately months 6-12 or Cycles 8-16 on protocol therapy. In these cases, GM-CSF will be re-administered D1-14 for 2 cycles (which will be named "R" along with original cycle number, e.g. RC8 and RC9) along with GM-CSF Patient Diary/Injection Record (Appendix 11.2) which will be provided along with instructions before re-induction and collected on D1 of each cycle following the 2 re-induction cycles.
n	CBCD must be checked day 1, day 5, day 8, and day 12 (±3 days) during Cycles 2 and 3 (induction GM-CSF) of Safety Cohort.
o	On Day 15 of Cycles 1, 2, and 3, the clinic visit for physical examination, vitals, and weight check may be omitted provided there are no clinically-significant AE requiring follow up at Day 8 visit at discretion of treating investigator. If clinic visit is omitted, telephone encounters must be performed to review AE and concomitant medications at these time points and documented in electronic medical record by treating investigator. Appropriate follow up for any new symptomatic or laboratory AE must be coordinated as needed based upon this encounter. Research PBMC sample may be omitted in cases which do not require clinic visit on Cycle 1, Day 15.
p	Screening tests and procedures do not need to be repeated on Cycle 1, Day 1 if performed within 3 days.

6.2 Main Study Flow Chart (Efficacy Population)

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3		To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days
Administrative Procedures														
Informed Consent	X													
Inclusion/Exclusion Criteria	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration[a]		X			X		X	X	X	X	X			
GM-CSF Administration Days 1-14[a,m]		D1-14[m]			D1-14[m]									
GM-CSF Patient Diary/Injection Record[c,m] (Appendix 11.2)		X[m]			X[m]									
Post-Study Anticancer Therapy Status												X	X	X
Survival Status												X	X	X
Clinical Procedures/Assessments														
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[d]		
Full Physical Examination	X	X	X	X[o]	X	X[o]	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X[o]	X	X[o]	X	X	X	X	X	X		
ECOG Performance Status (Appendix 11.4)	X	X			X		X	X	X	X	X	X		
Child Pugh Score (Appendix 11.5)	X													
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG[e]	X	X			X		X	X	X	X	X			

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3		To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days
PT/INR	X	X			X		X	X	X	X	X	X		
aPTT	X	X			X									
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[f]	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[g]	X	Every 8 weeks from C1D1 ± 14 days												
T3, FT4 and TSH[g]	X	Every 8 weeks from C1D1 ± 14 days												
Efficacy Measurements														
Tumor Imaging[h]	X	Every 8 weeks from C1D1 (±7 days for first 6 months of treatment, ±14 days after 6 months until end of treatment)[h]											X[h]	
CA 19-9 Tumor Marker[i]	X	Every 8 weeks from C1D1 ± 14 days										X[i]		
Archival Tissue Collection/Correlative Studies Blood (Appendix 11.6)														
Archival Tumor Tissue Collection[j]	X[j]											X[j]	X[j]	
PBMC Blood Collection[k]	X	X	X	X[o]	X		Every 8 weeks ± 14 days through C9D1					X	X[k]	

[a]	Cycle length is 21 days, ±3 days. Pembrolizumab is administered IV Q21 days ±3 up to 24 months or 35 cycles (Sections 5.2, 5.8, 7.1.5.2). GM-CSF is administered days 1-14 Q21 days, ±3 days for induction cycles 1 and 2 only with option for re-induction in cases meeting criteria in Section 7.1.5.1; Day 1 and subsequent doses are self-administered after self-injection teaching by infusion center RN or another qualified medical provider.
[b]	A 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. Though the Safety Follow-Up Visit and assessments should be performed at UCSF when possible, safety follow up assessments (including administrative, clinical, laboratory, and efficacy assessments) may be extracted from clinical data obtained from a subject's local physician's office visit, during a hospitalization, and/or during any other standard medical encounter, if travel to UCSF would confer hardship due to distance and/or due to initiation of new therapy. Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 8 weeks (56 ± 28 days) by radiographic imaging to monitor disease status. After 1 year, the Follow Up visits and imaging timepoints will occur approximately every 12 weeks (± 28 days). After 2 years, patients will be followed according to Survival Follow-Up phase.
[c]	GM-CSF Patient Diary/Injection Record and instructions will be provided to each patient on Day 1 of Cycles 1 and 2 and any subsequent re-induction cycles. The completed diaries will be collected on Day

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3		To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days

	1 of Cycles 2 and 3 and after any re-induction cycles. See Appendix 11.2.
d	Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to baseline or Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment, whichever occurs first, will also be followed and recorded.
e	Perform on women of childbearing potential only at screening and prior to each pembrolizumab infusion. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
f	See Section 7.1.3 and Table 5 for specific laboratory tests required as part of comprehensive metabolic panel.
g	Or more often if clinically indicated.
h	Cross-sectional imaging with CT or MRI abdomen plus pelvis (including triphasic/multiphase liver preferred) and CT chest with or without contrast is required at screening, every 8 weeks (±7 days) during treatment for first 6 months then every 8 weeks (±14 days days) after 6 months on treatment until end of treatment. In subjects without evidence progression at treatment discontinuation, scans should be every 8 weeks ±28 days for up to 1 year during Follow-Up Phase, then every 12 weeks ± 28 days (or more often if clinically indicated). Imaging may be performed more often if clinically indicated to evaluate for progression or toxicity. Imaging should be performed as close to time of Safety Follow-Up visit as possible in cases of discontinuation after confirmed response or completion of 24 months of treatment.
i	CA 19-9 should be checked at same timepoints as imaging. Note that CA 19-9 may be elevated due to biliary obstruction/stent occlusion independent of progression. CA 19-9 testing may be performed more often if clinically indicated to evaluate for progression.
j	Archival tumor samples (FFPE block when available and/or at least 10 unstained slides of approximately 10 µm thickness plus a paired H&E slide) should be obtained from prior tumor sampling/diagnostic procedure(s) such as prior resection, core biopsy, or cytology/cell button when available. FFPE block or slides should also be obtained from any subsequent tumor sampling which occurs during or after protocol therapy (such as repeat biopsy to confirm progression or palliative metastatectomy surgery). See Appendix 11.6.
k	Blood samples will be obtained in all patients for PBMC immune profiling at Screening, on Day 1, 8, and 15 of Cycle 1, on Cycle 2 Day 1, Cycle 3 Day 1, then Q8 weeks ± 14 days during subsequent cycles through C9D1. Screening sample may be used for Cycle 1, Day 1 if obtained within 3 days. Samples will be obtained at time of Safety Follow-Up visit (PBMC collection at this time-point may be omitted or delayed until next UCSF clinic visit if patient has Safety Follow-Up Visit assessments performed outside of UCSF),, and at time of progression if patient discontinued treatment without progression and is identified with progression during Follow-Up. See Appendix 11.6.
m	Re-induction GM-CSF will be allowed case-by-case according to Section 7.1.5.1, between approximately months 6-12 or Cycles 8-16 on protocol therapy. In these cases, GM-CSF will be re-administered D1-14 for 2 cycles (which will be named "R" along with original cycle number, e.g. RC8 and RC9) along with GM-CSF Patient Diary/Injection Record (Appendix 11.2) which will be provided along with instructions before re-induction and collected on D1 of each cycle following the 2 re-induction cycles. PTT will be repeated on Day 1 of each re-induction cycle and one cycle following re-induction to monitor for coagulopathy, as for Cycles 1-3.
o	On Day 15 of Cycle 1 and Day 8 of Cycles 2 and 3, the clinic visit for physical examination, vitals, and weight check may be omitted provided there are no clinically-significant AE requiring follow up at the discretion of treating investigator. If clinic visit is omitted, telephone encounters must be performed to review AE and concomitant medications at these time points and documented in electronic medical record by treating investigator. Appropriate follow up for any new symptomatic or laboratory AE must be coordinated as needed based upon this encounter. Research PBMC sample may be omitted in cases which do not require clinic visit on Cycle 1, Day 15.
p	Screening tests and procedures do not need to be repeated on Cycle 1, Day 1 if performed within 3 days.

6.3 Second Course* Pembrolizumab Flow Chart

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) S1			CS2, CS3		To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Second Course Screening	Day (D) 1	D8	D15	D1	D8	C S4 D1	C S5 D1	C S6 D1	C S7 D1	C S8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days
Administrative Procedures														
Inclusion/Exclusion Criteria for Second Course (Section 7.1.5.2)	X													
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration[a]		X			X		X	X	X	X	X			
Post-Study Anticancer Therapy Status												X	X	X
Survival Status												X	X	X
Clinical Procedures/Assessments														
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X[d]		
Full Physical Examination	X	X	X	X[o]	X	X[o]	X	X	X	X	X	X		
Vital Signs and Weight	X	X	X	X[o]	X	X[o]	X	X	X	X	X	X		
ECOG Performance Status (Appendix 11.4)	X	X			X	X	X	X	X	X	X	X		
Child Pugh Score (Appendix 11.5)	X													
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory														
Pregnancy Test – Urine or Serum β-HCG[e]	X	X			X		X	X	X	X	X			
PT/INR	X	X			X		X	X	X	X	X	X		
aPTT	X													
CBC with Differential	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[f]	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[g]	X	Every 8 weeks from C1D1 ± 14 days										X		

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) S1			CS2, CS3		To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Second Course Screening	Day (D) 1	D8	D15	D1	D8	C S4 D1	C S5 D1	C S6 D1	C S7 D1	C S8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days
T3, FT4 and TSH[g]	X	Every 8 weeks from C1D1 ± 14 days										X		
Efficacy Measurements														
Tumor Imaging[h]	X	Every 8 weeks from C1D1 (±7 days for first 6 months of treatment, ± 14 days after 6 months until end of treatment)[h]											X[h]	
CA 19-9 Tumor Marker[i]	X	Every 8 weeks from C1D1 ± 14 days										X[i]		
Archival Tissue Collection/Correlative Studies Blood (Appendix 11.6)														
Archival Tumor Tissue Collection[ij]	X[ij]											X[ij]	X[ij]	
PBMC Blood Collection[k]	X	X	X	X[o]	X		Every 8 weeks ± 14 days through C9D1					X	X[k]	

*	Requires approval on case-by-case basis from Study Chair and Merck.
a	Cycle length is 21 days, ±3 days. Pembrolizumab Second Course is administered IV Q21 days ±3 days for up to 12 additional months or 17 cycles (Section 7.1.5.2).
b	A 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. Though the Safety Follow-Up Visit and assessments should be performed at UCSF when possible, safety follow up assessments (including administrative, clinical, laboratory, and efficacy assessments) may be extracted from clinical data obtained from a subject's local physician's office visit, during a hospitalization, and/or during any other standard medical encounter, if travel to UCSF would confer hardship due to distance and/or due to initiation of new therapy. Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 8 weeks (56 ± 28 days) by radiographic imaging to monitor disease status. After 1 year, the Follow Up visits and imaging time points will occur approximately every 12 weeks (± 28 days). After 2 years, patients will be followed according to Survival Follow-Up phase.
d	Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to baseline or Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment, whichever occurs first, will also be followed and recorded.
e	Perform on women of childbearing potential only at screening and prior to each pembrolizumab infusion. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
f	See Section 7.1.3 and Table 5 for specific laboratory tests required as part of comprehensive metabolic panel.
g	Or more often if clinically indicated.
h	Cross-sectional imaging with CT or MRI abdomen plus pelvis (including triphasic/multiphase liver preferred) and CT chest with or without contrast is required at screening, every 8 weeks (±7 days) during treatment for first 6 months then every 8 weeks (±14 days days) after 6 months on treatment until end of treatment. In subjects without evidence progression at treatment discontinuation, scans should be every 8 weeks ±28

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) S1			CS2, CS3		To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Second Course Screening	Day (D) 1	D8	D15	D1	D8	C S4 D1	C S5 D1	C S6 D1	C S7 D1	C S8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days

	days for up to 1 year during Follow-Up Phase, then every 12 weeks ± 28 days (or more often if clinically indicated). Imaging may be performed more often if clinically indicated to evaluate for progression or toxicity. Imaging should be performed as close to time of Safety Follow-Up visit as possible in cases of discontinuation after confirmed response or completion of 24 months of treatment.
i	CA 19-9 should be checked at same timepoints as imaging. Note that CA 19-9 may be elevated due to biliary obstruction/stent occlusion independent of progression. CA 19-9 testing may be performed more often if clinically indicated to evaluate for progression.
jj	Archival tumor samples (FFPE block when available and/or at least 10 unstained slides of approximately 10 µm thickness plus a paired H&E slide) should be obtained from any new tumor sampling/diagnostic procedure(s) before or during Second Course pembrolizumab, such as core or needle biopsy to confirm progression. See Appendix 11.6.
k	Blood samples in all patients will be obtained for PBMC immune profiling at Screening, on Day 1, 8, and 15 of Cycle 1, on Cycle 2 Day 1, Cycle 3 Day 1, then Q8 weeks ± 14 days during subsequent cycles through C9D1. Screening sample may be used for Cycle 1, Day 1 if obtained within 3 days . Samples will be obtained at time of Safety Follow-Up visit (PBMC collection at this time-point may be omitted or delayed until next UCSF clinic visit if patient has Safety Follow-Up Visit assessments performed outside of UCSF), and at time of progression if patient discontinued treatment without progression and is identified with progression during Follow-Up. See Appendix 11.6.
o	On Day 15 of Cycle 1 and Day 8 of Cycles 2 and 3, the clinic visit for physical examination, vitals, and weight check may be omitted provided there are no clinically-significant AE requiring follow up at the discretion of treating investigator. If clinic visit is omitted, telephone encounters must be performed to review AE and concomitant medications at these time points and documented in electronic medical record by treating investigator. Appropriate follow up for any new symptomatic or laboratory AE must be coordinated as needed based upon this encounter. Research PBMC sample may be omitted in cases which do not require clinic visit on Cycle 1, Day 15.
p	Screening tests and procedures do not need to be repeated on Cycle 1, Day 1 if performed within 3 days.

6.4 Expansion Cohort Flow Chart

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**											**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days
Administrative Procedures															
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demographics and Medical History	X														
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pembrolizumab Administration[a]		X			X			X	X	X	X	X			
GM-CSF Administration Days 1-14[a,m]					D1-14[m]										
GM-CSF Patient Diary/Injection Record[c,m] (Appendix 11.2)					X[m]			X[m]							
Post-Study Anticancer Therapy Status													X	X	X
Survival Status													X	X	X
Clinical Procedures/Assessments															
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X[d]		
Full Physical Examination	X	X	X		X	X		X	X	X	X	X	X		
Vital Signs and Weight	X	X	X		X	X		X	X	X	X	X	X		
ECOG Performance Status (Appendix 11.4)	X	X	X		X	X		X	X	X	X	X	X		
Child Pugh Score (Appendix 11.5)	X														
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory															
Pregnancy Test – Urine or Serum □-HCG[e]	X	X			X			X	X	X	X	X			
PT/INR	X	X			X			X	X	X	X	X	X	X	

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**											**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles							
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days
aPTT	X														
CBC with Differential	X	X	X		X	X		X	X	X	X	X	X		
Comprehensive Serum Chemistry Panel[f]	X	X	X		X	X		X	X	X	X	X	X		
Urinalysis[g]	X		Every 8 weeks from C1D1 ± 14 days										X		
T3, FT4 and TSH[g]	X		Every 8 weeks from C1D1 ± 14 days										X		
Efficacy Measurements															
Tumor Imaging[h]	X		Every 8 weeks from C1D1 (±7 days for first 6 months of treatment, ± 14 days after 6 months until end of treatment)[h]											X[h]	
Confirmation of RECIST 1.1-Measurable[q]	X														
Confirmation of Biopsy-Accessible[q]	X														
CA 19-9 Tumor Marker[i]	X		Every 8 weeks from C1D1 ± 14 days										X[i]		
Archival Tissue Collection/Correlative Studies Blood (Appendix 11.6)															
Archival Tumor Tissue Collection[j]	X[j]												X[j]	X[j]	
On-Treatment Tumor Research Biopsy[r]				C1D 15			C3D 15 after scans								
PBMC Blood Collection[k]	X	X	X		X	X	Every 8 weeks ± 14 days through C9D1						X	X[k]	

[a] Cycle length is 21 days, ±3 days. Pembrolizumab is administered IV Q21 days ±3 up to 24 months or 35 cycles (Sections 5.2, 5.8, 7.1.5.2). GM-CSF is administered days 1-14 Q21 days, ±3 days for induction Cycles 2 and 3 only with option for re-induction in cases meeting criteria in Section 7.1.5.1; Dayday 1 and subsequent doses are self-is administered after self-injection teaching by infusion center RN or another qualified medical provider each cycle.

[b] A 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. Though the Safety Follow-Up Visit and assessments should be performed at UCSF when possible, safety follow up assessments (including administrative, clinical,

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles						
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days

	laboratory, and efficacy assessments) may be extracted from clinical data obtained from a subject's local physician's office visit, during a hospitalization, and/or during any other standard medical encounter, if travel to UCSF would confer hardship due to distance and/or due to initiation of new therapy. Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed approximately every 8 weeks (56 ± 28 days) by radiographic imaging to monitor disease status. After 1 year, the Follow Up visits and imaging timepoints will occur approximately every 12 weeks (± 28 days). After 2 years, patients will be followed according to Survival Follow-Up phase.
[c]	GM-CSF Patient Diary/Injection Record and instructions will be provided to each patient on Day 1 of Cycles 2 and 3 and any subsequent re-induction cycles. The completed diaries will be collected on Day 1 of Cycles 3 and 4 and after any re-induction cycles. See Appendix 11.2.
[d]	Subjects with at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to baseline or Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment, whichever occurs first, will also be followed and recorded.
[e]	Perform on women of childbearing potential only at screening and prior to each pembrolizumab infusion. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.
[f]	See Section 7.1.3 and Table 5 for specific laboratory tests required as part of comprehensive metabolic panel.
[g]	Or more often if clinically indicated.
[h]	Cross-sectional imaging with CT or MRI abdomen plus pelvis (including triphasic/multiphase liver preferred) and CT chest with or without contrast is required at screening, every 8 weeks (±7 days) during treatment for first 6 months then every 8 weeks (±14 days days) after 6 months on treatment until end of treatment. In subjects without evidence progression at treatment discontinuation, scans should be every 8 weeks ±28 days for up to 1 year during Follow-Up Phase, then every 12 weeks ± 28 days (or more often if clinically indicated). Imaging may be performed more often if clinically indicated to evaluate for progression or toxicity. Imaging should be performed as close to time of Safety Follow-Up visit as possible in cases of discontinuation after confirmed response or completion of 24 months of treatment.
[i]	CA 19-9 should be checked at same time points as imaging. Note that CA 19-9 may be elevated due to biliary obstruction/stent occlusion independent of progression. CA 19-9 testing may be performed more often if clinically indicated to evaluate for progression.
[j]	Archival tumor samples (FFPE block when available and/or at least 10 unstained slides of approximately 10 µm thickness plus a paired H&E slide) should be obtained from prior tumor sampling/diagnostic procedure(s) such as prior resection, core biopsy, or cytology/cell button when available. FFPE block or slides should also be obtained from any subsequent tumor sampling which occurs during or after protocol therapy (such as repeat biopsy to confirm progression or palliative metastatectomy surgery). See Appendix 11.6.
[k]	Blood samples will be obtained in all patients for PBMC immune profiling at Screening, on Days 1 and 8 of Cycles 1, 2, and 3, then Q8 weeks ± 14 days during subsequent cycles through C9D1. Screening sample may be used for Cycle 1, Day 1 if obtained within 3 days. Samples will be obtained at time of Safety Follow-Up visit (PBMC collection at this time-point may be omitted or delayed until next UCSF clinic visit if patient has Safety Follow-Up Visit assessments performed outside of UCSF), and at time of progression if patient discontinued treatment without progression and is identified with progression during Follow-Up. See Appendix 11.6.
[m]	Re-induction GM-CSF will be allowed case-by-case according to Section 7.1.5.1, between approximately months 6-12 or Cycles 8-16 on protocol therapy. In these cases, GM-CSF will be re-administered D1-14 for 2 cycles (which will be named "R" along with original cycle number, e.g. RC8 and RC9) along with GM-CSF Patient Diary/Injection Record (Appendix 11.2) which will be provided along with instructions before re-induction and collected on D1 of each cycle following the 2 re-induction cycles.
[o]	On Day 15 of Cycles 1, 2, and 3, the clinic visit for physical examination, vitals, and weight check may be omitted provided there are no clinically-significant AE requiring follow up at Day 8 visit at discretion of treating investigator. If clinic visit is omitted, telephone encounters must be performed to review AE and concomitant medications at these time points and documented in electronic medical record by treating investigator. Appropriate follow up for any new symptomatic or laboratory AE must be coordinated as needed based upon this encounter.
[p]	Screening tests and procedures do not need to be repeated on Cycle 1, Day 1 if performed within 3 days.
[q]	Screening for Expansion Cohort requires confirmation of RECIST 1.1-measurable disease with ≥ 1 target lesion not planned for research biopsy, as well as assessment of ≥ 1 lesion amenable percutaneous biopsy per Sections 5.1.3 and 7.1.4.3,

Trial Period:	**Screening Phase[p]**	**Treatment Cycles[a]**										**End of Treatment**	**Post-Treatment**	
		Cycle (C) 1			C2, C3			To be repeated on D1 each cycle beyond 8 cycles						
Treatment Cycle/Title:	Main Study Screening	Day (D) 1	D8	D15	D1	D8	D15	C4 D1	C5 D1	C6 D1	C7 D1	C8 D1	Safety Follow-Up Visit[b]	Follow-Up Visits[b]	Survival Follow-Up
Scheduling Window (Days):	-28 to 1	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	Approx. 30 days (±14 days) post last treatment	Every 8 weeks ±28 days for 1 year post last treatment then every 12 weeks ±28 days	Every 12 weeks ±28 days

r Core needle biopsies (CNB) will be obtained in Expansion Cohort subjects with lesions safely amenable to percutaneous biopsy (by assessment of proceduralist, Section 5.1.3) during Cycle 1 on approximately C1D15 (±3 days) and during Cycle 3 approximately C3D15 ±3 days, preferably after completion of restaging imaging for 8 week time point. See Appendix 11.6.3 for processing instructions.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Study Flow Charts in Section 6.0 summarize 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 additional or unscheduled time points if deemed clinically necessary by the investigator.

In some cases, the evaluations or testing may be potentially sensitive in nature (e.g., HIV, HBV, or HCV results), 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 treating investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

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 Study Chair requirements.

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 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any historical condition diagnosed within the prior approximately 5 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

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

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial treatment and during the Follow-Up Phase. All medications related to reportable SAEs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status, including current stage, stage at diagnosis, diagnostic test(s).

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including surgery, ablative treatments, arterial therapies (such as radioembolization), radiation, and systemic treatments.

7.1.1.5.3 Liver Disease Details

The investigator or qualified designee will review liver disease history including risk factors for biliary cancer (such as prior or intercurrent liver infections including viral hepatitis, alcohol use, non-alcoholic steatohepatitis or fatty liver disease diagnosis or risk factors, cirrhosis/fibrosis, autoimmune disease, any other prior injury to biliary tract). Biliary obstruction history and drainage procedures (e.g., percutaneous drain or indwelling stent placement) at baseline, during

treatment, and during the Follow-Up Phase will be documented. History of and any new episodes of cholangitis will be documented at baseline, during treatment, and during the Follow-Up Phase.

7.1.1.5.4 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-Up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated or if transition to palliative/end of life care such as Hospice enrollment occurs, the subject will move into Survival Follow-Up Phase.

7.1.1.6 Registration

All patients who consent will be registered in OnCore®, the UCSF Helen Diller Family Comprehensive Cancer Center Clinical Trial Management System (CTMS).

7.1.1.7 Enrollment

Once screening is completed, eligibility documents and checklist for all patients will be submitted via HIPAA-compliant method (e.g., secure e-mail or fax) for central review at UCSF by the Study Chair or designee. Once eligibility is confirmed by the Study Chair or designee, a study ID number will be assigned by the study coordinator and provided to treating investigator as confirmation of enrollment to proceed with protocol therapy.

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

See Section 5.2.3.3 and Appendix 11.2 for information on GM-CSF Patient Diary/Injection Record.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the Follow-Up Phase according to NCI CTCAE Version 4.0 (see Appendix 11.3). 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 pembrolizumab exposure should be evaluated to determine if it is possibly an immune-related adverse event (irAE). Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs and irAEs.

7.1.2.2 Complete Physical Examination

The investigator or qualified designee will perform a complete physical examination according to institutional practice for the management and monitoring of patients with biliary cancers during

the screening period, at all follow up visits, and at end of treatment visit according to standard of care. Clinically significant abnormal findings during Screening should be recorded as medical history.

7.1.2.3 Vital Signs

The investigator or qualified designee will obtain vital signs at the timepoints specified in the Study Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, oxygen saturation (pulse oximetry), weight and blood pressure. Height will be measured at screening only.

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 11.4) at the timepoints specified in the Trial Flow Chart (Section 6.0).

7.1.2.5 Liver Function Assessment

The investigator or qualified designee will assess liver function by Child Pugh score (see Appendix 11.5) at the timepoints specified in the Study Flow Chart (Section 6.0).

7.1.2.6 Tumor Imaging and Assessment of Disease

Cross-sectional imaging with CT (preferred) or MRI abdomen plus pelvis and CT chest with/without or without contrast is required at screening, every 8 weeks (±7 days) during first 6 months of treatment until ascertainment of PFS6, then every 8 weeks (±14 days for patient convenience in scheduling on same day as infusions) until end of treatment. In subjects without evidence progression at treatment discontinuation, scans should be every 8 weeks ±28 days for up to 1 year during Follow-Up Phase, then every 12 weeks ± 28 days (or more often if clinically indicated). for RECIST 1.1 response assessment[1] (see Section 6.0 – Study Flow Charts for timepoints). Multiphase/triphasic liver imaging should be included as appropriate. Additional baseline imaging such as PET scan, bone scan, or MRI brain are only required if clinically indicated by symptoms and/or to assess known bone metastases or other sites of known metastatic disease. All baseline evaluations will be performed as close as possible to the beginning of treatment and ≤ approximately 28 days before C1D1. The same imaging modality/modalities should be used if possible throughout study unless there is a clinical indication to use a different modality (i.e. based upon Radiology recommendation to better assess a target lesion, an event of new contrast allergy, etc.). RECIST 1.1 measurements will be performed by a radiologist or qualified investigator.

7.1.2.7 Assessment of Tumor Amenable to Percutaneous Biopsy in Expansion Cohort

Assessment of tumor likely to be safely accessible to acceptable mode of percutaneous core needle biopsy (punch, ultrasound-guided, or CT-guided) will be performed during Screening by Radiologist or qualified investigator.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Thyroid-stimulating hormone (TSH)
Red Blood Cell Count	Creatinine	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide (C02 or bicarbonate)	Urine pregnancy test †	Free thyroxine (T4)
Absolute Lymphocyte Count	Calcium		CA 19-9
	Chloride		Blood for correlative studies*
	Glucose		
	Phosphorus		Archival tumor sample accessioning*
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin		
	Blood Urea Nitrogen		

† Perform urine pregnancy test on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test is required. *See Section 7.1.4 and Appendix 11.6 for further information on research sample collection.

Laboratory tests for screening or entry on Second Course (S) should be performed within 10 days prior to the first dose of Second Course treatment (see Section 6.3 – Second Course Pembrolizumab Flow Chart). After Second Course Cycle 1 (SC1), pre-dose laboratory procedures must be obtained within 3 days prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Tumor and Blood Sample Collection for Correlative Analyses

Tumor and blood samples will be obtained and stored from all patients for planned future correlative analyses (see Section 8.7.3), which will be performed in batch after completion of study and pending funding. In addition, for patients who consent to optional specimen banking, any left-over blood and archival tumor samples will be banked in the UCSF Tissue Core for future

research as part of the UCSF Hepatobiliary Tissue Bank, CC#124512 as a companion to this protocol. See Appendix 11.67 for correlative specimen procurement and handling instructions.

7.1.4.1 Archival Tumor Tissue Collection

In all patients, left-over diagnostic tumor block and/or slides from any tumor sampling procedure(s) (e.g. biopsy, fine needle aspiration, cytology brushings, and/or resection specimens) performed prior to enrollment, during study treatment, and/or during the Follow-Up Phase will be obtained to determine tumor PD-L1 expression status, to characterize tumor immune infiltrates/T cell subsets, and (optional)to bank for future correlative analyses as part of the UCSF Hepatobiliary Tissue Bank and Registry (CC#124512) as a companion protocol to this study. Formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks will be accessioned whenever available. In addition to blocks or if a block is not available, at least 10 unstained slides (prefer 10 µm) plus 1 H&E slide from a tumor tissue block may be accessioned. Corresponding pathology reports from initial diagnosis and/or subsequent tumor sampling will be obtained. Specimens will be obtained from the Pathology Department for banking as soon as possible after consent and/or occurrence of post-enrollment tumor sampling and stored the Helen Diller Family Comprehensive Cancer Center (HDFCCC) Tissue Core (UCSF patients). Correlative analyses using archival tissue samples will be performed in batch at completion of study and pending funding. See Appendix 11.6 for correlative specimen procurement and handling instructions.

7.1.4.2 Peripheral Blood Mononuclear Cell (PBMC) Collection

In all patients, approximately 60 mL of whole blood will be collected into green top tubes (e.g. six 10 cc tubes filled approximately to 10 mL) at the time points listed in the Study Flow Chart in Section 6.0. The tubes will be delivered directly to the UCSF Immune Monitoring Core for PBMC isolation then freezing for future analysis in batch at end of study and pending funding. See Appendix 11.6 for correlative specimen procurement and handling instructions.

7.1.4.3 Expansion Cohort Research Biopsies

Expansion Cohort enrollment requires radiographic assessment of measurable disease by RECIST 1.1 with ≥ 1 target lesion not planned for biopsy, as well as tumor accessible to minimally-invasive percutaneous biopsy (by CT, ultrasound, or punch) based upon assessment of qualified radiologist. More invasive methods of biopsy such as surgery, laparoscopy, or endoscopy are not allowed for purposes of research biopsy on this study due to patient risk. Consent for paired research biopsies during Cycle 1 and Cycle 3 is required for enrollment to Expansion Cohort. Two to 4 core needle biopsies (CNB), preferred 18-gauge and 1 cm depth (or equivalent) if safely accessible based upon evaluation by proceduralist, should be obtained at each time point (Section 6.4) with prioritization and handling instructions per Appendix 11.6.3. Biopsy samples will be analyzed for exploratory biomarker endpoints as described in 4.3.6.4

7.1.4.4 Specimen Banking

For patients enrolled at UCSF who consent to optional specimen banking, all left-over blood and/or tumor samples will be banked in the UCSF Hepatobiliary Tissue Bank, CC#124512.

See Appendix 11.6 for correlative specimen procurement and handling instructions.

7.1.5 Other Procedures

7.1.5.1 Re-Induction with GM-CSF

In patients who demonstrate CR, PR, or prolonged stable disease ≥ 6 months with evidence of clinical benefit (such as minor response radiographically, decline in CA 19-9, and/or improved symptoms) after the Induction Phase but within 12 months from enrollment, but who subsequently progress on single-agent pembrolizumab between 6-12 months after enrollment (after the primary endpoint of PFS6 has been ascertained for that patient), re-induction with GM-CSF may be administered in case-by-case situations with approval from Study Chair provided patient remains eligible for ongoing treatment on protocol (section 7.1.5.3).

7.1.5.2 Second Course Pembrolizumab

Subjects who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress within 6 months after stopping study treatment, without any evidence of progression prior to discontinuation, with case-by-case approval from Study Chair and Merck. This retreatment is termed the Second Course of this study and is only available if the study remains open to enrollment and the subject meets the following conditions:

- **Either**
    - Stopped initial treatment with pembrolizumab after attaining an investigator-determined confirmed CR according to RECIST 1.1, and:
        - Was treated for at least 24 weeks with pembrolizumab before discontinuing therapy.
        - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared.

        OR
    - Had CR, PR, or SD with evidence of clinical benefit (such as minor response radiographically, decline in CA 19-9, and/or improved symptoms) and stopped pembrolizumab treatment after 24 months of study therapy due to protocol-defined treatment duration, without any evidence of disease progression or intolerability.

AND

- Experienced an investigator-determined confirmed radiographic disease progression within 6 months after stopping their initial treatment with pembrolizumab.
- Did not receive any other anti-cancer treatment since the last dose of pembrolizumab.

- Meets original entry criteria in Section 5.1 (with exception of exclusion 19 which is not applicable to re-induction or Second Course).

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

7.1.5.3 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of Safety Follow-Up Visit (Section 6). 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 a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2. After discontinuing treatment following assessment of CR, these subjects should return to the clinic for a Safety Follow-Up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Phase of the study (described in Section 7.1.5.4).

7.1.5.4 Blinding/Unblinding

Not applicable to this study.

7.1.6 Visit Requirements

7.1.6.1 Screening, On-Treatment, and Discontinuation/End of Treatment Visits

Visit requirements for the main study are outlined in Section 6.2 –Main Study Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.6.2 Re-Induction with GM-CSF

Visit requirements for patients eligible for re-induction with GM-CSF are outlined in Section 6.0 – Main Study Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures and 7.1.5.1 – Re-Induction with GM-CSF.

7.1.6.3 Post-Treatment Visits

7.1.6.3.1 Safety Follow-Up Visit

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. Though the Safety Follow-Up Visit and assessments should be performed at UCSF when possible, safety follow up assessments (including administrative, clinical, laboratory, and efficacy assessments, see Sections 6.1-6.3) may extracted from clinical data obtained from a subject's local physician's office visit, during a hospitalization, and/or during any other standard medical encounter, if travel to UCSF would confer hardship due to distance and/or due to initiation of new therapy. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with

an at least possibly treatment-related AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1, assessment as chronic or irreversible by investigator, or until the beginning of a new anti-neoplastic 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 Second Course of pembrolizumab (as described in Section 7.1.5.4.1) may have up to two Safety Follow-Up visits, one after the Treatment Period and one after the Second Course.

7.1.6.4 Follow-Up Phase

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed every 8 weeks (±28 days) by radiography to monitor disease status. After 1 year, the imaging time point will occur every 12 weeks (±28 days) or more often if clinically indicated. After 2 years in Follow-Up Phase, patients will discontinue active follow up and be followed only for survival according to Survival Follow-Up Phase (Section 7.1.6.4.2). Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, end of the study or if the subject begins retreatment with Second Course pembrolizumab as detailed in Section 7.1.5.2. Information regarding post-study anti-neoplastic treatment will be collected if new treatment is initiated.

7.1.6.4.1 Second Course Pembrolizumab

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.2 will move from the Follow-Up Phase to the Second Course when they experience disease progression. Visit requirements are provided in Section 6.3 – Second Course Pembrolizumab Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures and 6.3 – Second Course Pembrolizumab Flow Chart.

7.1.6.4.2 Survival Follow-Up Phase

Once a subject experiences confirmed disease progression, starts a new anti-cancer therapy, has no evidence of progression after 2 years in Follow-Up Phase (Section 7.1.6.4), or transitions to palliative/end of life care, the subject moves into the Survival Follow-Up Phase. Survival status should be ascertained by clinic visit (if appropriate for patient's medical care, chart review, or by telephone contact approximately every 12 weeks ±28 days to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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 unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (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 investigational product(s), is also an adverse event. Adverse events may occur during the course of the use of the investigational products during the Treatment Period or within the Follow-Up Phase of this study. Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

The investigational products in this study are pembrolizumab and GM-CSF.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and 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.

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Study Chair and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater or GM-CSF 1250 µg or greater in a single dose (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, 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 a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product 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 ECI, using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 business hours to the Study Chair and within 2 business days to Merck Global Safety, from the time of investigator awareness. See Appendix 11.7.

7.2.2 Reporting of Pregnancy and Lactation to the Study Chair and to Merck

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), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant 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 business hours to the Study Chair and within 2 business days to Merck Global Safety, from the time of investigator awareness. See Appendix 11.7.

7.2.3 Immediate Reporting of Adverse Events to the Study Chair, Merck, and the FDA

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of either investigational product (GM-CSF and/or pembrolizumab) 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 a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

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 that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to either or both investigational products, must be reported within 24 business hours to the Study Chair and within 2 business days to Merck Global Safety, from the time of investigator awareness. See Appendix 11.7.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician or health care professional to be related to either or both investigational products that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Study Chair and to Merck in the same manner as SAEs.

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

7.2.3.2 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to Study Chair, Merck, and FDA, unless there is evidence suggesting a causal relationship between the drug and the event.

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

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

The Study Chair will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not

progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study.

7.2.3.3 IND Safety Reporting to FDA

UCSF will report to the FDA all IND reportable events occurring in patients enrolled on this study using FDA Form 3500A (MedWatch, Appendix 11.7). Reportable events must meet the definition in Federal Regulations (21 CFR §312.32):

- Suspected adverse reaction (defined as a reasonable possibility that the investigational agent caused the adverse event)
- Unexpected (not listed in the investigator brochure or package insert(s), or is not listed at the specificity or severity that has been observed)
- Serious (as defined in 7.2.3.1)

If the adverse event does not meet all three of the definitions, it should not be submitted as an expedited IND safety report. The timeline for submitting an IND safety report to FDA is no later than 15 calendar days after the Investigator determines that the suspected adverse reaction qualifies for reporting (21 CFR 312.32(c)(1)). Any unexpected fatal or life-threatening suspected adverse reaction will be reported to FDA no later than 7 calendar days after the Investigator's initial receipt of the information (21 CFR 312.32(c)(2)).

Any relevant additional information that pertains to a previously submitted IND safety report will be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)).

A copy of all 15 Day Reports and Annual Progress Reports will be submitted as required by FDA. Investigators will cross-reference this submission according to local regulations to the Merck Investigational Compound Number (IND) at the time of submission. Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician or health professional (e.g., Nurse Practitioner) 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 6 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mild 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 of 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 Merck 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 [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); 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) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious important medical event 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 Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician or health care professional. 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 Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck 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 Merck 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 Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck 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 Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck 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) Merck 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 MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR 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 Merck 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 or health care professional 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 Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

7.2.5 Study Chair Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and other investigators by the Study Chair in accordance with all applicable local laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Study Statistical Design

This is an open-label, two-stage, single-arm phase 2 study of pembrolizumab plus GM-CSF as $\geq 2^{nd}$ line therapy for advanced biliary tract cancer. The sample size for Stages 1 and 2 was based on a two-stage Simon's Optimal Design using proportion with PFS at 6 months (%PFS6) as the primary efficacy endpoint. Based upon results of Stages 1 and 2, the study was amended to change primary endpoint to overall response rate (ORR) for overall study with addition of the Expansion Cohort.[47]

8.2 Study Objectives and Hypotheses

See Section 3.

8.3 Definition of Study Endpoints

8.3.1 Primary Endpoint

The primary endpoint was amended to be overall response rate (**ORR**) with addition of Expansion Cohort, based upon the promising responses observed during Stages 1 and 2 (Safety and Efficacy Cohorts). **ORR** is defined as the proportion of subjects with RECIST 1.1-measurable disease at study entry who have a complete response (CR) or partial response (PR) (confirmed + unconfirmed) using RECIST 1.1[1] at any time during the main study. Measurable disease has been added as a required inclusion criterion for Expansion Cohort eligibility. Re-induction and Second Course ORR (rORR, sORR) will be determined based upon response after first dose of re-induction or first dose of Second Course. Subjects with measurable disease at study entry who have unknown or missing response information will be treated as non-responders. Subjects with non-measurable disease at study entry will be excluded from ORR and DOR analyses.

8.3.2 Secondary Endpoints

1) **Safety** endpoint assessment is described in Section 7.2. The safety endpoints are AEs graded using CTCAE (Version 4.0) criteria. Safety will be assessed by quantifying the toxicities and grades experienced by subjects who have received pembrolizumab plus GM-CSF induction, including SAEs and ECIs. Other safety endpoints include laboratory safety assessments, ECOG performance status, Child Pugh score, vital signs, and physical examinations. The incidence and frequency of dose reduction, treatment delays, and discontinuation for lack of tolerability will be quantified. Re-induction and Second Course safety events will be addressed in the same manner.

2) **Tumor PD-L1 status** will be measured by IHC and classified as positive or negative by central laboratory testing (QualTek Laboratories) using pre-specified cut-points.

3) A key secondary endpoint is %PFS6 (formerly primary endpoint, changed by amendment with addition of Expansion Cohort). For each patient, PFS will be calculated in days and months from date of first dose of protocol therapy to date of first documented radiographic and/or clinical disease progression or death from any cause. For patients removed from study for other reasons than progression or death, PFS will be censored at the date last known to be progression-free. See Section 5.9 for Replacement policy for non-evaluable patients. The %PFS6 will be calculated as the proportion of evaluable patients progression-free at 6 months. Censored patients without progression will be treated as non-progression statistically and counted in denominator toward %PFS6.

   For patients who continue on treatment despite radiographic progression based upon impression of clinical benefit an/or assessment with possible pseudo-progression or a delayed response[46] (see Section 5.8), PFS will be calculated at time of first documented progression after subsequent imaging confirms progression. If subsequent imaging does not demonstrate progression, then a PFS event will not have occurred and the patient will continue with scheduled imaging assessments per protocol to determine PFS.

   Re-induction and Second Course PFS (rPFS, sPFS) will be calculated in months from date of first dose of re-induction or Second Course to date of first documented radiographic and/or clinical disease progression during or after re-induction or Second Course, or death from any cause. RPFS and sPFS will be reported descriptively.

4) **DOR** is defined in the subset of subjects with RECIST 1.1-measurable disease at study entry with a CR or PR as the time from first documented evidence of CR or PR until the first documented sign of disease progression or death. Re-induction and Second Course DOR (rDOR, sDOR) will be measured as the time from first documented CR or PR during or after re-induction or Second Course.

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

8.4 Sample Size and Accrual Rate

8.4.1 Sample Size

For the primary endpoint of ORR, a sample size of 37 response-evaluable subjects will provide power of 77% with 2-sided 5% alpha and 88% with 1-sided 5% alpha to show ORR improvement from H_0 of 5% to H_1 of 20%, under protocol treatment. Based upon a subset with non-measurable disease enrolled to Stages 1 and 2 before amendment requiring RECIST 1.1-measurable tumors for enrollment to Expansion Cohort, along with potential for dropout in this population with comorbidity of biliary obstruction and liver disease, it is estimated that total enrollment of 42 subjects will include at least 37 response-evaluable subjects.

The key secondary endpoint of %PFS6 was previously the primary endpoint for Stages 1 and 2, prior to amendment adding Expansion Cohort, which also changed to primary endpoint of ORR based upon the promising response rate observed in Stages 1 and 2. For the key secondary endpoint of PFS, an expected overall study PFS-evaluable sample size of at least 40 patients will have power 78% with 2-sided alpha 5% and power 87% with 1-sided alpha to show PFS improvement from H_0 of 20% to H_1 of 40% on protocol therapy.

Pre-amendment, a Simon's 2 stage design was employed to determine if adequate efficacy was observed in Stage 1 to warrant proceeding to Stage 2. The pembrolizumab/GM-CSF combination was considered worthy of additional investigation if the true %PFS6 is 50%, and hence the alternative hypothesis, $\%PFS_1=0.50$. Therefore assuming an α error probability of 5%, and a β error of 20%, the first stage had 9 patients. If $\leq$2 of 9 had been observed progression-free, the study would not proceed to second stage. Since $\geq$3 of 9 patients are observed progression-free at 6 months (4/9 achieved PFS6 in Stage 1), enrollment continued to the second stage with 18 additional patients, with a goal of at least 24 evaluable patients (with planned over-enrollment of 3 additional patients to account for expected 10% dropout rate). If $\leq$9 patients are observed progression-free at 6 months out of 24 evaluable patients by the end of second stage, then no further investigation of the drug is warranted under this PFS6 hypothesis. Conversely, if $\geq$10 patients are progression-free at 6 months among Stages 1 and 2 subjects, the study would be considered positive for the hypothesis: H_0: $\%PFS_0<25\%$ versus Ha: $\%PFS_1 >50\%$.

8.4.2 Accrual Rate

Accrual of approximately 2 patients per month was achieved for Stages 1 and 2, with completion of enrollment to Stages 1 and 2 within 16 months. Owing to additional eligibility requirements for paired biopsies and measurable disease, accrual rate for Expansion Cohort is expected to be slower, approximately 1-1.5 per month with enrollment completion within 12 months.

8.4.3 Interim Analyses

8.4.4 Interim Safety Analysis and Stopping Rules

An interim safety analysis was performed after completion of 1st stage enrollment corresponding to approximately 33% enrollment (9 patients in Safety Cohort). The interim safety analysis examined safety during first 3 cycles of treatment (1 cycle single-agent pembrolizumab followed by 2 induction cycles with GM-CSF for total of 9 weeks). If >20% or more SAE and/or ECI, and/or >50% Grade $\geq$ 3 adverse events by NCI CTCAE v.4.0, have occurred during first 3 cycles of treatment and are assessed as both clinically relevant and at least possibly treatment-related, a decision would have been required whether to amend or close the study after the 1st stage. The interim safety analysis showed overall rate of Grade ≥3 at least possibly related AE rate of 11%, with 1 related SAE event (11%), meeting criteria to proceed with enrollment to Stage 2 Efficacy Cohort.

The target rate of $\leq$ 50% at least possibly treatment-related $\geq$ Grade 3 events during the first 3 cycles was conservative based upon rate of 70% for all-cause Grade 3 or 4 toxicity observed with standard first-line chemotherapy in this population,[9] and treatment-related Grade 3-5 rate of approximately 45% for the combination of ipilimumab plus GM-CSF in advanced melanoma

patients.[34] Accrual was placed on hold after the 9th patient was enrolled during 1st stage safety analysis, until at least 8 of the 9 patients had potential to complete 3 cycles (9 weeks) of treatment or had a qualifying safety event. Accrual resumed after completion of safety interim analysis without unexpected safety signals identified.

8.4.5 Interim Efficacy Analysis

An interim efficacy analysis examined %PFS6 after the first stage (n=9) are evaluable for PFS6. See Section 8.2. Three or more patients ($r_1 \geq 3$) were required to be progression-free at 6 months to continue 2nd stage enrollment. If ≤2 patients were progression-free at 6 months in first stage, the study would have been placed on hold and evaluated for closure for lack of efficacy. If the true %PFS is 0.25, the probability of terminating the study during the first stage is 0.60. If the true %PFS is 0.50, the probability that the study will be stopped during the first stage is 0.09. Accrual was continued during interim efficacy analysis. Four of 9 patients enrolled to Stage 1 were determined to be progression-free at 6 months, thus Stage 2 enrollment was continued and completed in September 2017.

8.5 Analysis Populations

8.5.1 Safety Population

The safety population will include all enrolled patients who receive at least one dose each of pembrolizumab plus GM-CSF and have the potential to complete 3 cycles (9 weeks) of safety assessments. All patients will be evaluable for toxicity and safety assessment from the time of their first treatment with the investigational combination. Patients who are determined ineligible after enrollment or who are not evaluable for safety analysis (e.g., due to withdrawal of consent or complications of biliary obstruction or drainage procedures assessed as not related to tumor progression and not treatment-related toxicity) prior to completing 3 cycles (9 weeks) will be replaced (see Section 5.9).

8.5.2 Efficacy Population

The evaluable population for the primary endpoint of ORR will include all enrolled patients who have measurable disease present at baseline, have received at least one complete cycle of therapy, and have had at least 1 radiographic response assessment or been removed from study due to event of clinical progression. Over-enrollment by approximately 10% is planned to ensure at least 37 patients are evaluable for primary endpoint of ORR.

8.6 Planned Analyses

8.6.1 Primary Endpoint Analysis

With expectation of at least 37 subjects with RECIST 1.1-measurable disease evaluable for response, ORR calculated as the proportion with CR + PR (confirmed + unconfirmed) by RECIST 1.1 at any time during the main study. Subjects with measurable disease at study entry who have unknown or missing response information will be treated as non-responders. Subjects with non-measurable disease at study entry will be excluded from ORR and DOR analyses.

For the primary endpoint of ORR, a sample size of 37 response-evaluable subjects will provide power of 77% with 2-sided 5% alpha and 88% with 1-sided 5% alpha to show ORR improvement from H_0 of 5% to H_1 of 20% on protocol treatment, using Fisher's Exact tests. Based upon a subset with non-measurable disease enrolled to Stages 1 and 2 before amendment requiring RECIST 1.1-measurable tumors for study enrollment to Expansion Cohort, along with potential for dropout in this population with comorbidity of biliary obstruction and liver disease, it is estimated that total enrollment of 42 subjects will yield approximately 37 response-evaluable subjects.

8.6.2 Secondary and Exploratory Endpoints

For secondary endpoints, due to the limited sample size in the study, descriptive statistics with mean and 95% confidence intervals will be used. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, min and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. For comparison between subgroups, ANOVA and t-tests will be used when appropriate to determine the association of the efficacy endpoints and specific biomarkers.

8.6.2.1 Safety

Safety events will be summarized based on frequency and proportion of total subjects, by system organ class and preferred term. Separate summaries with descriptive statistics will be presented according to anatomic subtype of biliary cancer (e.g. intrahepatic, hilar/perihilar, extrahepatic, GBC).

8.6.2.2 Tumor PD-L1 Expression Rate

The proportion of subjects overall and according to anatomic subtype with archival tumor samples positive for PD-L1 expression using the protocol-defined central IHC assay (QualTek Laboratories) (see Section 4.3.5.3.1) will be reported along with 95% CI. For subjects with more than one tumor sample available for testing, designation as positive for PD-L1 expression will be based upon ≥1 positive sample. With an expected evaluable sample size of approximately 36 tumor samples adequate for PD-L1 testing expected out of planned 42 total enrollment in the study, assuming 40% of tumors will be PD-L1+ expression, we will be able to estimate the 95%CI of the PD-L1+ expression as 27.7% - 53.9%]. Concordance and rates of positivity between primary and metastatic site, tumor location (e.g. liver vs. non-liver), and pre- and post-treatment samples will be described individually due to expectation of small subset/paired sample sizes.

8.6.2.3 PFS6

Proportion with PFS at 6 months (%PFS6) %PFS6 will be a key secondary endpoint for the overall study. With H_0 %PFS6 of approximately 20% (Section 4.3.6.2) and H_1 %PFS6 of 40% if n=40 are evaluable for PFS6, the power is 78% for 2-sided 5% alpha, or 87% with 1-sided 5% alpha using Fisher's Exact tests.

8.6.2.4 Median DOR, PFS, and OS

Median DOR will be summarized overall and according to anatomic subtype. Kaplan-Meier medians and quartiles may be provided if data warrant. Median PFS and OS will be summarized overall and according to anatomic subtype. If data warrant, Kaplan-Meier quartile estimates along with the 95% CI will be calculated. Descriptive summaries, including swim lane plots, may also be generated depending on results.

8.6.2.5 Re-Induction and Second Course Endpoints

Re-induction and Second Course outcomes for PFS, ORR, DOR, and OS will be measured as defined in Section 8.3.

8.6.3 Exploratory Correlative Analyses

For exploratory endpoints, due to the limited sample size in the study, descriptive statistics with mean and 95% confidence intervals will be used. We will explore immunologic and genomic biomarkers (including PBMC immune cell subsets, TCR clonotypes frequency and diversity, tumor immune subset composition and immune infiltrates, and tumor genotype) for relationships to anatomic subtype of biliary cancer, treatment received, and to the primary and secondary efficacy endpoints. No type I error will be adjusted for multiple endpoints. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, min and maximum. For categorical variables, descriptive statistics will include counts and percentages per category. For comparison between subgroups, ANOVA and t-tests will be used when appropriate to determine the association of the efficacy endpoints and the specific biomarkers. For association between biomarkers, Spearman correlations will be calculated to determine the significance of the association between the biomarkers of interest. Planned analyses are described further below.

8.6.3.1 PBMC Immune Cell Subsets, TCR Clonotype Frequency and Diversity, and Other Molecular and Genetic Analyses on PBMC

Serial blood samples will be collected at timepoints in Section 6.0 – Study Flow Chart. Circulating immune cell subsets will be measured using flow cytometry as has been previously described.[33,39] Pending funding and to be guided by clinical results of the overall study, frequency of individual TCR clonotypes and the diversity of overall TCR clonotype repertoire may be measured by next-generation sequencing as has been previously described.[40]

Baseline levels of individual PBMC immune cell subset components as well as change in levels after GM-CSF induction will be explored for relationship with ORR, PFS at 6 months, and other safety and efficacy endpoints (including DOR, OS, and CA 19-9 response) to determine if there is an association using Fisher's Exact tests.

If TCR sequencing is performed on PBMC derived T cells, the frequency of TCR clonotypes with identical sequences[40] would be calculated by dividing the number of identical sequence reads by the total number of sequencing reads for that sample. TCR repertoire diversity will be calculated as the number of unique clonotypes comprising the top 25% of cumulative reads sorted by

abundance.[40] Baseline frequency and diversity as well as changes in these parameters after GM-CSF induction would be explored for relationship with PFS at 6 months as well as secondary efficacy endpoints using Fisher's Exact tests.

Exploratory analyses will be conducted to compare clonotype diversity/frequency in the safety population and Expansion Cohort after single agent pembrolizumab on Cycle 2, Day 1 before initiation of GM-CSF, with clonotype diversity/frequency after initiation of GM-CSF (intra-patient comparison), as well as to compare clonotype diversity/frequency between the safety population and Expansion Cohort (after single-agent pembrolizumab) and the efficacy population (after combination therapy) on Cycle 2, Day 1 to better understand the relative impacts and timecourse of each study drug. TCR clonotypes frequency and diversity in PBMC samples may also be compared to tumor TCR analyses if adequate sample and funding for these analyses.

Additional analyses such as immune cell gene expression profiles may also be performed depending on sample adequacy for additional testing, procurement of funding, and the main study clinical outcomes.

8.6.3.2 Tumor Immune Infiltrating Cells (TIIC) and Immune Cell Subsets in Pre-Treatment and On-Treatment Tumor Samples

The presence of tumor immune infiltrating cells (TIIC) and tumor immune cell profiles will be explored for relationship with ORR, PFS at 6 months, and other secondary efficacy endpoints (including DOR, OS, CA 19-9 response) and with tumor PD-L1 status by IHC to determine if there is a relationship using Fisher's Exact tests.

Descriptive comparisons between baseline and on-treatment or post-treatment tumor samples, or between primary and metastatic site samples and according to tumor location (e.g. liver vs. non-liver), will be performed in cases with paired samples available and between subsets in the overall study.

8.6.3.3 Tumor Mutation Profile

For patients with available tumor sequencing results, specific mutations, TMB, pathways, and presence of genomic instability-related mutations will be described and explored for relationship to clinical outcomes including PFS, RR, DOR, OS, and CA 19-9 response. The tumor mutation profile will also be explored for association with PD-L1 status and presence of TIIC, based upon emerging evidence that specific tumor mutations can impact immune cell infiltration and activation.[19,45] Based upon current practice patterns at UCSF, it is expected that over 75% of the study population will have commercial tumor next-generation sequencing results available for these analyses.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Products

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.

9.1.1 Pembrolizumab

Clinical Supplies will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

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

9.1.2 GM-CSF (Sargramostim)

GM-CSF vials will be ordered by the Investigational Pharmacist from commercial supply. Vials will be provided along with syringes for injection and alcohol wipes for injection site sterilization at the start of each cycle. Day 1 dose for each Induction Cycle will be administered after pembrolizumab infusion by an infusion center RN or another qualified provider, along with self-injection training/re-training. Treatment adherence will be monitored by GM-CSF Patient Diary/Injection Record (see Section 5.2.3).

Table 8 Product Descriptions

Product Name & Potency	Dosage Form
GM-CSF solution	Liquid formulation containing benzyl alcohol in vials containing 500 µg

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person. Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.5 Returns and Reconciliation

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

9.6 Disposal and Destruction of Unused Investigational Products

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Pre-Study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Study Chair will have written and dated approval from the UCSF IRB for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

All investigators must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

10.2 Institutional Review Board Approval

The protocol, the proposed informed consent form, and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the UCSF IRB (Institutional Review Board). Prior to obtaining IRB approval, the protocol must be

approved by the Helen Diller Family Comprehensive Cancer Center GI Oncology Site Committee and by the Protocol Review Committee (PRC). The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

10.3 Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

10.4 Changes in the Protocol

Once the protocol has been approved by the UCSF IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the Investigator and approved by PRC and the IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five (5) working days after implementation.

10.5 Handling and Documentation of Clinical Supplies

The UCSF Study Chair will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The UCSF Study Chair or Pharmacy designee will maintain written records of any disposition of the study drug.

The Study Chair shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the Study Chair will not allow the investigational drug to be used in any manner other than that specified in this protocol.

10.6 Case Report Forms (CRFs)

The Study Chair and/or qualified designees will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs in accordance with the CTMS study calendar (see Section 6.0), using single data entry with a secure access account. The Clinical Research Coordinator (CRC) will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by UCSF personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The Study Chair or another qualified investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and CTMS data will be available for review/monitoring by the UCSF DSMC and regulatory agencies.

The Study Chair will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

10.7 Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center DSMC will be the monitoring entity for this study. The UCSF DSMC will monitor the study in accordance with the NCI-approved Data and Safety Monitoring Plan (DSMP). The DSMC will routinely review all adverse events and suspected adverse reactions considered "serious". The DSMC will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as applicable. See Appendix 11.1 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study, for additional information.

10.8 Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the study drugs, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, Study Chair-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the study shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being

investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

11.0 APPENDICES

11.1 Data and Safety Monitoring Plan for a Phase 2 or 3 Institutional Study

1. Oversight and Monitoring Plan

The UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC) Data and Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and subject safety for all HDFCCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of patient data.
- Review of serious adverse events.
- Auditing every six months (depending on study accrual).
- Minimum of a yearly regulatory audit.

2. Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety and discuss each patient's treatment at monthly site committee meetings. These discussions are documented in the site committee meeting minutes. The discussion will include the number of patients, significant toxicities in accordance with the protocol, and observed responses.

All institutional Phase II and III studies are designated with a moderate risk assessment (see Appendix H). The data is audited twice per year with twenty percent of the patients monitored (or at least three patients if the calculated value is less than three).

3. Review and Oversight Requirements

3.1 Adverse Event Monitoring

All Grade 3-5 Adverse Events (AEs), whether or not considered to be expected or unexpected and whether or not considered to be associated with the use of the study drug, will be entered into OnCore®, UCSF's Clinical Trial Management System.

Adverse Events are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) (version 4.03) as developed and revised by the Common Therapy Evaluation Program (CTEP) of the National Cancer Institute. Adverse events are further given an assignment of attribution or relationship to treatment or medical procedure. Attribution categories are:
• Definite – The adverse event is clearly related to the investigational agent(s) or medical procedure.
• Probable – The adverse event is likely related to the investigational agent(s) or medical procedure.
• Possible – The adverse event may be related to the investigational agent(s) or medical procedure.

• Unlikely – The adverse event is doubtfully related to the investigational agent(s) or medical procedure.
• Unrelated – the adverse event is clearly not related to the investigational agent(s) or medical procedure

All Grade 3-5 adverse events entered into OnCore® will be reviewed on a monthly basis at the Site Committee meetings. The Site Committee will review and discuss the selected toxicity, the toxicity grade, and the attribution of relationship of the adverse event to the administration of the study drug(s).

3.2 Serious Adverse Event Reporting

By definition, an adverse event is defined as a serious adverse event (SAE) according to the following criteria:

• Death.
• Life-threatening (i.e., results in an immediate risk of death).
• Requires inpatient hospitalization or prolongation of existing hospitalization.
• Permanent or significant disability/incapacity.
• Gives rise to a congenital anomaly/birth defect, or cancer, or any experience that suggests a significant hazard, contraindication, side effect, or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above.
• Event occurring in a gene therapy study.
• Event that changes the risk/benefit ratio of a study.
• Any other event the Principal Investigator judges to be serious or which would suggest a significant hazard, contraindication, side effect, or precaution.

Serious Adverse Event reporting will be in accordance with the UCSF IRB Regulations and Code of Federal Regulation Title 21 Part 312.32. The SAE will be reported on a Med Watch form.

UCSF IRB website for guidance in reporting serious adverse events:
https://irb.ucsf.edu/adverse-event

FDA website for guidance in reporting serious adverse events:
www.fda.gov/Safety/MedWatch/HowToReport/default.htm

Med Watch forms and information:
www.fda.gov/medwatch/getforms.htm

All serious adverse events are entered into OnCore®, as well as submitted to the IRB (per IRB guidelines) via iRIS®. The SAEs are reviewed and monitored by the Data and Safety Monitoring Committee on an ongoing basis and discussed at DSMC meetings, which take place every six weeks. The date the SAE is sent to all required reporting agencies will be documented in OnCore®.

If the SAE involves a subject death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or Vice Chair within 1 business day.

The reporting procedure is by communication via phone or in person with written documentation of the one-on-one communication via e-mail, with a copy of the e-mail to the DSMC Manager.

3.3 Review of Adverse Event Rates

If an increase in the frequency of Grade 3 or 4 adverse events (above the rate reported in the Investigator Brochure or package insert) is noted in the study, the Principal Investigator will notify the DSMC at the time the increased rate is identified. The report will indicate if the incidence of adverse events observed in the study is above the range stated in the Investigator Brochure or package insert.

If at any time the Investigator stops enrollment or stops the study due to safety issues, the DSMC Chair and DSMC Director must be notified within 1 business day via e-mail. and the IRB must be notified within 10 business days via an iRIS Reporting Form.

Data and Safety Monitoring Committee Contacts:

[redacted]
Box 1705
UCSF HDFCCC
San Francisco, CA 94158

DSMC Monitors
Box 0128
UCSF HDFCCC
San Francisco, CA 94143

(HDFCCC DSMP version 08Dec2017)

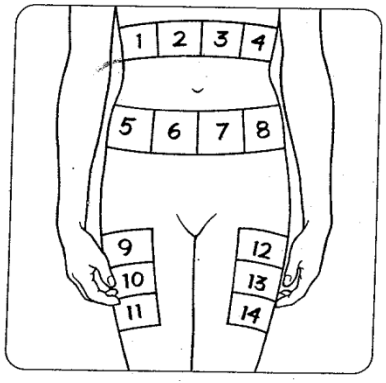
11.2 Patient Diary/Injection Record for GM-CSF

KEY-G GM-CSF Injection Record

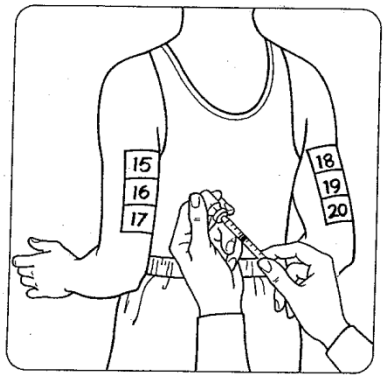
Patient Name _____ Dates of Treatment _____

Physician _____ Cycle Number (1, 2, 3 or R(number)) _____

Use a different injection site each day. Record the date, time, and injection site below.
Instructions: Inject once daily for 14 days in a row.



Abdomen & Thighs



Back of arms

Date	Time	Site	Date	Time	Site

Patient Signature _____ Date _____

11.3 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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).

11.4 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.5 Child Pugh Score

The Child Pugh score will be calculated at timepoints specified in Section 6.0, Study Flow Chart. Ascites should be assessed by clinical examination (rather than radiographic findings). Encephalopathy and ascites are considered as present (i.e. at least 2 points) in any patient taking medications for these conditions (e.g., lactulose, diuretics) even if well-controlled at the time of Child Pugh score assessment.

Appendix C: Child-Pugh Scoring System

Modified Child-Pugh classification of severity of liver disease (Pugh 1973, Lucey 1997) according to the degree of ascites, total bilirubin and albumin, prothrombin time, and degree of encephalopathy. Each measure is scored 1-3, with 3 indicating greatest severity:

	Points assigned		
Parameter	**1**	**2**	**3**
Ascites	absent	slight	moderate
Total bilirubin, mg/dL	≤ 2	2–3	> 3
Albumin, g/dL	> 3.5	2.8–3.5	< 2.8
Prothrombin time			
Seconds over control	1–3	4–6	> 6
or			
INR	< 1.8	1.8–2.3	> 2.3
Encephalopathy	none	Grade 1–2	Grade 3–4

11.6 Specimen Collection and Shipping Instructions and Laboratory Contact Information

11.6.1 Archival FFPE Tumor Blocks

Samples of all available archival specimens (preferentially at least 1 representative FFPE block(s) plus H&E slide(s) from prior diagnostic core biopsy or biopsies and/or resection specimen(s), or if block not available, at least 10*10µm unstained slides plus H&E slide will be requested, or maximum available in cases of limited sample) will be accessioned from UCSF and/or outside institution clinical laboratories as soon as possible after consent is obtained for study participation. Archival block will be logged and stored according to UCSF Tissue Core SOP or returned at end of study (after all planned tissue extraction for study correlative analyses in Section 8.7 has been completed) to outside institutions' Pathology departments depending on whether subject consented for any leftover material to be banked in companion banking and registry study, CC#124512 (see below). If multiple tumors and/or satellite nodules are present, at least 1 block and/or at least 10 unstained slides plus matching H&E slide should be requested for each discrete lesion whenever available.

Block/slides should be delivered or shipped to:

Attn: CC#154524

UCSF-Biospecimen Repository and Tissue Biomarker Technology Lab
UCSF Helen Diller Family Comprehensive Cancer Center
[redacted]

11.6.2 Whole Blood for PBMC Isolation

In all patients, approximately 60 mL of whole blood will be collected into green top (sodium heparin) tubes (e.g. six 10 cc tubes filled approximately to 10 mL) at the timepoints listed in the Study Flow Chart in Section 6.0 and according to instructions below. The tubes will be delivered by study coordinator or approved courier directly to the UCSF Immune Monitoring Core for PBMC isolation then freezing for future analysis in batch at end of study and pending funding.

Whole blood for PBMC Sample Collection and Delivery Instructions:

- Draw 60 mL into the appropriate number of green top tubes (e.g. six 10cc tubes) by phlebotomist or other trained health care provider.
- Invert the tube gently several times to avoid clotting.
- Label samples with study ID (CC#154524), subject ID, cycle/day, date, time of blood draw.
- For each delivery, an inventory of the samples should accompany the delivery. This inventory should include the study ID (CC#154524), subject ID, cycle/day, date, and time of blood draw.

- All samples should be delivered on a Monday through Thursday between approximately 9am-5pm PST or on a Friday between approximately 9am-1pm PST by a coordinator or approved courier service:
- Samples should not be sent after approximately 1pm Friday through Sunday or on University holidays, to prevent arrival over the weekend or on holidays, unless by special arrangement with the Fong lab staff.
- Samples have to be packed according to the ICAO/IATA-Packing-Instructions in a room temperature shipper or specimen bag.

Deliver samples at room temperature within approximately 12 hours or less after time of blood collection to:

Attn: CC#154524

Dr. Lawrence Fong's laboratory/UCSF HDFCCC Immune Monitoring Core
[redacted]

11.6.3 Expansion Cohort Research Biopsies

Among n=15 subjects enrolled to Expansion Cohort, it is expected that at least 12 will undergo paired tumor biopsy during Week 3 and Week 9 (Sections 6.4, 7.1.4.3). Two to 4 core needle biopsies (CNB), preferred 18-gauge (or smaller if needed to optimize safety) and 1 cm depth (or equivalent) if safely accessible based upon evaluation by proceduralist, should be obtained at each time point (Section 6.4) with the prioritization below. A fine needle aspirate is not acceptable unless CNB determined not feasible during procedure.

- Core biopsies (at least 2, up to 4) in order of priority depending on tissue accessibility:
- FFPE (1 core)
- Fresh (2 cores) with mirror matched FFPE slide
- Snap frozen (1 core) with mirror matched FFPE slide

FFPE and frozen research biopsy samples will be procured and stored by UCSF Biorepository:

Attn: CC#154524

UCSF-Biospecimen Repository and Tissue Biomarker Technology Lab
UCSF Helen Diller Family Comprehensive Cancer Center
[redacted]

[redacted]

Fresh research biopsy samples will be stored in the Fong Laboratory:

Attn: CC#154524

Dr. Lawrence Fong's laboratory/UCSF HDFCCC Immune Monitoring Core
[redacted]

11.6.4 Optional Specimen Banking in UCSF Hepatobiliary Tissue Bank CC#124512

For patients who consent to the companion study CC#124512, left-over specimens will be collected, processed, and banked according to CC#124512 protocol.

11.7 Adverse Event Reporting to Merck and FDA

Merck: Attn: Worldwide Product Safety; [redacted]

FDA

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B., initials, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (the patient identifiers are important so that the new information is added to the correct initial report).

MedWatch 3500A (Mandatory Reporting) form is available at:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

Additional Reporting Requirements for IND Holders

For Investigator-Sponsored IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited IND Safety Reports, according to the following guidance and timelines.

Seven (7) Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of pembrolizumab and GM-CSF. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event.

Fifteen (15) Calendar Day Written Report:

The investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of pembrolizumab and GM-CSF. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filled by the investigatory with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND Safety Reports with Analysis of Similar Events are to be submitted to the FDA within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A form, but alternative formats are acceptable (e.g. summary letter).

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