STATUS PAGE

PROTOCOL **16-257**

Closed To New Accrual

Closure Effective Date: 07/17/2017

Reason: Study Accrual Goal Met

No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Date Submitted: ***05/24/2017***

Alert Page

DF/HCC Protocol #: **16-257**

Safety / Drug (includes preparation, administration, dose modifications, equations)

Protocol Section 6.1: Dose modifications for Pegylated Liposomal Doxorubicin

Toxcity	Dose Adjustment
Neutropenia and Thrombocytopenia	
Grade 1	No dose reduction
Grade 2	Delay until ANC ≥ 1500 and plts ≥ **100,000**; resume treatment at previous dose
Grade 3	Delay until ANC ≥ 1500 and plts ≥ **100,000**; resume treatment at previous dose
Grade 4	Delay until ANC ≥ 1500 and plts ≥ **100,000**; resume at 25% dose reduction or continue previous dose with prophylactic granulocyte growth factor.

DANA-FARBER CANCER INSTITUTE
DANA-FARBER / HARVARD CANCER CENTER

Office for Human Research Studies

Protocol Front Sheet

DFCI Protocol No.: 16-257

1. PROTOCOL INFORMATION

Title: A Phase II Study of Pembrolizumab combined with pegylated liposomal doxorubicin (PLD) for recurrent platinum resistant ovarian, fallopian tube or peritoneal cancer

Phase: Phase 2 **Sponsor Study Number:** N/A

2. DF/HCC STUDY CONTACT INFORMATION

Primary Study Contact: Juliadele Male **Email:** jmale@partners.org **Phone:** 617-632-7496

INVESTIGATORS: (List only those under DFCI IRB, *i.e.*, from institutions listed in Section 6 below)

Overall PI:	Ursula A. Matulonis, MD	**Phone:**	617-632-2334	**Institution(s):**	DFCI	**Mgmt group:**	GYN Oncology
Site Responsible PI:	Richard Penson, MD	**Phone:**	617-724-4800	**Institution(s):**	MGH	**Mgmt group:**	GYN Oncology

3. DRUG / DEVICE INFORMATION N/A:

☒ **Drug(s), Biologic(s)**: Pembrolizumab, Doxil
Provided by: Merck
IND Exempt: ☐ -or-
IND#: 130120 **Holder Type:** DF/HCC Investigator
IND Holder Name: Ursula A. Matulonis, MD

☐ **Device(s) Name**:
Provided by:
IDE Exempt: ☐ -or-
IDE #: **Holder Type:** [pull down]
IDE Holder Name:

4. PROTOCOL COORDINATION, FUNDING, MODE

Regulatory Sponsor:
DF/HCC Investigator Ursula A. Matulonis, MD

CTEP Study: No

Funding/Support (check all that apply):
☒ Industry: Merck
☐ Federal Organization:
Grant #:
☐ Internal Funding:
☐ Non-Federal:
☐ Other:

Primary Disease Group: GYN Oncology

Protocol Involves (check all that apply as listed in the protocol document, even if not part of the research but is mandated by the protocol document):

☒ Chemotherapy
☒ Immunotherapy
☐ Surgery
☐ Bone Marrow/Stem Cell Transplant
☐ Cell Based Therapy
☐ Gene Transfer (use of recombinant DNA or synthetic nucleic acid molecules)
☐ Radiation Therapy
☐ Hormone Therapy
☐ Vaccine
☐ Engineered Cell Therapy (ECT)
☐ Data Repository
☐ Exercise/Physical Therapy
☐ Genetic Studies
☐ Human Material Banking
☒ Human Material Collection
☒ Medical Record Review
☐ Questionnaires/Surveys/Interviews
☒ Radiological Exams
☐ Required Biopsy Study
☐ Human Embryonic Stem Cell
☐ Quality of Life
☐ Other:

5. SUBJECT POPULATION (also applies to medical record review and specimen collection studies)

Total Study-Wide Enrollment Goal: 26 **Greater than 25% of the overall study accrual will be at DF/HCC:** ☒ Yes ☐ No

Total DF/HCC Estimated Enrollment Goal: 26 **Adult Age Range:** 18+ **Pediatric Age Range:** N/A

Will all subjects be recruited from pediatric clinics? ☐ Yes ☒ No

If enrolling both adults and pediatric subjects, anticipated percent of pediatric subjects: N/A

Retrospective Medical Record Reviews only (Please provide date range): from to

6. DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Beth Israel Deaconess Medical Center (BIDMC)
☐ Boston Children's Hospital (BCH)
☒ Brigham and Women's Hospital (BWH)
☒ Dana-Farber Cancer Institute (DFCI)
☒ Massachusetts General Hospital (MGH)
☐ Beth Israel Deaconess Medical Center – Needham (BIDMC-Needham)
☐ Dana-Farber/New Hampshire Oncology-Hematology (DFCI @ NHOH)
☐ Dana-Farber at Steward St. Elizabeth's Medical Center (DFCI @ SEMC)
☐ Dana-Farber at Milford Regional Cancer Center (DFCI @ MRCC)
☐ Mass General/North Shore Cancer Center (MGH @ NSCC)
☐ Mass General at Emerson Hospital – Bethke (MGH @ EH)
☐ DF/BWCC in Clinical Affiliation with South Shore Hospital (DFCI @ SSH)

7. NON-DF/HCC PARTICIPANTS UNDER DFCI IRB (check all that apply)

☐ Cape Cod Healthcare (CCH)
☐ Lowell General Hospital (LGH)
☐ New Hampshire Oncology-Hematology-P.A. (NHOH)
☐ Newton-Wellesley Hospital (NWH)
☐ Faulkner Hospital (FH)
☐ New England Cancer Specialists (NECS)
☐ Broad Institute

8. DF/HCC INITIATED STUDIES ONLY - INSTITUTIONAL PARTICIPANTS UNDER OTHER IRB (N/A:)

DF/HCC Multi-Center Protocols: (list institution/location)
Northwell Health/ Monter Cancer Center — Lake Success, NY

DF/PCC Network Affiliates: (list institution/location)

Protocol Number: 16-257

Approval Date: 07/19/2016 (IRB meeting date when protocol/consent approved or conditionally approved)

Activation Date: 09/01/2016 (Date when protocol open to patient entry)

Approval signatures are on file in the Office for Human Research Studies, tel. 617-632-3029.

Date Posted	Revised Sections	IRB Approval Date	OnCore Version Date
09/30/16	Protocol replaced due to Amendment # 1	08/31/16	n/a
Date Posted	**Revised Sections**	**Approved Date**	**Version Date (OnCore)**
11/04/16	MGH site added but not active: Consent Form and Front Sheet replaced due to Amendment #2	10/12/16	10/24/16
11/14/2016	Protocol, Eligibility Checklist and Consent Form replaced due to Amendment #3	10/31/2016	11/14/2016
12/29/16	Delayed Activation Amendment Status Page removed: MGH now active	N/A	N/A
01/10/17	Front Sheet replaced due to Amendment #4	01/05/17	N/A
01/11/17	Protocol and Eligibility Checklist replaced due to Amendment #5	01/01/17	N/A
03/10/17	Protocol, Eligibility Checklist and Consent Form replaced due to Amendment #6	03/06/17	03/10/17
06/15/17	Protocol replaced; Alert Page added due to Amendment #7	05/04/17	N/A
07/17/17	Study Closed – Study Accrual Goal Met	07/17/17	n/a
07/17/17	Study renewal/ Consent Form footer replaced per Continuing Review #1	06/15/2017	06/23/2017
09/11/17	Consent Form and Front Sheet replaced due to Amendment #8	08/18/2017	08/29/2017
12/29/2017	Consent Form, Protocol replaced per Amendment #9	12/09/2017	12/26/2017
04/24/2018	No updates to Online Documents per Amendment #10	04/18/2018	N/A
05/22/2018	Study renewal/Consent Form footer replaced per Continuing Review #2	05/22/2018	05/22/2018
09/19/2018	Protocol, Consent Form replaced per Amendment #12	09/19/2018	09/19/2018
09/19/18	Correction AM#12: AM 12 not ready to activate; previous documents posted	N/A	N/A
10/17/2018	Consent Form, Protocol replaced per Amendment #11	09/04/2018	n/a
10/17/2018	Consent Form, Protocol replaced per Amendment #12	09/19/2018	10/17/2018
04/24/2019	Study renewal/Consent Form footer replaced per Continuing Review #3	04/24/2019	04/24/2019

DF/HCC Protocol #: 16-257

TITLE: A Phase II Study of Pembrolizumab combined with pegylated liposomal doxorubicin (PLD) for recurrent platinum resistant ovarian, fallopian tube or peritoneal cancer.

Coordinating Center: Dana-Farber Cancer Institute
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Boston, MA 02215

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Agents:
Pegylated liposomal doxorubicin
Pembrolizumab (MK3475)

IND #: 130120
IND Sponsor: Ursula Matulonis, M.D.

SCHEMA

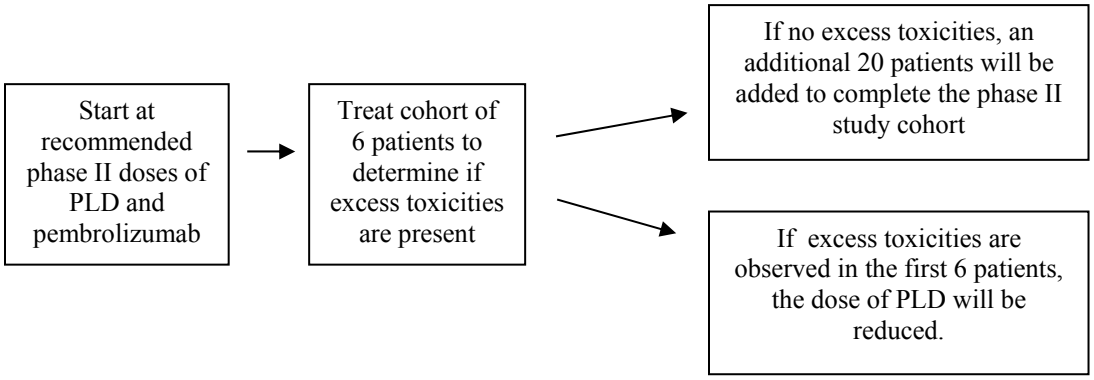
Start at recommended phase II doses of PLD and pembrolizumab
Treat cohort of 6 patients to determine if excess toxicities are present
If no excess toxicities, an additional 20 patients will be added to complete the phase II study cohort
If excess toxicities are observed in the first 6 patients, the dose of PLD will be reduced.

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a phase II study with a safety lead in of the combination of the recommended phase II doses of pegylated liposomal doxorubicin (PLD) and pembrolizumab for the treatment of platinum resistant recurrent ovarian, fallopian tube or peritoneal cancer.

1.2 Primary Objectives

1.2.1 To assess the clinical benefit (complete response + partial response or stable disease > 24 weeks) of the combination of PLD and pembrolizumab in patients with platinum resistant recurrent ovarian cancer. Initially, a six patient safety lead in will be performed of these 2 drugs combined together when used to treat patients with recurrent ovarian, peritoneal or fallopian tube cancer. If no more than 1 patient of the first 6 patients has evidence of dose limiting toxicities, an additional 20 patients will be added to complete the phase II study.

1.3 Secondary Objectives

1.3.1 To gain an estimate of toxicities for these agents when combined to treat platinum resistant recurrent ovarian, fallopian tube or peritoneal cancer

1.3.2 To gain an estimate of preliminary response rate for these agents when combined for the treatment of platinum resistant ovarian cancer, progression free survival (PFS), overall survival (OS), time to progression (TTP), and duration of response.

1.3.3 To perform exploratory translational studies on formalin fixed paraffin embedded tumor that include nanostring as well as PDL1 and exploratory immune markers.

2. BACKGROUND

2.1 Study Disease: Ovarian Cancer

Ovarian cancer is a lethal cancer that affects women globally, is diagnosed at an advanced stage in most patients and has no effective screening tests for early detection (1-3). The worldwide incidence of this cancer is 225,500 diagnoses per year; in the United States in 2015, approximately 21,980 women will be diagnosed with ovarian cancer (1, 2). Global mortality of this cancer remains high with 140,200 deaths per year, and minimal improvement in mortality has been observed for women diagnosed with advanced ovarian cancer over the past decade (1, 2).

Treatment strategies that have led to an overall survival (OS) improvement for newly diagnosed patients have included the addition of paclitaxel to platinum, the use of intraperitoneal cisplatin in patients with optimally cytoreduced cancer (<1 cm of residual cancer after upfront

cytoreductive surgery), and incorporation of weekly paclitaxel versus every 3 week paclitaxel as part of upfront treatment for ovarian cancer (4-6). Neoadjuvant chemotherapy has emerged as a treatment alternative especially in patients who are unable to undergo upfront cytoreductive surgery because of the extent of cancer or those patients who are too ill or frail to undergo upfront cytoreductive surgery (7, 8). Anti-angiogenics, specifically bevacizumab, were the first biologic to be tested in ovarian cancer but to date addition of bevacizumab in randomized trials has demonstrated progression free survival (PFS) benefit, but no OS benefit (9-11).

Unfortunately, most patients will recur after being diagnosed with advanced ovarian cancer; for patients with platinum-sensitive recurrence (defined as cancer recurring ≥6 months after the last platinum), additional platinum-based therapy is given. For patients with recurrent platinum resistant cancer (defined as cancer recurring <6 months after last platinum), single agent chemotherapy is administered. New agents and rationale combinations of biologics and chemotherapy are needed to improve outcomes in women with recurrent ovarian cancer, such as chemotherapy combined with immunotherapy agents. The first 2 agents since the last approval in 2006 (carboplatin and gemcitabine for platinum sensitive recurrence) were approved by the Food and Drug Administration (FDA) in 2014: bevacizumab in combination with chemotherapy in patients with platinum resistant ovarian cancer and the oral PARP inhibitor olaparib for women with a g*BRCA* mutation, recurrent ovarian cancer and who have received at least 3 lines of prior chemotherapy.

Many chemotherapy options exist for women with recurrent ovarian cancer but none of them are curative, and most agents used in the platinum resistance recurrent setting have response rates that are 10% or less. Pegylated liposomal doxorubicin (PLD) is a standard of care treatment for recurrent ovarian cancer (12-14).

2.2 Pegylated Liposomal Doxorubicin (PLD)

PLD is approved in the U.S., Canada, and Europe for use in ovarian cancer following progression of cancer after platinum-based chemotherapy and represents a standard of care treatment for women with relapsed ovarian cancer (15).

PLD has demonstrated anti-cancer activity in both phase II and III studies; phase III studies have compared PLD to topotecan as well as other agents. Response rates for platinum resistant recurrent ovarian cancer are approximately 10%. Progression-free survival (PFS) for PLD in patients with recurrent ovarian cancer is approximately 3-4 months (12-14). Known toxicities of PLD include: hand-foot syndrome, mucositis, cardiotoxicity, myelosuppression, liver impairment, and infusion-related reactions. See the PLD Package Insert for other reported toxicities and additional details of clinical studies as well as toxicity management.

2.3 Pembrolizumab

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

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. 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 participants with melanoma (MEL). 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 States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

2.4 Rationale

2.4.1 Rationale for testing PLD and pembrolizimab in recurrent ovarian cancer

The rationale to combine the anti-PD1 monoclonal antibody pembrolizumab with chemotherapy to treat ovarian cancer includes the following;

1) PDL1 is overexpressed in ovarian cancer and PD1 is overexpressed in TILs. The presence of TILs in advanced stage ovarian carcinomas predicts for a better overall outcome with improved PFS and OS compared to those cancers which lack TILs (1,2). Increased frequency of Treg cells in patients with ovarian cancer can predict a poorer survival.

2) Anti-cancer synergy has been demonstrated with anti-PD1 antibodies and chemotherapy (16-18). Several clinical trials are open using both chemotherapy and immunotherapy agents.

3) Reduction in tumor burden through chemotherapy can potentiate an immune response, thus the rationale exists to combine a chemotherapy agent such as PLD with a PD1 inhibitor (16-18).

2.4.2 Rationale for flat dose of pembrolizumab

An open-label Phase I trial (Protocol 001) is being 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 participants 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, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. 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 simplifies 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.

2.5 Correlative Studies Background

FFPE will be collected for exploratory immune markers as tested by immunohistochemical (IHC) staining of specific markers and PDL1 expression to be done at Merck.

1) Formalin fixed-paraffin embedded (FFPE) tumor slices will be prepared and H&E stained for assessment of TIL in tumor samples. To identify different immune cell populations (effector/memory/ CD8 cells, T regulatory cells, dendritic cells, tumor associated macrophages, NK cells, TEM) IHC staining will be performed on FFPE tumor slices using the following antibodies: CD3, CD4, CD8, CD25, FoxP3, Indoleamine 2,3 deoxygenase-1 (IDO), CD11c, CD83, CD86, CD56, CD14, and CD16. Also included will be recently developed IHC staining on FFPE samples for PD-L1, PD-L2, TIM-3 and LAG-3 through the center for Immuno-oncology Pathology Core at the Dana-Farber Cancer Institute (Scott Rodig, M.D., Ph.D. Core Director).

2) PDL1 IHC staining at Merck: Merck has asked that tumor samples also be sent to their facility for PDL1 staining using their technique and staining. QualTek has developed and validated a PD-L1 IHC assay using Merck's proprietary 22C3 antibody. This assay has served as the prototype companion diagnostic assay and has been used by QualTek to test thousands of clinical samples, including those for prospective enrollment in other clinical trials. The PD-L1 IHC assay has been validated and tested in over 20 different tumor indications in various clinical

studies and on thousands of archived FFPE samples.

3) Nanostring analysis will be performed at Merck. Merck will perform gene profiling analysis using the nanostring platform to identify new biomarkers and gain insight to molecular basis of anti-PD-1 resistance with samples from this study. For each patient enrolled in the study, 4 unstained slides (4-5 micron sections) per sample of FFPE tumor will be sent to Merck. Samples will be analyzed for gene expression using nanostring which is an 800 gene immune-response focused panel and results will be shared with the overall PI, Dr. Matulonis.

3. PARTICIPANT SELECTION

3.1 Participant Inclusion Criteria

In order to be eligible for participation in this trial, the participant must meet the following eligibility criteria:

3.1.1 Be willing and able to provide written informed consent/assent for the trial.

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

3.1.3 Have measurable disease based on RECIST 1.1 criteria.

3.1.4 Have a histologically confirmed diagnosis of epithelial ovarian cancer, fallopian tube or peritoneal cancer. All histologies of epithelial ovarian cancer are eligible except for carcinosarcomas.

3.1.5 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, biologic/targeted (non-cytotoxic) agents (e.g., bevacizumab) or extended therapy administered after surgical or non-surgical assessment.

3.1.6 Patients must have platinum resistant cancer with a platinum free interval of < 6 months. Progression after last platinum is based on investigator assessment.

3.1.7 Patients are allowed to receive, but are not required to receive, up to two additional cytotoxic regimens for management of recurrent or persistent disease, with no more than 1 prior non-platinum cytotoxic chemotherapeutic regimen.

Patients are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy as part of prior treatment. For the purposes of this study, Poly (ADP-ribose) polymerase (PARP) inhibitors will be considered "cytotoxic." Patients are allowed to receive, but are not required to receive, PARP inhibitors for management of primary or recurrent/persistent disease (either alone or in combination with cytotoxic chemotherapy). Single agent hormonal therapies will not be counted as a line of treatment.

3.1.8 Have confirmation of available tissue from an archived specimen of ovarian cancer. If there is no archival tissue available, the participant will be required to undergo a biopsy to obtain a fresh tumor sample.

3.1.9 Have a performance status of 0 or 1 on the ECOG Performance Scale (Appendix A).

3.1.10 Demonstrate adequate organ function as defined in Table 1, all screening labs must be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
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 participant with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for participants with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless participant 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.	

3.1.11 Female participants of childbearing potential must have a negative 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.

3.1.12 Female participants of childbearing potential must 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. Participants of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

3.2 Participant Exclusion Criteria

The participant must be excluded from participating in the trial if the participant has any of

the following:

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

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

3.2.3 Patients cannot have primary platinum refractory cancer, i.e. documented cancer progression while receiving platinum or within one month of receipt of a platinum based regimen.

3.2.4 Has received a prior anthracycline chemotherapy either for ovarian cancer treatment or another previous malignancy.

3.2.5 Left ventricular ejection fraction (LVEF) defined by multigated acquisition (MUGA) or echocardiogram which is below the institutional lower limit of normal prior to starting study treatment.

3.2.6 Has a known history of active TB (Bacillus Tuberculosis)

3.2.7 Known hypersensitivity to pembrolizumab or any of its excipients and/or liposomal doxorubicin.

3.2.8 Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy 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.

i. Note: If participant underwent major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

ii. Note: Participants with alopecia are an exception to this criterion.

3.2.9 Has a known additional malignancy that is progressing or requires active treatment. In addition, patients cannot have been diagnosed with another malignancy within 3 years of starting treatment. Exceptions include fully resected basal cell carcinoma of the skin or squamous cell carcinoma of the skin, in situ cervical cancer, fully resected ductal carcinoma in situ, and stage IA, noninvasive grade I endometrial cancer, that has undergone curative therapy.

3.2.10 Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Participants 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 clinically active and significant carcinomatous meningitis which is excluded regardless of clinical stability.

3.2.11 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 (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

3.2.13 Has an active infection requiring systemic therapy.

3.2.14 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the participant's participation for the full duration of the trial, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

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

3.2.16 Is pregnant or breastfeeding, or expecting to conceive 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.

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

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

3.2.19 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.20 Has received a live vaccine within 30 days of planned start of study therapy.
Note: 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.

3.2.21 The following are additional exclusion criteria for patients enrolling post safety run in:

3.2.21.1 Any clinical or radiographic evidence of a partial or complete bowel obstruction (small or large bowel) currently or within the past 6 months.

3.2.21.2 No current dependency on total parental nutrition (TPN) or within the past 30 days.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the ODQ protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC and DF/PCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the ODQ.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Project Manager. All sites should email or fax the documentation listed in section 4.4 to the Project Manager to verify treatment availability.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Project Manager should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the research nurse or study coordinator should email the following documentation to the Project Manager or fax to 617-394-2662:

- Copy of clinic visit note documenting medical history and physical exam
- Lab documentation as per eligibility criteria
- Pathology report
- CT (chest/abdomen/pelvis) scan report
- ECHO/MUGA report
- EKG report
- Signed participant consent form, and consent process note
- HIPAA authorization form
- Completed Eligibility checklist

To complete the registration process, the Project Manager will

- follow the DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) and register the participant on the protocol
- call and fax or email the research nurse or data manager at the participating site with the participant study number, and to confirm registration

NOTE: Registration can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

5. TREATMENT PLAN

5.1 Treatment Regimen

The treatment to be used in this trial is outlined below in Table 2:

Table 2 Trial Treatment

Drug*	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pegylated Liposomal Doxorubicin	40 mg/m^2	Once every 4 weeks	IV infusion over one hour per FDA package insert	One cycle = 28 days	FDA approved treatment for platinum resistant ovarian cancer
Pembrolizumab	200 mg as a flat dose	Once every 3 weeks	IV infusion per the FDA package insert	One cycle = 28 days	Experimental

*The drugs may be held independent of one another, however, the study clock will not stop as far as determining the cycle/day of treatment.

If there are 2 DLTs within the first 6 patients during the safety lead-in, the dose of PLD will be lowered to 30 mg/m2.

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

Participants must continue to meet all eligibility criteria prior to dosing on Cycle 1, Day 1, as outlined in Protocol Section 3.1.

5.2.2 Subsequent Cycles, on PLD treatment days: Patients must have all of the following:

Absolute Neutrophil Count: ≥ 1,500/mcL
Hemoglobin: ≥ 9g/dL
Platelets: ≥ 100,000/mcL
Serum Creatinine ≤ 1.5 x ULN
Liver Function Test ≤ 2.5 x ULN
ECOG performance status of 0-1

5.3 Agent Administration

5.3.1 Pegylated Liposomal Doxorubicin (PLD):

5.3.1.1 Administration

PLD is administered intravenously, and the first dose of PLD should be administered at a range of 1 mg per minute as per the FDA package insert. If no infusion reactions occur, the infusion rate can be increased to complete the administration of the drug over one hour. The infusion line should not be rapidly flushed.

5.3.1.2 Dosing

The dose used in this study will be 40 mg/m2 IV once every 4 weeks. The drug may be administered $\pm$3 days from the scheduled next infusion because of vacations, weather, holidays, etc. The dose should be calculated using the weight and height on the day of infusion, and actual body weight should be used as per the package insert.

5.3.1.3 Drug, Tubing and Filtration

PLD should not be used with in-line filters. Please see the PLD package insert for additional details, and PLD should be administered per the FDA package insert and institutional policies.

5.3.1.4 Hydration

There is no required hydration. Any hydration will be determined by the treating investigator.

5.3.1.5 Special Equipment

No special equipment is needed for PLD infusion.

5.3.1.6 Observation period

There is no stated length of observation for PLD, and should be determined by the treating investigator.

5.3.1.7 Infusion Reactions

Infusion reactions are described with PLD. The PLD package insert and standard institutional policy should be followed for management of these reactions. Desensitization procedures are permitted in participants who experience an allergic reaction to PLD. Patients who have an allergic reaction to PLD are allowed to continue on the protocol after a discussion with the Overall PI and a consultation with allergy. A desensitization procedure administers the total planned dose of PLD over a longer period of time under the guidance of the Investigator and Allergist. The duration of the infusion of PLD may vary with each patient's specific symptoms.

5.3.1.8 Order of Administration

If PLD and pembrolizumab infusions do occur on the same day, pembrolizumab should be given first, followed by PLD.

5.3.1.9 Caregiver Precautions

There are no specific caregiver precautions. Patients may develop, after PLD infusion, a reddish-orange color to their urine and other body fluids. This non-toxic reaction is due to the color of the PLD product and will dissipate as the drug is eliminated.

5.3.2 **Pembrolizumab**:

5.3.2.1 Administration and Dosing

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. The drug may be administered $\pm$3 days from the scheduled next infusion because of vacations, weather, holidays, etc. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

5.3.2.2 Drug, Tubing and Filtration

No special IV tubing and/or filtration are necessary.

5.3.2.3 Hydration

There is no required hydration. Any hydration will be determined by the treating investigator as clinically indicated.

5.3.2.4 Observation period

Per package insert for pembrolizumab.

5.3.2.5 Protocol specific procedures

Vital signs should be taken as per institutional policy.

5.3.2.6 Infusion Reactions

Infusion reactions are described with pembrolizumab. Please see section 6.3. Desensitization procedures are permitted in participants who experience an allergic reaction to pembrolizumab. Patients who have an allergic reaction to pembrolizumab are allowed to continue on the protocol after a discussion with the Overall PI and a consultation with allergy. A desensitization

procedure administers the total planned dose of pembrolizimab over a longer period of time under the guidance of the Investigator and Allergist. The duration of the infusion of pembrolizumab may vary with each patient's specific symptoms.

5.3.2.7 Order of Administration

If PLD and pembrolizumab infusions do occur on the same day, pembrolizumab should be given first, followed by PLD.

5.4 Definition of Dose-Limiting Toxicity (DLT)

Toxicities that are considered DLT toxicities that occur during the first 4 weeks of treatment will be monitored; if 2 out of the first 6 patients develop a DLT, the dose of PLD will be reduced to 30 mg/m^2.

Definition of DLT: Dose limiting toxicity (DLT) refers to both non-hematologic and hematologic toxicities deemed by the treating physician to be related to study treatment experienced during the first cycle (i.e. first 4 weeks) of treatment.

A DLT will be defined as any of the following, occurring during Cycle 1:

1. Non-Hematologic Toxicity
   Any Grade 3 or 4 event, excluding:
   - Fatigue
   - Grade 3 nausea and/or vomiting controlled with supportive measures within 24 hours,
   - Grade 3 constipation controlled with supportive measures within 24 hours,
   - Grade 3 diarrhea controlled with supportive measures within 24 hours,
   - Grade 3 hypophosphatemia,
   - Grade 3 hyponatremia,
   - Grade 3 hypomagnesemia
   - Grade 3 rash that does not resolve to grade 2 or grade 1 within $\leq$ 5 days

2. Hematologic Toxicity
   - Grade 4 neutropenia of > 7 day's duration
   - Febrile neutropenia (a disorder characterized by an ANC < 1000/mm^3 and a single temperature of > 38.3 °C (101 °F) or a sustained temperature of $\geq$ 38 °C (100.4 °F) for more than one hour.
   - Dose delay of greater than 3 weeks (21 days) due to failure to recover counts.
   - Grade 4 thrombocytopenia or bleeding associated with grade 3 thrombocytopenia. Any other hematologic toxicities of Grade 4

   Requirement for repeated blood transfusion within 4-6 weeks

3. Any study treatment related death.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for 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 Overall Principal Investigator, who will then contact the Merck Clinical team as needed. The final decision on any supportive therapy or vaccination rests with the Overall Principal Investigator and/or the participant's primary physician.

5.5.2 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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

5.5.3 Prohibited Concomitant Medications

Participants 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
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after discussion with the Overall PI..
- 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 an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Overall PI and Sponsor.

Participants 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.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Participant has completed 35 treatments (approximately 2 years) with pembrolizumab (Note: participant may continue on study receiving only PLD at the discretion of the treating investigator)

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

Regarding length of duration of treatment of PLD, investigator should follow the FDA package insert for PLD.

Before participants continue on PLD for more than 8 cycles, the treating physician must confer with the Overall PI and obtain approval to do so.

If participants are removed from PLD therapy because of PLD toxicities, they are tolerating Pembrolizumab, and there is no evidence of RECIST progression, participants may continue on Pembrolizumab alone after discussion and approval from the Overall PI.

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff. Other investigative sites will inform the Project Manager as soon as a participant is taken off protocol therapy. The Project Manager will then make the relevant updates in OnCore.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI,

- Ursula Matulonis, M.D. at umatulonis@partners.org.

5.7 Duration of Follow Up

Participants will be followed for 4 weeks after removal from protocol therapy for adverse events. Participants will be followed for survival. Follow-up will be reported in 3 month intervals for up to two years after removal from study treatment or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.8 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team submits a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff. Other investigative sites will inform the Project Manager as soon as a participant is taken off study. The Project Manager will then make the relevant updates in OnCore.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Investigators should assess toxicities and make a determination which agent(s) is responsible for the toxicity and grade the toxicity. Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Dose modifications for Pegylated Liposomal Doxorubicin

If patients experience treatment-related toxicities, their PLD dose should be reduced according to institutional prescribing and dose-reduction standards per the below tables.

If greater than two dose reductions are required, discussion and approved must be obtained by the Overall PI.

Recommended dose reductions for PLD (Doxil) per the FDA package insert:

Hand Foot Syndrome

Toxicity	Dose Adjustment
Hand Foot Syndrome	
Grade 1: Mild erythema, swelling, or desquamation not interfering with daily activities	• If no previous Grade 3 or 4 HFS, no dose adjustment. • If previous Grade 3 or 4 HFS, delay dose up to 2 weeks, then decrease dose by 25%.
Grade 2: Erythema, swelling, or desquamation interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2 cm. in diameter.	• Delay dosing up to 2 weeks or until resolved to grade 0 or 1. • Discontinue doxil if no resolution after 2 weeks. • If resolved to grade 0 or 1 within 2 weeks: <u>and no</u> previous grade 3 or 4 HFS, continue treatment at previous dose or <u>And</u> previous Grade 3 or 4 toxicity; decrease dose by 25%
Grade 3: Blistering, ulceration, or swelling interfering	• Delay dosing up to 2 weeks or until resolved to grade 0 or 1,

with walking or normal daily activities; cannot wear regular clothing.	then decrease dose by 25% • Discontinue doxil if no resolution after 2 weeks
Grade 4: Diffuse or local process causing infectious complications, or a bed ridden state or hospitalization.	• Delay dosing up to 2 weeks or until resolved to grade 0 or 1, then decrease dose by 25% • Discontinue doxil if no resolution after 2 weeks

Stomatitis

Toxicity	Dose Adjustment
Stomatitis	
Grade 1: Painless ulcers, erythema, or mild soreness	• If no previous Grade 3 or 4 toxicity, no dose adjustment. • If previous Grade 3 or 4 toxicity, delay dose up to 2 weeks, then decrease dose by 25%.
Grade 2: Painful erythema, edema or ulcers but can eat.	• Delay dosing up to 2 weeks or until resolved to grade 0 or 1. • Discontinue doxil if no resolution after 2 weeks. • If resolved to grade 0 or 1 within 2 weeks: <u>and no</u> previous grade 3 or 4 HFS, continue treatment at previous dose or <u>And</u> previous Grade 3 or 4 toxicity; decrease dose by 25%
Grade 3: Painful erythema, edema or ulcers and cannot eat.	• Delay dosing up to 2 weeks or until resolved to grade 0 or 1. Decrease dose by 25% and return to original dose interval • Discontinue doxil if no resolution after 2 weeks
Grade 4: Diffuse or local process causing infectious complications, or a bed ridden state or	• Delay dosing up to 2 weeks or until resolved to grade 0 or 1, then decrease dose by 25% and

hospitalization.	return to original dose interval • Discontinue doxil if no resolution after 2 weeks

Neutropenia and Thrombocytopenia

Toxcity	Dose Adjustment
Neutropenia and Thrombocytopenia	
Grade 1	No dose reduction
Grade 2	Delay until ANC ≥ 1500 and plts ≥ 100,000; resume treatment at previous dose
Grade 3	Delay until ANC ≥ 1500 and plts ≥ 100,000; resume treatment at previous dose
Grade 4	Delay until ANC ≥ 1500 and plts ≥ 100,000; resume at 25% dose reduction or continue previous dose with prophylactic granulocyte growth factor.

6.2 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. See Section 6.3.1 and Events of Clinical Interest Guidance Document for supportive care guidelines (**Appendix B**), including use of corticosteroids.

Table 3
Dose Modification Guidelines for Drug-Related Adverse Events (Please also see Appendix B)

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Participant
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated	Resume pembrolizumab when patients are clinically and metabolically stable.

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Participant
Hyperglycemia		with evidence of beta cell failure.	
Hypophysitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	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.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue

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

[1] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

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

After discussion and approval from the Overall PI, dosing interruptions are permitted in the case

of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). The reason for interruption should be documented in the patient's study record.

6.3 Rescue Medications & Supportive Care

6.3.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator 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 6 for dose modification.

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

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

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

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

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

Table 4 below shows treatment guidelines for participants 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant 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 participant should be premedicated for the next scheduled dose.	Participant 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
	Participants who develop Grade 2 toxicity despite adequate premedication should be referred to allergy after discussion with the PI.	
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 participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Participant 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.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting in addition to routine reporting. For Events of Clinical Interests (ECIs) please see Appendix B for reporting guidelines to Merck.

7.1. Expected Toxicities

7.1.1 PLD

The most common adverse reactions observed with DOXIL are asthenia, fatigue, fever, nausea, stomatitis, vomiting, diarrhea, constipation, anorexia, hand-foot syndrome, rash and neutropenia, thrombocytopenia and anemia.

Other more rare toxicities include:
1) Cardiac toxicity: Special attention must be given to the risk of myocardial damage from cumulative doses of doxorubicin HCl. Acute left ventricular failure may occur with doxorubicin, particularly in patients who have received a total cumulative dosage of doxorubicin exceeding the currently recommended limit of 550 mg/m$_2$. Lower (400 mg/m$_2$) doses appear to cause heart failure in patients who have received radiotherapy to the mediastinal area or concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. Prior use of other anthracyclines or anthracenodiones should be included in calculations of total cumulative dosage. Congestive heart failure or cardiomyopathy may be encountered after discontinuation of anthracycline therapy. Patients with a history of cardiovascular disease should be administered

DOXIL only when the potential benefit of treatment outweighs the risk. Cardiac function should be carefully monitored in patients treated with DOXIL. The most definitive test for anthracycline myocardial injury is endomyocardial biopsy. Other methods, such as echocardiography or multigated radionuclide scans, have been used to monitor cardiac function during anthracycline therapy. Any of these methods should be employed to monitor potential cardiac toxicity in patients treated with DOXIL. If these test results indicate possible cardiac injury associated with DOXIL therapy, the benefit of continued therapy must be carefully weighed against the risk of myocardial injury.

2) Infusion reactions: Acute infusion-related reactions were reported in 7.1% of patients treated with DOXIL in the randomized ovarian cancer study. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension.

In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

The majority of infusion-related events occurred during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the DOXIL liposomes or one of its surface components. The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions.

3) Radiation recall: can rarely occur.

4) Fetal mortality: Most of our patients will not be child-bearing and if they are, eligibility requirements require use of contraception.

7.1.2 **Pembrolizumab**:

The most common adverse reactions (reported in ≥20% of patients) include: Fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea.

Immune-mediated adverse reactions include the following:

- Immune-mediated pneumonitis
- Immune-mediated colitis
- Immune-mediated hepatitis
- Immune-mediated hypophysitis
- Immune-mediated nephritis
- Immune-mediated hyperthyroidism and hypothyroidism
- Embryofetal toxicity

Other more rare toxicities include:
1) Immune-mediated adverse reactions occurred in less than 1% of patients, and include the

following : exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, andadrenal insufficiency. Across clinical studies with pembrolizumab, in approximately 2000 patients, the following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients: myasthenic syndrome, optic neuritis, and rhabdomyolysis.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of DF/HCC Expedited Reporting Guidelines.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.2 For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, both expected (unless listed in the protocol as not requiring expedited reporting) and unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

7.3.3 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC and DF/PCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Overall PI within the timeframes detailed in the table below.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.					

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

8.1 Pegylated Liposomal Doxorubicin

8.1.1 Description

Per the package insert: PLD or DOXIL (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in STEALTH® liposomes for intravenous administration (PLD package insert). Doxorubicin is an anthracycline topoisomerase inhibitor isolated from *Streptomyces peucetius* var. *caesius*. Doxorubicin HCl, which is the established name for (8S,10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycolyl-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione hydrochloride. The active ingredient of DOXIL is doxorubicin HCl. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind DNA and inhibit nucleic acid synthesis. Cell structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations.

PLD is doxorubicin HCl encapsulated in long-circulating STEALTH® liposomes. Liposomes are microscopic vesicles composed of a phospholipid bilayer that are capable of encapsulating active drugs. The STEALTH® liposomes of DOXIL are formulated with surface-bound methoxypolyethylene glycol (MPEG), a process often referred to as pegylation, to protect liposomes from detection by the mononuclear phagocyte system (MPS) and to increase blood circulation time. STEALTH® liposomes have a half-life of approximately 55 hours in humans. They are stable in blood, and direct measurement of liposomal doxorubicin shows that at least 90% of the drug (the assay used cannot quantify less than 5-10% free doxorubicin) remains liposome-encapsulated during circulation. It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated DOXIL liposomes are able to penetrate the altered and often compromised vasculature of tumors.

8.1.2 Form

PLD is a sterile, translucent, red liposomal dispersion for IV administration. PLD is supplied at a concentration of 2 mg/mL in 10-mL or 30-mL single-use vials. PLD doses up to 90 mg must be diluted in 250 mL of 5% dextrose injection, USP, prior to infusion. PLD doses exceeding 90 mg must be diluted in 500 mL of 5% dextrose injection, USP, prior to infusion. Diluted PLD should be refrigerated at 2°Cto 8°C (36°Fto 46°F). Each vial and carton will contain a label, either single-panel or booklet, affixed to the vial or carton. PLD should not be administered using an in-line filter.

8.1.3 Storage and Stability

PLD should be stored as per Institutional pharmacy guidelines and the FDA package insert for PLD. Per the package insert, unopened vials of PLD should be refrigerated between 2 and 8 degrees C and should not be frozen.

8.1.4 Compatibility

There are no known compatibility effects between PLD and pembolizumab.

8.1.5 **Handling**
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 **Availability**
PLD is available per Institutional pharmacy guidelines since this is an FDA-approved agent for recurrent ovarian cancer.

8.1.7 **Preparation**
PLD should be prepared as per Institutional pharmacy guidelines and the FDA package insert for PLD.

8.1.8 **Administration**
PLD should be administered as per Institutional pharmacy guidelines and the FDA package insert for PLD. PLD should not be administered as an IV push or bolus. Infusion reactions may occur. To attenuate infusion reactions, premedication consisting of acetaminophen (or paracetamol), diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (e.g., up to 100 mg or an equivalent dose of methylprednisolone) may be administered beginning with the first infusion, per standard clinical practice.

8.1.9 **Ordering**
Investigative sites will order their own supply of PLD as per institutional guidelines.

8.1.10 **Accountability**
The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent according to institutional guidelines for commercial agents.

8.1.11 **Destruction and Return**
Investigative sites will destroy PLD as per institutional guidelines

8.2 Pembrolizumab

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

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

hydroxide to adjust pH to 5.5. Pembrolizumab is a sterile, preservative-free, latex free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

8.2.3 Compatibility

There are no known compatibility effects between PLD and pembolizumab.

8.2.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) and should be protected from light. Note: vials should be stored in the original box to ensure the drug product is protected from light. The vials should not be shaken.

MK-3475 infusion solutions should be prepared in 0.9% Sodium Chloride Injection, USP (normal saline) and the final concentration of MK-3475 in the infusion solutions should be between 1.0 mg/mL and 10.0 mg/mL. If rounding is necessary, round up to one decimal place. Availability Pembrolizumab will be provided by Merck and will be ordered by the pharmacy of each institution.

Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. The 6 hour countdown begins when the vial is pierced, and includes room temperature storage of reconstituted drug product solution in vials, room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6 hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)

In addition, reconstituted vials and/or IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

8.2.3 Availability

Pembrolizumab will be provided by Merck and will be ordered by the pharmacy of each institution.

8.2.4 Preparation

Aseptic technique must be strictly observed throughout the preparation procedure preferably in a biologic safety cabinet or hood since no anti-microbial preservative is present in the solutions. Equilibrate required number of MK-3475 vials to room temperature. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard vial if opaque or extraneous particulate matter other than proteinaceous particles is

observed.

Sites may choose to select an IV bag size based on their institutional practice provided that the following conditions are met:

- Concentration of MK-3475 is between 1.0 mg/mL and 10.0 mg/mL
- The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity. Otherwise a lower capacity bag must be used to prepare the infusion solution.
- Choose a suitable infusion bag material from the following list:
  - PVC plasticized with DEHP
  - Non-PVC (polyolefin)
  - EVA (ethylene vinyl acetate)
  - PE lined polyolefin

  *Contact Sponsor for materials not listed above

8.2.5 Administration

Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a participant has a central venous catheter in place, it is recommended that it be used for the infusion.

The following infusion set materials are compatible with MK-3475:

- PVC Infusion set that is plasticized using DEHP
- PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
- Polyethylene lined PVC infusion set
- PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
- Polyurethane set

* Contact the Sponsor for materials not listed above.

A sterile, non-pyrogenic, low-protein binding 0.2 to 5 μm in-line filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain a 0.2 to 5 μm in-line filter, it is recommended to use a 0.2 to 5 μm add-on filter which may contain an extension line (the materials of the extension line and filter should be as mentioned above).

Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion. Infuse MK-3475 over approximately 30 minutes with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter. Maximum rate of infusion should not exceed 6.7 mL/min. through a peripheral line or indwelling catheter. Use 30 mL normal saline to flush the infusion line at the end of infusion. If institutional guidelines to not allow the flushing of the infusion line at the completion of the infusion, the specific volume of drug/diluent solution should be prepared that is required to make up for the volume of the dosing solution lost in the infusion line.

8.2.6 Ordering
Investigative sites will order their own supply of pembrolizumab.

8.2.7 Accountability
The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

8.2.8 Destruction and Return
Investigative sites will destroy pembrolizumab as per institutional guidelines

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

1) DFCI Immuno-oncology program IHC staining of FFPE samples:

   To identify different immune cell populations (effector/memory/ CD8 cells, T regulatory cells, dendritic cells, tumor associated macrophages, NK cells, TEM) immunohistochemical staining will be performed on FFPE tumor slices using the following antibodies:
   CD3, CD4, CD8, CD25, FoxP3, Indoleamine 2,3 deoxygenase-1 (IDO), CD11c, CD83, CD86, CD56, CD14, and CD16. Also included will be IHC staining for PD-L1, PD-L2, TIM-3 and LAG-3 through the center for Immuno-oncology Pathology Core (Scott Rodig, M.D., Ph.D.).

   12 unstained slides that are amenable for IHC will be needed for these studies. 4 μm slice thickness is preferred, but 4 -5 μm is acceptable.

   Tissue can be sent to:

   Scott Rodig MD/ Evisa Gjini PhD
   Thorn building, room 603
   Department of Pathology, Brigham & Women's Hospital
   20 Shattuck Street
   Boston MA 02115

2) Merck PDL1 staining: 5 unstained slides cut from an FFPE tissue block will be needed. See section 2.5 and appendix C for details.

3) Nanostring: For each patient enrolled in the study, 4 unstained slides (4-5 micron sections) per sample of FFPE tumor will be sent to Merck at the following address:

   Katherine Bohrer
   Merck Sharp and Dohme Corp
   Anatomic Pathology
   Attention: Tissue Accessioning
   901 South Carolina Ave
   Palo Alto, CA 94304-1104

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Baseline labs must be performed within 14 days of treatment initiation. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Pre-Study	**C1 D1**	C1 D8	C1 D15	C1 D22	**C2 D1**	C2 D15	**C3 D1**	C3 D8	**Cycle 4 and beyond** [f]	Off Study[c]
PLD[5]		A				A		A		A	
Pembroluzimab[5]		B			B		B		B	B	
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X----------X[f]									
Physical exam[1]	X	X			X	X	X	X	X	X[f]	X
Vital signs[2]	X	X			X	X	X	X	X	X[f]	X
Height and weight[3]	X	X			X	X	X	X	X	X[f]	
Performance status[4]	X	X			X	X	X	X	X	X[f]	X
CA-125	X	X				X		X		X	
CBC w/diff, plts	X	X	X	X	X	X	X	X	X	X[f]	X
Serum chemistry[a]	X	X	X	X	X	X	X	X	X	X[f]	X
TSH	X	X				X				X	
EKG (as indicated)	X										
Adverse event evaluation		X----------X[f]									X
Tumor measurements	X	Tumor measurements are repeated every *[8 weeks ±1 week]* weeks. Documentation (radiologic) must be provided for participants removed from study for progressive disease.[g]									X
B-HCG	X[b]										
FFPE blocks [d]	X										
ECHO or MUGA[e]	X									X[e]	

A: PLD 40 mg/m2 IV every 28 days ±3 days window
B: Pembrolizumab 200 mg IV every 21 days ±3 days window
1: Will include skin examination in addition to physical exam
2: Including blood pressure, temperature, respiratory rate, heart rate
3: Height should be performed at screening and Cycle 1 Day 1 only, weight should be performed at each visit
4: ECOG performance status as per Appendix 1.

5:	The schedules for pembrolizumab and doxil can be delayed independently, however, the clock does not stop for each 28 day cycle regarding the cycle/day.
a:	Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b:	Serum pregnancy test (only for women of childbearing potential).
c:	Off-study evaluation. Patients will be followed for 4 weeks post treatment for adverse events. Patients will be followed for survival every 3 months for two years or until death, whichever occurs first.
d.	Obtained as part of eligibility criteria and will include PDL1 and nanostring analysis
e.	Up to a week before cycle 4 of PLD, and subsequent cycles (every 3 cycles).
f.	Physical exam, vital signs, PS as well as the following labs: CBC with plts, serum chemistry should be performed on a treatment day regardless if patients are receiving PLD alone, pembrolizumab alone or both agents.
g.	Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Patients with initial PD will be allowed to stay on trial with a repeat scan in 4 weeks. If repeat imaging confirms PD, patients will be discontinued from study therapy.

11. MEASUREMENT OF EFFECT

Although response is not the primary endpoint of this trial, participants with measurable disease will be assessed by standard criteria. For the purposes of this study, participants should be re-evaluated every 8 weeks.

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks (± 1 week).

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 **Definitions**

- Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.1.2 **Disease Parameters**

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

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

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

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

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

- Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- Non-target lesions. All other lesions (or sites of disease) including any

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

11.1.3 **Methods for Evaluation of Disease**

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

- Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

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

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

Body scans should be performed with breath-hold scanning techniques, if possible.

- FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
    - No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
    - FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

- PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

- Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin*

Oncol 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

- Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

11.1.3.1 Evaluation of Target Lesions

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

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

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

  Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

  Patients with initial PD will be allowed to stay on trial with a repeat scan in 4 weeks. If repeat imaging confirms PD, patients will be discontinued from study therapy.

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

11.1.3.2 Evaluation of Non-Target Lesions

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

- Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

- Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.3.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*

CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.4 **Duration of Response**

- Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

- Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.5 **Progression-Free Survival, Overall Survival and Time to Progression:**

- Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

- Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

- Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 **Method**

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 **Responsibility for Data Submission**

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that

raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix D.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.

- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

This is a non-randomized single-arm phase II study designed to evaluate the safety and efficacy of pegylated liposomal doxorubicin (PLD) and pembrolizumab for the treatment of platinum resistant recurrent ovarian, fallopian tube or peritoneal cancer. A six patient safety lead will be performed of these 2 drugs given in combination at their recommended phase II doses, respectively. If 2 out of the first 6 patients develop a DLT, the dose of PLD will be reduced to 30 mg/m2. If no more than 1 patient of the first 6 patients has evidence of dose limiting toxicities, the dose level will be considered the maximum tolerated dose (MTD), an additional 20 patients will be enrolled to complete the phase II study.

13.1 Study Design/Endpoints

Primary safety endpoint:

- Dose limiting toxicity that occur during the first 4 weeks of treatment, as defined in Section 5.4

For the safety run-in using cohorts of 6 patients at any dose level, the following table gives the probability of continuing to the phase II portion of the study under varying true rates of dose-limiting toxicity.

	Acceptable dosage using 6 subjects						
True DLT rate	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**
Probability	89%	66%	42%	23%	11%	4%	1%

Primary efficacy endpoint:

- Clinical benefit rate (CR + PR + SD ≥ 24 weeks)

Secondary endpoints include:

- Toxicity by CTCAE version 4.0
- Objective response by RECIST 1.1.
- Progression-free survival
- Overall survival
- Time to progression
- Duration of response

Patients who withdraw study consent before receiving any study treatment will be replaced. Patients who are receive study treatment, but who go off-treatment or off-study in cycle 1 and are not evaluable for DLT will be replaced for the safety run-in, but will be considered as non-responders in the final efficacy analysis.

13.2 Sample Size, Accrual Rate and Study Duration

Because of the possibility that both objective response and prolongment of progression –free intervals are enhanced when chemotherapy and immune checkpoint blockade inhibitors are combined, the primary endpoint of this study is clinical benefit rate, using an interval of at least 24 weeks of stable disease. Pujade-Lauraine et al reported a 12% objective response rate in control arm to the AURELIA of single-agent chemotherapy for platinum-resistant ovarian cancer; the probability of being progression-free at 6 months was approximately 20%.

Therefore, a true clinical benefit rate of 25% or less would not be of clinical interest, and is the null hypothesis to a binomial test for a single-stage A'Hern design. A true clinical benefit rate of 50% would be considered a clinically meaningful level of response. Sample size was chosen to have high power (≥90%) to declare the combination effective at this rate, while controlling the one-sided Type I error at no more than 10% under the null (exact alpha = 0.091)

13.3 Interim Monitoring Plan

During the safety run-in, the first 6 patients within a dosing cohort need to complete at least one cycle of treatment, and safety data will be reviewed before enrolling additional patients.

13.4 Analysis of Primary Endpoints

Under the exact binomial test, if clinical benefit is seen at least 10 of 26 patients (38%), the null hypothesis will be rejected and the regimen will be considered worthy of further study. The observed clinical benefit rate will be reported with a two-sided 90% exact confidence interval.

13.5 Analysis of Secondary Endpoints

Treatment-related toxicities will be summarized by maximum grade and by term using CTCAE v4.0 in all patients treated at the MTD.

Best overall response will be evaluated using RECIST 1.1 and objective response requiring confirmation will be reported in all patients who receive at least one dose of treatment at the MTD.

PFS, OS, TTP and duration of response as defined in section 11.1.5 and 11.1.4, will be described using the method of Kaplan-Meier, and summarized as median PFS, OS, TTP and duration of response as well as estimates of PFS and OS at landmark time points.

All secondary endpoints will be reported with 95% confidence intervals.

14. PUBLICATION PLAN

The results will be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active 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.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B: EVENTS OF CLINICAL INTEREST GUIDANCE DOCUMENT

PEMBROLIZUMAB PROGRAM (MK-3475)

EVENT OF CLINICAL INTEREST

GUIDANCE DOCUMENT

Version 5.0

TABLE OF CONTENTS

1. OVERVIEW

The purpose of this document is to provide study sites with guidance on the identification and management of Events of Clinical Interest for the MK-3475 (also known as pembrolizumab) program.

Based on the literature review [1-11], and consideration of mechanism of action of pembrolizumab, potential immune-related adverse events (irAEs) are the primary Event of Clinical Interest (ECI). Immune-related AEs are adverse events associated with the treatment of patients with immunotherapy treatments that appear to be associated with the immune therapy's mechanism of action. Based on these potential irAEs, the sponsor has defined a list of specific adverse event terms (ECIs) that are selected adverse experiences that **must be reported to Merck within 24 hours to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220)**from the time the Investigator/physician is aware of such an occurrence, regardless of whether or not the investigator/physician considers the event to be related to study drug(s). In addition, these ECIs require additional detailed information to be collected and entered in the study database. ECIs may be identified through spontaneous patient report and / or upon review of subject data. **Table 1** provides the list of terms and reporting requirements for AEs that must be reported as ECIs for MK-3475 protocols. Of note, the requirement for reporting of ECIs applies to all arms, including comparators, of MK-3475 clinical trials

Given that our current list of events of clinical interest is not comprehensive for all potential immune-related events, it is possible that AEs other than those listed in this document may be observed in patients receiving pembrolizumab. Therefore any Grade 3 or higher event that the investigator/physician considers to be immune-related should be reported as an ECI regardless of whether the specific event term is in Table 1 **and reported to Merck within 24 hours to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220)** from the time the Investigator/physician is aware of such an occurrence. Adverse events that are both an SAE and an ECI should be reported one time as an SAE only, however the event must be appropriately identified as an ECI as well in in the database.

Table 1: Events of Clinical Interest

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

Each of the events above is described within this guidance document, along with site requirements for reporting these events to the Sponsor. The information collected should be entered into the narrative field(s) of the Adverse Event module in the database (please note, if narrative entry into the database is not available, please use the narrative text box on the 1727/AER Form). If additional Medical History or Concomitant Medications are reported, the Medical History and Concomitant Medication modules in the database must be updated.

In addition, the guidelines include recommendations on the management of these ECIs. These guidelines are intended to be applied when the physician determines the events to be related to pembrolizumab. Note: if after the evaluation the event is determined not to be related, the physician is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (below). Therefore, these recommendations should be seen as guidelines and the treating physician should exercise individual clinical judgment based on the patient. For any question of dose modification or other treatment options, the specific language in the protocol should be followed. Any questions pertaining to the collection of this information or management of ECIs should be directed to your local Sponsor contact.

Dose Modification/Discontinuation

The treatment guidance provides specific direction when to hold and/or discontinue pembrolizumab for each immune related adverse event. Of note, when the guidance states to "discontinue" pembrolizumab this is the permanent discontinuation of treatment with pembrolizumab. "Hold" means to stop treating with pembrolizumab but resumption of treatment may be considered assuming the patient meets the criteria for resumption of treatment.

2. ECI REPORTING GUIDELINES

ECIs are selected non-serious and serious adverse experiences that must be reported to Merck **within 24 hours** regardless of attribution to study treatment. The AEs listed in this document and any event that meets the ECI criteria (as noted) in Table 1 or in the respective protocol (event term and Grade) must be reported regardless of physician-determined causality with study medication and whether or not considered immune-related by the physician (unless otherwise specified). Physicians/study coordinators/designated site personnel are required to record these experiences as ECIs on the Adverse Experience electronic Case Report Forms (eCRFs) (or on paper) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event.

- Please refer to the Data Entry Guidelines (DEGs) for your protocol (Section 12.1).
- Please refer to protocol for details on reporting timelines and reporting of Overdose and Drug Induced Liver Injury (DILI) (Section 7.0).

3. ECI CATEGORIES AND TERMS

This section describes the ECI categories and outlines subject management guidelines when an ECI is reported.

3.1 Pneumonitis

The following AE terms, if considered ≥ Grade 2, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Pneumonitis
- Interstitial lung disease
- Acute interstitial pneumonitis

If symptoms indicate possible new or worsening cardiac abnormalities additional testing and/or a cardiology consultation should be considered.

All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection**. It is important that patients with a suspected diagnosis of pneumonitis be managed as per the guidance below until treatment-related pneumonitis is excluded. Treatment of both a potential infectious etiology and pneumonitis in parallel may be warranted. Management of the treatment of suspected pneumonitis with steroid treatment should not be delayed for a therapeutic trial of antibiotics.** If an alternative diagnosis is established, the patient does not require management as below; however the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab.
- Consider pulmonary consultation with bronchoscopy and biopsy/BAL.
- Consider ID consult
- Conduct an in person evaluation approximately twice per week
- Consider frequent Chest X-ray as part of monitoring
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Second episode of pneumonitis – discontinue pembrolizumab if upon re-challenge the patient develops a second episode of Grade 2 or higher pneumonitis.

Grade 3 and 4 events:

- Report as ECI
- Discontinue pembrolizumab.
- Hospitalize patient
- Bronchoscopy with biopsy and/or BAL is recommended.
- Immediately treat with intravenous steroids (methylprednisolone 125 mg IV). When symptoms improve to Grade 1 or less, a high dose oral steroid (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) taper should be started and continued over no less than 4 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, treat with additional anti-inflammatory measures. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures, as needed
- Add prophylactic antibiotics for opportunistic infections.

3.2 Colitis

The following AE terms, if considered ≥ Grade 2 or resulting in dose modification or use of systemic steroids to treat the AE, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Colitis
- Colitis microscopic
- Enterocolitis
- Enterocolitis hemorrhagic
- Gastrointestinal perforation
- Intestinal obstruction
- Necrotizing colitis
- Diarrhea

All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, a Clostridium difficile titer and endoscopy. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 Diarrhea/Colitis (4-6 stools/day over baseline, dehydration requiring IV fluids < 24 hours, abdominal pain, mucus or blood in stool):

- Report as ECI
- Hold pembrolizumab.
- Symptomatic Treatment
- For Grade 2 diarrhea that persists for greater than 3 days, and for diarrhea with blood and/or mucus,
  - Consider GI consultation and endoscopy to confirm or rule out colitis
  - Administer oral corticosteroids (prednisone 1-2 mg/kg QD or equivalent)
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If symptoms worsen or persist > 3 days treat as Grade 3

Grade 3 Diarrhea/Colitis (or Grade 2 diarrhea that persists for > 1 week):

- Report as ECI
- Hold pembrolizumab.
- Rule out bowel perforation. Imaging with plain films or CT can be useful.
- Recommend consultation with Gastroenterologist and confirmation biopsy with endoscopy.
- Treat with intravenous steroids (methylprednisolone 125 mg) followed by high dose oral steroids (prednisone 1 to 2 mg/kg once per day or dexamethasone 4 mg every 4 hours) When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6 to 8 weeks in patients with diffuse and severe ulceration and/or bleeding.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48 to 72 hours, consider treatment with additional anti-inflammatory measures as described in the literature [5]. Discontinue additional anti-inflammatory measures upon symptom relief and initiate a prolonged steroid taper over 45 to 60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer additional anti-inflammatory measures as needed.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab.
- Manage as per Grade 3.

3.3 Endocrine

The following AE terms, if considered ≥Grade 3 or if ≥Grade 2 and require holding/discontinuation/ modification of pembrolizumab dosing, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Adrenal insufficiency
- Hyperthyroidism
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Thyroid disorder
- Thyroiditis

All attempts should be made to rule out other causes such as brain metastases, sepsis and/or infection. However the AE should be reported regardless of etiology.

Hypophysitis or other symptomatic endocrinopathy other than hypo- or hyperthyroidism

Grade 2-3 events:

- Report as ECI if appropriate
- Hold pembrolizumab
- Rule out infection and sepsis with appropriate cultures and imaging.
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Pituitary gland imaging should be considered (MRIs with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).
- Treat with prednisone 40 mg p.o. or equivalent per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis.
- Consultation with an endocrinologist may be considered.

Hyperthyroidism and 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, Grade 2-4 hypothyroidism events:

- Report as ECI if appropriate (see Table 1)
- Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.
- Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.
- Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted.
- 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.
- Consultation with an endocrinologist may be considered.

Grade 3 hyperthyroidism events:

- Report as ECI
- Hold pembrolizumab.
- Rule out infection and sepsis with appropriate cultures and imaging.
- Treat with an initial dose of methylprednisolone 1 to 2 mg/kg intravenously followed by oral prednisone 1 to 2 mg/kg per day. 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.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 hyperthyroidism events:

- Report as ECI
- Discontinue pembrolizumab.
- Manage as per Grade 3

Type 1 diabetes mellitus (if new onset) and ≥ Grade 3 Hyperglycemia

The following AE terms are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Type I diabetes mellitus (T1DM), if new onset, including diabetic ketoacidosis (DKA)
- Grade 3 or higher hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA).

Immune-mediated diabetes may present as new onset of Type 1 diabetes or an abrupt worsening of pre-existing diabetes associated with laboratorial evidence of beta cell failure. All attempts should be made to rule out other causes such as type 2 diabetes mellitus (T2DM), T2DM decompensation, steroid-induced diabetes, physiologic stress-induced diabetes, or poorly controlled pre-existing diabetes (either T1DM or T2DM), but events meeting the above criteria should be reported as ECIs regardless of etiology. The patients may present with hyperglycemia (abrupt onset or abrupt decompensation) with clinical evidence of diabetic ketoacidosis or laboratory evidence of insulin deficiency, such as ketonuria, laboratory evidence of metabolic acidosis, or low or undetected c-peptide.

Course of Action

T1DM should be immediately treated with insulin.

T1DM or Grade 3-4 Hyperglycemia events:

- Report as ECI if appropriate (see Table 1)
- Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure, and resume pembrolizumab when patients are clinically and metabolically stable.
- 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.
- Consultation with an Endocrinologist is recommended.
- Consider local testing for islet cell antibodies and antibodies to GAD, IA-2, ZnT8, and insulin may be obtained.

3.4 Hematologic

The following AE term, if considered Grade ≥3 or requiring dose modification or use of systemic steroids to treat the AE, are considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hemolytic anemia
- Aplastic anemia
- Disseminated Intravascular Coagulation (DIC)
- Haemolytic Uraemic Syndrome (HUS)
- Idiopathic (or immune) Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenic Purpura (TTP)
- Any Grade 4 anemia regardless of underlying mechanism

All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Report as ECI
- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation.
  Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:
- Report as ECI
- Hematology consultation.
- Hold pembrolizumab Discontinuation should be considered as per specific protocol guidance.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Report as ECI
- Hematology consultation
- Discontinue pembrolizumab for all solid tumor indications; refer to protocol for hematologic malignancies.
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

3.5 Hepatic

The following AE terms, if considered ≥ Grade 2 or greater (or any grade with dose modification or use of systemic steroids to treat the AE), are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune hepatitis
- Hepatitis
- Transaminase elevations

All attempts should be made to rule out other causes such as metastatic disease, infection or other hepatic diseases. However the AE should be reported regardless of etiology.

Drug Induced Liver Injury (DILI)

In addition, the event must be reported as a Drug Induced Liver Injury (DILI) ECI, if the patient meets the laboratory criteria for potential DILI defined as:

- An elevated alanine transaminase (ALT) or aspartate transaminase (AST) lab value that is greater than or equal to three times (3X) the upper limit of normal (ULN) and
- An elevated total bilirubin lab value that is greater than or equal to two times (2X) ULN and
- At the same time, an alkaline phosphatase (ALP) lab value that is less than 2X ULN,
- As a result of within-protocol-specific testing or unscheduled testing.

Note that any hepatic immune ECI meeting DILI criteria should only be reported once as a DILI event.

Course of Action

Grade 2 events:

- Report as ECI
- Hold pembrolizumab when AST or ALT >3.0 to 5.0 times ULN and/or total bilirubin >1.5 to 3.0 times ULN.
- Monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab per protocol
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.
- Permanently discontinue pembrolizumab for patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT, and AST or ALT increases ≥50% relative to baseline and lasts ≥1 week.

Grade 3 events:

- Report as ECI
- Discontinue pembrolizumab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.
- Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary
- Treat with high-dose intravenous glucocorticosteroids for 24 to 48 hours. When symptoms improve to Grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1 to 2 mg/kg should be started and continued over no less than 4 weeks.
- If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.

- Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Report as ECI
- Permanently discontinue pembrolizumab
- Manage patient as per Grade 3 above

3.6 Neurologic

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Autoimmune neuropathy
- Demyelinating polyneuropathy
- Guillain-Barre syndrome
- Myasthenic syndrome

All attempts should be made to rule out other causes such as metastatic disease, other medications or infectious causes. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Report as ECI
- Moderate (Grade 2) – consider withholding pembrolizumab.
- Consider treatment with prednisone 1-2 mg/kg p.o. daily as appropriate
- Consider Neurology consultation. Consider biopsy for confirmation of diagnosis.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 and 4 events:

- Report as ECI
- Discontinue pembrolizumab
- Obtain neurology consultation. Consider biopsy for confirmation of diagnosis
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day. If condition worsens consider IVIG or other immunosuppressive therapies as per local guidelines

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.7 Ocular

The following AE terms, if considered Grade ≥2 or requiring dose modification or use of systemic steroids to treat the AE, is considered an ECI and should be reported to the Sponsor within 24 hours of the event:

- Uveitis
- Iritis

All attempts should be made to rule out other causes such as metastatic disease, infection or other ocular disease (e.g. glaucoma or cataracts). However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Evaluation by an ophthalmologist is strongly recommended.
- Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.
- Discontinue pembrolizumab as per protocol if symptoms persist despite treatment with topical immunosuppressive therapy.

Grade 3 events:

- Evaluation by an ophthalmologist is strongly recommended
- Hold pembrolizumab and consider permanent discontinuation as per specific protocol guidance.
- Treat with systemic corticosteroids such as prednisone at a dose of 1 to 2 mg/kg per day. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Evaluation by an ophthalmologist is strongly recommended
- Permanently discontinue pembrolizumab.
- Treat with corticosteroids as per Grade 3 above

3.8 Renal

The following AEs if ≥ Grade 2 are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Nephritis
- Nephritis autoimmune
- Renal failure
- Renal failure acute

Creatinine elevations ≥ Grade 3 or any grade with dose modification or use of systemic steroids to treat the AE.

All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury due to other chemotherapy agents. A renal consultation is recommended. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:

- Hold pembrolizumab
- Treatment with prednisone 1-2 mg/kg p.o. daily.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3-4 events:

- Discontinue pembrolizumab
- Renal consultation with consideration of ultrasound and/or biopsy as appropriate
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone IV or equivalent once per day.

When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9 Skin

Rash and Pruritus

The following AEs should be considered as ECIs, if ≥ Grade 3 and should be reported to the Sponsor within 24 hours of the event:

- Pruritus
- Rash
- Rash generalized
- Rash maculo-papular
- In addition to CTCAE Grade 3 rash, any rash that is considered clinically significant, in the physician's judgment, should be treated as an ECI. Clinical significance is left to the physician to determine, and could possibly include rashes such as the following:
  - rash with a duration >2 weeks; OR
  - rash that is >10% body surface area; OR
  - rash that causes significant discomfort not relieved by topical medication or temporary cessation of study drug.

Other Skin ECIs

The following AEs should **always** be reported as ECIs, regardless of grade, and should be reported to the Sponsor within 24 hours of the event:

- Dermatitis exfoliative
- Erythema multiforme
- Steven's Johnson syndrome
- Toxic epidermal necrolysis

Please note, the AE should be reported regardless of etiology.

Course of Action

Grade 2 events:
- Symptomatic treatment should be given such as topical glucocorticosteroids (e.g., betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral anti-pruritics (e.g., diphenhydramine HCl or hydroxyzine HCl).
- Treatment with oral steroids is at physician's discretion for Grade 2 events.

Grade 3 events:
- Hold pembrolizumab.
- Consider Dermatology Consultation and biopsy for confirmation of diagnosis.
- Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:
- Permanently discontinue pembrolizumab.
- Dermatology consultation and consideration of biopsy and clinical dermatology photograph.
- Initiate steroids at 1 to 2 mg/kg prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

3.9.1. Immediate Evaluation for Potential Skin ECIs

A. Photographs:
Every attempt should be made to get a photograph of the actual ECI skin lesion or rash as soon as possible**. Obtain appropriate consent for subject photographs if a consent form addendum is required by your IRB/ERC.**

- Take digital photographs of:
  - the head (to assess mucosal or eye involvement),
  - the trunk and extremities, and
  - a close-up of the skin lesion/rash.

- If possible, a ruler should be placed alongside the site of a skin occurrence as a fixed marker of distance.
- The time/date stamp should be set in the 'ON' position for documentation purposes.
- Photographs should be stored with the subject's study records.
- The Sponsor may request copies of photographs. The local study contact (e.g., CRA) will provide guidance to the site, if needed.

B. Past Medical History:
Collect past medical history relevant to the event, using the questions in Appendix 2 (Past Medical History Related to Dermatologic Event) as a guide. Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

C. Presentation of the Event:
Collect information on clinical presentation and potential contributing factors using the questions in Appendix 3 (Presentation of the Dermatologic Event) as a guide. This information should be summarized and entered in narrative format in the AE eCRF. Please use the available free-text fields, such as Signs and Symptoms. Note pertinent negatives where applicable to reflect that the information was collected. Any treatments administered should be entered on the Concomitant Medication eCRF.

D. Vitals Signs and Standard Laboratory Tests:
Measure vital signs (pulse, sitting BP, oral temperature, and respiratory rate) and record on the Vital Signs eCRF. Perform standard laboratory tests (CBC with manual differential and serum chemistry panel, including LFTs).

E. Focused Skin Examination:
Perform a focused skin examination using the questions in Appendix 4 (Focused Skin Examination) as a guide. Information should be summarized and entered on the Adverse Experience eCRF as part of the narrative.

F. Dermatology Consult
Refer the subject to a dermatologist as soon as possible.

- For a **"severe rash"**, the subject must be seen within **1-2 days** of reporting the event.
- For **clinically significant rash**, the subject should be seen within **3-5 days**.

The dermatologist should submit a biopsy sample to a certified dermatopathology laboratory or to a pathologist experienced in reviewing skin specimens.

The site should provide the dermatologist with all relevant case history, including copies of clinical photographs and laboratory test results.

3.10 Other

The following AEs, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Myocarditis
- Pericarditis
- Pancreatitis
- Any additional Grade 3 or higher event which the physician considers to be immune related

All attempts should be made to rule out other causes. Therapeutic specialists should be consulted as appropriate. However the AE should be reported regardless of etiology.

Course of Action

Grade 2 events or Grade 1 events that do not improve with symptomatic treatment:

- Withhold pembrolizumab.
- Systemic corticosteroids may be indicated.
- Consider biopsy for confirmation of diagnosis.
- If pembrolizumab held and corticosteroid required, manage as per grade 3 below.

Grade 3 events:

- Hold pembrolizumab
- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks. Otherwise, pembrolizumab treatment may be restarted and the dose modified as specified in the protocol

Grade 4 events:

- Treat with systemic corticosteroids at a dose of 1 to 2 mg/kg prednisone or equivalent once per day.
- Discontinue pembrolizumab

3.11 Infusion Reactions

The following AE terms, regardless of grade, are considered ECIs and should be reported to the Sponsor within 24 hours of the event:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

Please note, the AE should be reported regardless of etiology.

Course of Action

Refer to infusion reaction table in the protocol and below.

Infusion Reactions

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.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

3.12 Follow-up to Resolution

Subjects should be followed to resolution. The Adverse Experience eCRF should be updated with information regarding duration and clinical course of the event. Information obtained from the consulting specialist, including diagnosis, should be recorded in the appropriate AE fields. Free-text fields should be used to record narrative information:

- Clinical course of the event
- Course of treatment
- Evidence supporting recovery
- Follow-up to the clinical course

Any treatments administered for the event should also be entered in the Concomitant Medication eCRF.

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APPENDIX 1 –Events of Clinical Interest (ECI) – Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

APPENDIX 2 – Past Medical History Related to Dermatologic Event

Past Medical History:
Any preexisting conditions not previously reported (e.g., drug allergy) should be entered into the Medical History eCRF.

1. Does the subject have any allergies? □ Yes □ No

If yes, please obtain the following information:

a. Any allergy to drugs (including topical or ophthalmic drugs)? □ Yes □ No

List the drug name(s) and describe the type of allergic response (e.g. rash, anaphylaxis, etc):
_____
_____

b. Any allergy to external agents, such as laundry detergents, soaps, poison ivy, nickel, etc.? □ Yes □ No

Describe the agent and type of allergic response: _____
_____

c. Any allergy to food? □ Yes □ No

Describe the food and type of allergic response: _____
_____

d. Any allergy to animals, insects? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

e. Any other allergy? □ Yes □ No

Describe the allergen and type of allergic response: _____
_____

2. Does the subject have any other history of skin reactions, skin eruptions, or rashes? □ Yes □ No

If so what kind? _____

3. Has the subject ever been treated for a skin condition? □ Yes □ No

If so what kind? _____

4. Is the current finding similar to a past experience? □ Yes □ No

APPENDIX 3 – Presentation of the Dermatologic Event

Presentation of the event:
Collect information on clinical presentation and potential contributing factors. Key information should be summarized and entered on the Adverse Experience eCRF. Any treatments administered should be entered on the Concomitant Medication eCRF.

1. What is the onset time of the skin reaction, skin eruption, or rash relative to dose of study drug?
_____

2. Has the subject contacted any known allergens? □ Yes □ No

If so what kind? _____

3. Has the subject contacted new, special, or unusual substances (e.g., new laundry detergents, soap, personal care product, poison ivy, etc.)? □ Yes □ No

If so what kind? _____

4. Has the subject taken any other medication (over the counter, prescription, vitamins, and supplement)? □ Yes □ No

If so what kind? _____

5. Has the subject consumed unaccustomed, special or unusual foods? □ Yes □ No

If so what kind? _____

6. Does the subject have or had in the last few days any illness? □ Yes □ No

If so what kind? _____

7. Has the subject come into contact with any family or house members who are ill? □ Yes □ No

If so who and what? _____

8. Has the subject recently been near children who have a skin reaction, skin eruption, or rash (e.g. *Molluscum Contagiosum*)? □ Yes □ No

9. Has the subject had recent sun exposure? □ Yes □ No

10. For the current rash, have there been any systemic clinical signs? □ Yes □ No

If so what kind? _____

i. Anaphylaxis? □ Yes □ No
ii. Signs of hypotension? □ Yes □ No
iii. Signs of dyspnea? □ Yes □ No
iv. Fever, night sweats, chills? □ Yes □ No

11. For the current rash, has the subject needed subcutaneous epinephrine or other systemic catecholamine therapy? □ Yes □ No

If so what kind? _____

12. For the current rash, has the subject used any other medication, such as inhaled bronchodilators, antihistaminic medication, topical corticosteroid, and/or systemic corticosteroid? □ Yes □ No

List medication(s) and dose(s): _____
_____

13. Is the rash pruritic (itchy)? □ Yes □ No

APPENDIX 4 – Focused Skin Examination

Focused Skin Examination:
Key information should be summarized and entered on the Adverse Experience eCRF.

Primary Skin Lesions Description
Color: _____

General description:

_____
_____

Describe the distribution of skin reaction, skin eruption, or rash on the body:

_____
_____

Is skin reaction, skin eruption, or rash resolving or continuing to spread?

_____
_____

Any associated signs on physical examination?

_____

APPENDIX C: BIOASSAY TEMPLATES

MISP Sample Handling Manual

QualTek Molecular Laboratories
300 Pheasant Run
Newtown, PA 18940
Phone: 215.504.7402
Fax: 805.830.6379
Email: MISPsamples@qmlabs.com

Introduction

Here we describe the collection of sectioned slides from tumor samples for the purpose of immunohistochemical (IHC) analysis. Sectioned slides from formalin-fixed, paraffin-embedded (FFPE) samples will be stained for the biomarker(s) of interest, and then evaluated by a pathologist for review of biomarker staining expression levels.

Protocol Requirements

1. For patient samples, the provided positively charged ProbeOn Plus slides **(Fisher ProbeOn Plus Catalog Number 22-230-900)** are strongly recommended for tissue sections. If a sample has existing sections already cut, slide measurements should be 75mm x 25mm x 1mm (other slide sizes may not be able to be accommodated - please contact QualTek to discuss further).

2. Tumor tissue for biomarker analysis should be provided as **five (5) unstained slides** cut from an FFPE tissue block. Three (3) sectioned slides per sample are *necessary* for H&E, PD-L1, and isotype control staining. The 4th and 5th sections are for a repeat staining if needed.

    a. Existing H&E slides may be provided along with 2 unstained slides if less tissue is available (assumes H&E stained section is fairly close to section level of unstained slides sent for analysis). A PD-L1 and isotype control stain will be performed. Isotype control will only be run if first section staining for PD-L1 is successful otherwise a second attempt will be made for PD-L1 staining.

    b. If no H&E is available and only 2 unstained sections are sent, then an H&E and a PD-L1 stain will be performed.

3. If additional markers beyond PD-L1 are requested to be tested as per the service contract established between QualTek and the Investigator Site, 2 additional sections per marker are the minimum to allow staining for the additional marker and the isotype control, however 4 sections will allow for repeat staining if needed.

4. Samples may be held as blocks indefinitely at the site and then cut in batches. Slides should be shipped to QualTek as immediately as possible after sectioning.

5. As per Merck protocol requirements, sectioned slides should be shipped cold (2-8°C) and in the dark using the shipping materials provided by QualTek **pages 8-9**. Be advised that slides received that do not meet these conditions may affect PD-L1 staining.

6. Sectioned slides provided should contain tumor specimen sufficient for pathology review and analysis of the tumor sample. If available, greater than 50% tumor content is

preferred. At least fifty viable neoplastic cells overall or at least five viable, PD-L1-staining neoplastic cells are necessary to be scored by the pathologist.

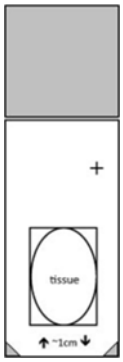
7. Non-acceptable sample types for IHC analysis include brushing, bone metastases, lavage specimen, frozen sample, plastic embedded sample, or formalin fixed sample that was frozen at any point.

8. Needle core biopsies or endo-bronchial ultrasound (EBUS) preps that are formalin-fixed and paraffin-embedded are acceptable. Fine-needle aspiration (FNA) or cell pellet from pleural effusion samples that are formalin-fixed and paraffin-embedded will be accepted for testing with the following caveats:

    a. The PD-L1 IHC assay is not validated for FNA or cell pellet from pleural effusion samples. However, on a research basis QualTek has successfully PD-L1 stained FNA samples.
    b. The scoring parameter for assessing stromal interface (presence/ absence) will not be provided for FNAs or cell pellets from pleural effusion due to the nature of the sample.

Sectioning of Tissue onto ProbeOn Plus Slides from Formalin-Fixed, Paraffin-Embedded (FFPE) Block(s)

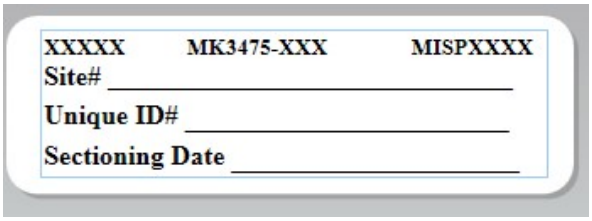
1. Prepare freshly-cut serial sections at 4 micron thickness onto the provided Fisher ProbeOn Plus Slides, Cat Number 22-230-900. Sections must be placed on the painted/textured side of the slide.
    - No adhesives should be used in the water bath since the slides are positively-charged.
2. Ensure that the sample has the institutional block ID clearly marked on each slide as well as the slide section levels, if possible.
    - **<u>Ensure that the block ID is referenced on the manifest</u>**
    - Note that the sample must be labeled with 2 patient identifiers (Refer to the label provided for the slide holder)



3. When placing the sections onto the slides, ensure that the tissue is towards the bottom third of the slide as pictured at right.
    - Ensure tissue sections are oriented the same direction on all slides.
    - No adhesive labels directly on slides. Slide / patient identifiers must be hand written with indelible / chemical proof ink.
    - Number the slides sequentially (serially), one section per slide.
4. **DO NOT OVEN DRY SLIDES.** Air dry until completely dry (12-24 hours).
5. Complete an electronic Sample Manifest for each shipment (Excel Spreadsheet provided by QualTek to the Site Contact at study initiation).
    - Email the completed electronic manifest prior to shipment to: **MISPsamples@qmlabs.com**
    - Make a copy of the manifest to include with the shipment of the sample(s)
    - Retain the original at the site for your records
6. Email or enclose a de-identified (redacted) pathology report(s) if available. Write the block ID on the top of each page of the pathology report
7. Prepare samples for shipping as detailed on **pages 6-7.**

Packaging Instructions for Formalin-Fixed Paraffin Embedded Slides

1. Affix and complete the label provided for the slide holder with Unique Patient ID number, Site Number/Identifier and Sectioning Date using indelible ink. Ensuring that the patient identifiers on the slide holder match the patient slides.



Top line of the label are the Study Identifiers and will be pre-printed for the specific study
Left - Investigator Study Number
Center – Merck Protocol Number
Right – QualTek Project Number

2. Place the newly sectioned slides (air dried until completely dry (12-24 hours), into the labeled slide holder. Ensure only one patient per slide holder and no more than 5 slides per slide holder.
3. Place the piece of small foam between the top of the slides and the holder's lid to prevent the slides from breaking. Tape the lid closed.
4. Insert the slide holders into the Amber UV bag labeled as "Biohazard" and seal the bag.
5. Place the Amber UV bag into a bubble wrap bag, or wrap in a sheet of bubble wrap.
6. More than one shipping box size may have been provided, choose the appropriate size as follows:
    - If shipping 1 patient slide holder:

      Use a 9x12 Insulated Shipping mailer. Place 1 freezer pack in the cooler liner, place the bubble wrap bag containing slides on top of the freezer pack.
    - If shipping between 2 and 10 patient slide holders:

      Use a 10x10x10 Shipping box and cooler box liner. Place 1 freezer pack on the bottom of the cooler liner, place the bubble wrap bag containing slides on top of the freezer pack and include 1 freezer pack on top of the bubble wrap bag.
    - If shipping between 11 and 20 patient slides holders:

      Use a 12x12x12 shipping box and cooler box liner. Place 2 freezer packs on the bottom of the cooler liner place the bubble wrap bag containing the slides on top of the freezer pack and include 2 freezer packs on top of the bubble wrap bag.
7. Fill remaining space with appropriate cushioning, i.e. additional bubble wrap or other packing material. For extreme temperature conditions additional ice packs may be required. Samples should be shipped cold (2-8°C) and in the dark.

8. Enclose the de-identified (redacted) pathology report and the Sample Manifest, ensure that an electronic copy of the Manifest has been emailed to MISPsamples@qmlabs.com
9. Seal the mailer/box to ensure it will not open during shipping. Package & ship to QualTek.
10. Complete the pre-printed air bill provided by QualTek with sender information.
11. Verify correct shipping address as:

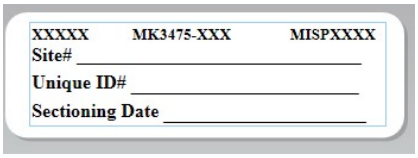
QualTek Molecular Laboratories
MISP Receiving
300 Pheasant Run
Newtown, PA USA 18940

12. Adhere the pre-printed air bill to the top of the shipping mailer/box.
13. For all U.S. domestic shipments, ship **Standard Overnight** Monday through Thursday, do not ship Friday, Saturday or Sunday.

Investigator Studies Supply List for FFPE Sectioned Slides Shipping to QualTek

The following supplies, or their equivalent, will be provided by QualTek:

1. Positively charged microscope slides used for sectioning of slides (5 per patient) • Fisher ProbeOn Plus 25mm x 75mm x 1mm Capillary Gap Microscope Slides catalog 22-230-900 • http://www.fishersci.com	
2. Plastic slide holders (1 per patient, each hold maximum of 5 slides) • Catalog 12-587-17B • http://www.fishersci.com	
3. Paraffin embedding cassette sponge to cushion slides in the plastic slide holder during shipping • "square" biopsy foam pad sized 1 7/8" x 1" x 1/16" (catalog 60872-492) • http://us.vwr.com	
4. Amber UV bags with biohazard sticker (to keep the slides in dark) • Amber UV bag (6x8 Inches) – catalog 89005-326 • http://us.vwr.com • Biohazard Sticker – catalog ML1022 • http://www.marketlab.com	
5. Shippers • 9x12 **(Mailer)** *For shipping 1 sample holder* – catalog S18306 (http://www.uline.com) • 10x10x10 ***(Small)*** *For shipping between 2 to 10 patient slide holders* – catalog s4105 (http://www.uline.com) • 12x12x12 ***(Large)*** *For bulk shipments, between 11 to 20 patient slide holders* – catalog s18283 (http://www.uline.com) • Insulated shippers – catalog s18282 (http://www.uline.com)	  

6. Cold Packs (12 oz. Ice Packs, 1 for the Mailer, 2 for the Small Shipper, 4 for the Large Shipper) • Catalog s7889 • http://www.uline.com	
7. Bubble wrap • Catalog s-683 • http://www.uline.com	
8. Miscellaneous • Labels for the slide holders • FedEx Pre-Printed Air bills • Site Supply Inventory • Sample Manifest Template (Excel Spreadsheet provided electronically to site contact)	

(EXAMPLE) Site Supply Inventory

Date	
QualTek Project #	
Investigator Study #	
Merck Protocol #	
Site Name	
Site Address	
Address Continued	

Quantity	Description	Quantity	Description
X	Positively Charged Capillary Gap (ProbeOn Plus) Microscope Slides	X	Freezer Packs
X	Plastic Five (5) Slide Holder (with small Foam Pad)	X	Fed-Ex Pre-Printed Air bill(s)
X	Labels for Slide Holder	X	10x10x10 Shipping Box with Cooler Box Liner
X	Amber UV Bags (labeled Biohazard)	X	12x12x12 Shipping Box with Cooler Box Liner
X	Bubble Wrap Bags	X	Other (If Applicable)

Unpacking Instructions

1. Confirm material counts and check for breakage.
2. Remove freezer packs and place in freezer as soon as possible.
3. Retain all other materials for return of samples to QualTek Molecular Labs.
4. When ready to section, remove Positively Charged Capillary Gap (ProbeOn Plus) Microscope Slides from slide holder and use these slides for sectioning. Retain foam pad for repackaging.

APPENDIX D: DATA SAFETY MONITORING PLAN

DFCI IRB Protocol #: 16-257

APPENDIX D

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

TABLE OF CONTENTS

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures.

1.2 Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity (i.e. Lead Institution, Medical Monitor, Contract Research Organization (CRO), etc) that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol

document and DSMP, and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Clinical Trials Research Informatics Office (CTRIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1 DF/HCC Sponsor

The DF/HCC Sponsor, Ursula Matulonis, M.D., will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training (and/or a Site Initiation Visit prior to enrolling participants) and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials), as applicable.
- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.

- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2 Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed.
- Oversee the data collection process from Participating Institutions.
- Maintain documentation of Serious Adverse Event (SAE) reports and deviations/violation submitted by Participating Institutions and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out plan to monitor Participating Institutions either by on-site or remote monitoring.
- Maintain Regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc) and maintain documentation all relevant communications.

2.3 Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).

- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Serious Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1 Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2 Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the

Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for PI-Initiated Multi-Center Protocols. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that only attending physicians obtain informed consent and re-consent for all interventional drug, biologic, or device research.

3.4 IRB Documentation

The following must be on file with the Coordinating Center:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution's IRB.
- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5 IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6 Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any

information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB, will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1 DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned protocol case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7 DF/HCC Multi-Center Protocol Registration Policy

3.7.1 Participant Registration and Randomization

Please see section 4 of the protocol.

3.7.2 Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.3 Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.8 DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the

participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.8.1 Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.8.2 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.8.3 Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines. DF/HCC will forward all violation reports to CTEP via an internal DF/HCC process, as applicable.

3.9 Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.9.1 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.9.2 Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review/submit to their IRB according to their institutional policies and procedures.

3.10 Data Management

DF/HCC CTRIO develops case report forms (CRF/eCRFs), for use with the protocol. These forms are designed to collect data for each study. DF/HCC CTRIO provides a web based training for all eCRF users.

3.10.1 Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8.

Participating Institutions should order their own agent regardless of the supplier. (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

5.1 Ongoing Monitoring of Protocol Compliance

The Participating Institutions may be required to submit participant source documents to the Coordinating Center for monitoring. Participating Institution may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. At a minimum, the DF/HCC Lead Institute, or designee, will monitor each participating site twice a year while patients are receiving treatment. Should a Participating Institution be monitored once and then not accrue any additional patients or participant visits, then a second monitoring visit may not be necessary. Additional monitoring practices may include but are not limited to; source verification, review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, response assessments, and data management.

Participating institutions will be required to participate in Coordinating Center initiated teleconferences, as scheduled. The Coordinating Center will keep in close touch with the Participating Institutions via email and phone. Source documents from Participating Institutions, will be collected at specific data points that support the primary and or secondary endpoints.

On-Site Monitoring: On-site monitoring will occur on an as-needed basis. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled. On site monitoring visits can be supplemented with virtual monitoring assessments, provided that the minimum monitoring frequencies are adhered to.

Remote Monitoring: The Coordinating Center will request source documentation from Participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward de-identified copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

5.2 Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.3 Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable Standard Operating Procedures (SOPs), and the Code of Federal Regulations (CFR).

6.1 DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2 day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.2 Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.3 Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.4 Participating Institution Performance

The DF/HCC Sponsor and DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the

probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.

DANA-FARBER CANCER INSTITUTE
Nursing Protocol Education Sheet

Protocol Number:	**16-257**
Protocol Name:	**A Phase II Study of Pembrolizumab combined with pegylated liposomal doxorubicin (PLD) for recurrent platinum resistant ovarian, fallopian tube, or peritoneal cancer.**
DFCI Site PI:	Ursula Matulonis
DFCI Research Nurse:	Stephanie Morrissey, Cate Cavanaugh, Brittany Bowes, Christin Whalen

Page the DFCI research nurse or DFCI site PI if there are any questions/concerns about the protocol.
Please also refer to ONC 15: Oncology Nursing Protocol Education Policy
***** Remember to check the ALERT PAGE*****

SPECIAL NURSING CONSIDERATIONS UNIQUE TO THIS PROTOCOL

Study Design	• PLD is an approved drug in the U.S., Canada, and Europe for use in ovarian cancer following progression of cancer after platinum-based chemotherapy. • 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 • The Study Design is in Section 1.1 • The Study Rationale is in Section 2.4 • A cycle is defined as 28 days (Section 5.1).
Dose Calc.	• PLD is dosed in mg/m2 IV every 28 days (Section 5.3.1). • Pembrolizumab will be flat dosed every 21 days (Section 5.3.2.1) • PLD will be dosed according institutional standard (Section 5.3.1.2).
Study Drug Administration	Agent *Administration* Guidelines are found in Section 5.3.1 and 5.3.2 • PLD administration should be at a range of 1mg/min per the FDA package insert. If no infusion reaction occurs, the infusion can be increased to complete drug in 1 hour (Section 5.3.1.1) • Pembrolizumab will be administered IV over 30 minutes and has a -5/+10minute infusion window (Section 5.3.2.1) • Pembrolizumab should be administered **before** PLD on days where both are indicated (5.3.2.7) • Criteria to treat for C1D1 must meet eligibility criteria in section 3.1 • Criteria to treat for subsequent cycles, Day 1 is in Section 5.2.2. • There is no required hydration for PLD or Pembro. (Section 5.3.1.4 & Section 5.3.2.3) • There is a +/- 3day window for infusions (Section 5.3.1.2 & Section 10).
Dose Mods & Toxicity	*Dose Modifications/Dosing Delay for Toxicity* are outlined in Section 6. • This protocol uses NCI CTCAE criteria, version 4.0 (Section 6). • The definition of a DLT is found in Section 5.4.
Con Meds	*Concomitant Therapy* Guidelines are in Section 5.5. • Please review the cited sections for permitted, prohibited, and "use with caution" medications/therapies/foods • No live vaccines are allowed while participating in the trial (Section 5.5.3).
Required Data	*Study Calendar and Assessment Required data* are outlined in Section 10. • The study calendar is in Section 10 • **Vital signs:** The time points are in Section 5.3.2.5 & Section 10. • **ECGs**: The time points are in Section 10.
Charting Tips	**All study drugs require documentation of exact administration time.** Please be sure to DOCUMENT study medication **actual** UP/DOWN times in medical record (e.g. LMR, eMAR, nursing notes). **Edit eMAR as needed to match the exact time given**. • If there is a discrepancy in the infusion time, delay in administration, or the infusion takes longer than is permitted by the guidelines of the protocol, please **document the reason for the discrepancy in the medical record.** Please be sure to also DOCUMENT any required observation periods, any additional vital signs, routes of administration, injection sites, and exact time of PK collections.

Institutional Conflict of Interest Information Sheet

A Phase II Study of Pembrolizumab combined with pegylated liposomal doxorubicin (PLD) for recurrent platinum resistant ovarian, fallopian tube or peritoneal cancer

Protocol #16-257

You are invited to take part in a clinical trial, a type of research study. This research study is studying a targeted therapy as a possible treatment for this diagnosis. Merck is supporting this research study by providing the study drug, Pembrolizumab. You are receiving this Information Sheet because Dana-Farber Cancer Institute has a financial interest in Pembrolizumab, which may be affected by the outcome of this research. This is known as a potential "institutional conflict of interest."

Pembrolizumab is considered an investigational drug in this research, which means that the intervention is being studied and has not been approved for your type of cancer by the FDA (U.S. Food and Drug Administration). It is possible that, as the result of this clinical trial and other clinical trials involving this drug that may follow, this investigational drug could be approved by the FDA, and become widely available for sale. Specifically, the drug being investigated involves a technology that was discovered through research conducted at DFCI. As a result, a concern exists that DFCI could be biased because it stands to benefit financially from the outcome of clinical trials involving this drug.

Dana-Farber Cancer Institute ("DFCI") is committed to ensuring that all of its research and clinical activities are conducted with integrity. As part of this commitment, DFCI fully discloses the existence of all actual or potential conflicts of interest to research participants, sponsors, and regulatory bodies. Also, we have made sure that appropriate steps have been taken to ensure the safety of research participants and the reliability of research results.

First, DFCI will disclose the existence and nature of its financial interest to all research participants.

Second, DFCI will disclose the existence and nature of its financial interest to all research collaborators and in all public presentations and publications of data related to this research.

Finally, and most importantly, we want to be certain that all research participants are fully informed about the financial interest, and are able to consider this information in deciding whether to participate in this trial. To that end, if you have additional questions about DFCI's financial interests and their potential impact upon this clinical trial, or any of the steps taken by DFCI to safeguard the integrity of this research, please contact:

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